WHO global air quality guidelines

Particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide

World Health Organization

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Foreword

Clean air is fundamental to health. Compared to 15 years ago, when the previous edition of these guidelines was published, there is now a much stronger body of evidence to show how air pollution affects different aspects of health at even lower concentrations than previously understood. But here's what hasn't changed: every year, exposure to air pollution is still estimated to cause millions of deaths and the loss of healthy years of life. The burden of disease attributable to air pollution is now estimated to be on a par with other major global health risks such as unhealthy diets and tobacco smoking.

In 2015, the World Health Assembly adopted a landmark resolution on air quality and health, recognizing air pollution as a risk factor for noncommunicable diseases such as ischaemic heart disease, stroke, chronic obstructive pulmonary disease, asthma and cancer, and the economic toll they take. The global nature of the challenge calls for an enhanced global response.

These guidelines, taking into account the latest body of evidence on the health impacts of different air pollutants, are a key step in that global response. The next step is for policy-makers around the world to use these guidelines to inform evidence-based legislation and policies to improve air quality and reduce the unacceptable health burden that results from air pollution.

We are immensely grateful to all the scientists, colleagues and partners around the world who have contributed time and resources to the development of these guidelines. As with all WHO guidelines, a global group of experts has derived the new recommendations based on a robust and comprehensive review of the scientific literature, while adhering to a rigorously defined methodology. This process was overseen by a steering group hosted and coordinated by the WHO European Centre for Environment and Health.

Although the burden of air pollution is heterogeneous, its impact is ubiquitous. These guidelines come at a time of unprecedented challenges, in the face of the ongoing COVID-19 pandemic and the existential threat of climate change. Addressing air pollution will contribute to, and benefit from, the global fight against climate change, and must be a key part of the global recovery, as prescribed by the WHO Manifesto for a healthy recovery from COVID-19.

A guideline is just a tool. What matters is that countries and partners use it to improve air quality and health globally. The health sector must play a key role in monitoring health risks from air pollution, synthesizing the evidence, providing the tools and resources to support decision-making, and raising awareness of the impacts of air pollution on health and the available policy options. But this is not a job for one sector alone; it will take sustained political commitment and bold action and cooperation from many sectors and stakeholders. The payoff is cleaner air and better health for generations to come.

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Glossary

Abatement. The reduction or elimination of pollution, which involves either legislative measures or technological procedures, or both.

Accountability research. Assessment of the effectiveness of interventions. Knowledge gained from such assessments can provide valuable feedback for improving regulatory or other action.

AirQ+. A software tool for health risk assessment of air pollution that looks at the effects of short-term changes in air pollution (based on risk estimates from time-series studies) and of long-term exposures (using the life-tables approach and based on risk estimates from cohort studies).

Air quality guidelines. A series of WHO publications that provide evidence-informed, non-binding recommendations for protecting public health from the adverse effects of air pollutants by eliminating or reducing exposure to hazardous air pollutants and by guiding national and local authorities in their risk management decisions. The current volume is the latest issue of the series.

Air quality guideline level. A particular form of a guideline recommendation consisting of a numerical value expressed as a concentration of a pollutant in the air and linked to an averaging time. It is assumed that adverse health effects do not occur or are minimal below this concentration level. For the purposes of this document, a long-term air quality guideline level is defined as the lowest exposure level of an air pollutant above which the guideline development group is confident that there is an increase in adverse health effects; the short-term air quality guideline level is defined as a high percentile of the distribution of daily values, for example the 99th percentiles equivalent to three to four days a year exceeding this value.

Air quality standard. A given level of an air pollutant (for example, a concentration or deposition level) that is adopted by a regulatory authority as enforceable. Unlike an air quality guideline level, a number of elements in addition to the effect-based level and averaging time must be specified in the formulation of an air quality standard. These elements include:

- measurement technique and strategy
- data handling procedures (including quality assurance/quality control)
- statistics used to derive, from the measurements, the value to be compared with the standard.

The numerical value of a standard may also include a permitted number of exceedances of a certain numerical value in a given time period.

Ambient air pollution. Air pollution in the outdoor environment, that is, in outdoor air, but which can enter or be present in indoor environments.

Averaging time. For the purposes of this document, the duration of the exposure with a given mean concentration associated with certain health effects**.**

Black carbon. An operationally defined term that describes carbon as measured by light absorption. As such, it is not the same as elemental carbon, which is usually monitored with thermal-optical methods.

Concentration–response function. A statistical function or model based on the results of epidemiological studies to estimate the relative risk from air pollution for a disease or health outcome (e.g. premature death, heart attack, asthma attack, emergency room visit, hospital admission) in a population per unit concentration of an air pollutant.

Dust storm (or sand storm). A mix of dust and/or sand particles that has been elevated to great heights by a strong, turbulent wind and can travel great distances and reduce visibility. Dust or sand readily penetrates into buildings, results in severe soiling and may also cause considerable erosion. The particles are usually lifted to greater heights in a dust storm than in a sand storm.

Good practice statement. A statement formulated when a guideline development group is confident that a large body of diverse evidence, which is hard to synthesize, indicates that the desirable effects of a particular course of action far outweigh its undesirable effects. In other words, there is high certainty that implementing a measure would be beneficial, without the need for conducting numerous systematic reviews and detailed assessments of evidence.

Hot spot. For the purposes of this document, an area where air pollution levels are higher than the average levels in the local environment.

Household fuel combustion. Air pollution generated by the inefficient combustion of fuels in the household environment that results in household air pollution and contributes to local ambient air pollution.

Integrated exposure–response function. Models that combine exposure and risk data for different sources of combustion-related pollution, such as outdoor air, second-hand tobacco smoke, active smoking and household air pollution.

Interim target. An air pollutant concentration associated with a specific decrease of health risk. Interim targets serve as incremental steps in the progressive reduction of air pollution towards the air quality guideline levels and are intended for use in areas where air pollution is high. In other words, they are air pollutant levels that are higher than the air quality guideline levels, but which authorities in highly polluted areas can use to develop pollution reduction policies that are achievable within realistic time frames. The interim targets should be regarded as steps towards ultimately achieving air quality guideline levels, rather than as end targets.

Particulate matter. A mixture of solid and liquid particles in the air that are small enough not to settle out on to the Earth's surface under the influence of gravity, classified by aerodynamic diameter.

Ultrafine particle. Particles of an aerodynamic diameter less than or equal to 0.1 μm (that is, 100 nm). Owing to their small mass, their concentrations are most commonly measured and expressed in terms of particle number concentration per unit volume of air (for example, number of particles per cm^3).

Abbreviations

AAQS	ambient air quality standards
ACTRIS	Aerosol, Clouds and Trace Gases Research Infrastructure
APM	anthropogenic particulate matter
AQG level	air quality guideline level
BC/EC	black carbon or elemental carbon (an indicator of airborne soot-like carbon)
BenMAP-CE	Environmental Benefits Mapping and Analysis Program – Community Edition
CanCHEC	Canadian Census Health and Environment Cohort
CCAC	Climate and Clean Air Coalition
CEN	European Committee for Standardization
CI	confidence interval
CO	carbon monoxide
COMEAP	Committee on the Medical Effects of Air Pollutants
COPD	chronic obstructive pulmonary disease
CRF	concentration–response function
EEA	European Environment Agency
ERG	external review group
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GBD	Global Burden of Disease (study)
GDG	guideline development group
Global update 2005	Air quality guidelines – global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HEI	Health Effects Institute
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th edition
IHD	ischaemic heart disease

ISA	(US EPA) Integrated Science Assessment
MCC	Multi-Country Multi-City
NCD	noncommunicable disease
NDPM	net dust particulate matter
NO_2	nitrogen dioxide
O_3	ozone
PECOS	population, exposure, comparator, outcome and study design
PM	particulate matter
$PM_{2.5}$	particulate matter, where particles have an aerodynamic diameter equal to or less than 2.5 μm
PM_{10}	particulate matter, where particles have an aerodynamic diameter equal to or less than 10 μm
PNC	particle number concentration
ppb	parts per billion
ppm	parts per million
RBPM	regional background particulate matter
REVIHAAP	Review of evidence on health aspects of air pollution (project)
RoB	risk of bias
RR	relative risk
SDG	Sustainable Development Goal
SDS	sand and dust storms
SDS-WAS	Sand and Dust Storm Warning Advisory and Assessment System
SO_2	sulfur dioxide
Swiss TPH	Swiss Tropical and Public Health Institute
UFP	ultrafine particles
UN	United Nations
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environment Programme
US EPA	United States Environmental Protection Agency
VOC	volatile organic compound
WMO	World Meteorological Organization

Executive summary

The global burden of disease associated with air pollution exposure exacts a massive toll on human health worldwide: exposure to air pollution is estimated to cause millions of deaths and lost years of healthy life annually. The burden of disease attributable to air pollution is now estimated to be on a par with other major global health risks such as unhealthy diet and tobacco smoking, and air pollution is now recognized as the single biggest environmental threat to human health.

Despite some notable improvements in air quality, the global toll in deaths and lost years of healthy life has barely declined since the 1990s. While air quality has markedly improved in high-income countries over this period, it has generally deteriorated in most low- and middle-income countries, in step with large-scale urbanization and economic development. In addition, the global prevalence of noncommunicable diseases (NCDs) as a result of population ageing and lifestyle changes has grown rapidly, and NCDs are now the leading causes of death and disability worldwide. NCDs comprise a broad range of diseases affecting the cardiovascular, neurological, respiratory and other organ systems. Air pollution increases morbidity and mortality from cardiovascular and respiratory disease and from lung cancer, with increasing evidence of effects on other organ systems. The burden of disease resulting from air pollution also imposes a significant economic burden. As a result, governments worldwide are seeking to improve air quality and reduce the public health burden and costs associated with air pollution.

Since 1987, WHO has periodically issued health-based air quality guidelines to assist governments and civil society to reduce human exposure to air pollution and its adverse effects. The WHO air quality guidelines were last published in 2006. *Air quality guidelines – global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide* (WHO Regional Office for Europe, 2006) provided health-based guideline levels for the major health-damaging air pollutants, including particulate matter (PM),[1] ozone (O_3), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2). *Global update 2005* has had a significant impact on pollution abatement policies all over the world. Its publication led to the first universal frame of reference.

In various ways, these guidelines have stimulated authorities and civil society alike to increase efforts to control and study harmful air pollution exposures.

[1] That is, $PM_{2.5}$ (particles with an aerodynamic diameter of ≤ 2.5 μm) and PM_{10} (particles with an aerodynamic diameter of ≤ 10 μm).

In response to this growing awareness, the Sixty-eighth World Health Assembly adopted resolution WHA68.8, *Health and the environment: addressing the health impact of air pollution*, which was endorsed by 194 Member States in 2015 (WHO,2015). This resolution stated the need to redouble efforts to protect populations from the health risks posed by air pollution. In addition, the United Nations (UN) Sustainable Development Goals (SDGs) were designed to address the public health threat posed by air pollution via specific targets to reduce air pollution exposure and the disease burden from household and ambient exposure.

More than 15 years have passed since the publication of *Global update 2005*. In that time there has been a marked increase in evidence on the adverse health effects of air pollution, built on advances in air pollution measurement and exposure assessment and an expanded global database of air pollution measurements (discussed in Chapter 1). New epidemiological studies have documented the adverse health effects of exposure to high levels of air pollution in low- and middle-income countries, and studies in high-income countries with relatively clean air have reported adverse effects at much lower levels than had previously been studied.

In view of the many scientific advances and the global role played by the WHO air quality guidelines, this update was begun in 2016.

Objectives

The overall objective of the updated global guidelines is to offer quantitative health-based recommendations for air quality management, expressed as long- or short-term concentrations for a number of key air pollutants. Exceedance of the air quality guideline (AQG) levels is associated with important risks to public health. These guidelines are not legally binding standards; however, they do provide WHO Member States with an evidence-informed tool that they can use to inform legislation and policy. Ultimately, the goal of these guidelines is to provide guidance to help reduce levels of air pollutants in order to decrease the enormous health burden resulting from exposure to air pollution worldwide.

Specific objectives are the following.

- Provide evidence-informed recommendations in the form of AQG levels, including an indication of the shape of the concentration–response function in relation to critical health outcomes, for $PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide for relevant averaging times.

These pollutants were chosen because of their worldwide importance. However, this choice does not imply that other air pollutants are irrelevant.

- Provide interim targets to guide reduction efforts towards the ultimate and timely achievement of the AQG levels for countries that substantially exceed these levels.
- Provide qualitative statements on good practices for the management of certain types of PM (i.e. black carbon or elemental carbon (BC/EC),[2] ultrafine particles (UFP), and particles originating from sand and dust storms (SDS)) for which the available information is insufficient to derive AQG levels but indicates risk.

Methods used to develop the guidelines

The guidelines were formulated by following a rigorous process involving several groups with defined roles and responsibilities (Chapter 2). In particular, the different steps in the development of the AQG levels included:

- a determination of the scope of the guidelines and formulation of systematic review questions;
- a systematic review of the evidence and meta-analyses of quantitative effect estimates to inform updating of the AQG levels;
- an assessment of the level of certainty of the bodies of evidence resulting from systematic reviews for the pollutants; and
- the identification of AQG levels, that is, the lowest levels of exposure for which there is evidence of adverse health effects.

In addition, the 2005 air quality interim targets were updated to guide the implementation of the new AQG levels, and good practice statements were formulated to support the management of the specific types of PM of concern. Interim targets are air pollutant levels that are higher than the AQG levels, but which authorities in highly polluted areas can use to develop pollution reduction policies that are achievable within realistic time frames. Therefore, the interim targets should be regarded as steps towards the ultimate achievement of AQG levels in the future, rather than as end targets. The number and numerical values of the interim targets are pollutant specific, and are justified in the relevant sections of Chapter 3.

The process and methods for developing these guidelines are described in detail in Chapter 2.

[2] An indicator of airborne soot-like carbon.

The systematic reviews that informed the formulation of AQG levels and other related evidence discussed during the process are available in a special issue of *Environment International*, entitled *Update of the WHO global air quality guidelines: systematic reviews* (Whaley et al., 2021).

Recommendations on classical air pollutants

In this guideline update, recommendations on AQG levels are formulated, together with interim targets, for the following pollutants: $PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide (Table 0.1). The evidence-informed derivation of each AQG level and an indication of the reduction in health risk associated with the achievement of consecutive interim targets can be found in Chapter 3. Only evidence assessed as having high or moderate certainty of an association between a pollutant and a specific health outcome was used to define the recommended AQG levels, and all recommendations are classified as strong according to the adapted Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (discussed in Chapter 2).

Table 0.1. Recommended AQG levels and interim targets

Pollutant	Averaging time	Interim target				AQG level
		1	2	3	4	
$PM_{2.5}$, µg/m³	Annual	35	25	15	10	5
	24-hour[a]	75	50	37.5	25	15
PM_{10}, µg/m³	Annual	70	50	30	20	15
	24-hour[a]	150	100	75	50	45
O_3, µg/m³	Peak season[b]	100	70	–	–	60
	8-hour[a]	160	120	–	–	100
NO_2, µg/m³	Annual	40	30	20	–	10
	24-hour[a]	120	50	–	–	25
SO_2, µg/m³	24-hour[a]	125	50	–	–	40
CO, mg/m³	24-hour[a]	7	–	–	–	4

[a] 99th percentile (i.e. 3–4 exceedance days per year).
[b] Average of daily maximum 8-hour mean O_3 concentration in the six consecutive months with the highest six-month running-average O_3 concentration.

It is important to note that the air quality guidelines recommended in previous WHO air quality guidelines for pollutants and those averaging times not covered in this update remain valid. This includes the short averaging times for nitrogen dioxide, sulfur dioxide and carbon monoxide that were included in *Global update 2005* and indoor air quality guidelines from 2010 (and not re-evaluated in this update). Table 0.2 shows existing air quality guidelines for nitrogen dioxide, sulfur dioxide and carbon monoxide with short averaging times. The reader is referred to previous volumes of air quality guidelines – *Air quality guidelines for Europe* (WHO Regional Office for Europe, 1987), *Air quality guidelines for Europe, 2nd edition* (WHO Regional Office for Europe, 2000a); and *WHO guidelines for indoor air quality: selected pollutants* (WHO Regional Office for Europe, 2010) – for other pollutants that are not covered in this 2021 update.

Table 0.2. Air quality guidelines for nitrogen dioxide, sulfur dioxide and carbon monoxide (short averaging times) that were not re-evaluated and remain valid

Pollutant	Averaging time	Air quality guidelines that remain valid
NO_2, µg/m³	1-hour	200
SO_2, µg/m³	10-minute	500
CO, mg/m³	8-hour	10
	1-hour	35
	15-minute	100

Good practice statements about other PM types

As yet, insufficient data are available to provide recommendations for AQG levels and interim targets for specific types of PM, notably BC/EC, UFP and SDS. However, due to health concerns related to these pollutants, actions to enhance further research on their risks and approaches for mitigation are warranted. Good practice statements for these pollutants are summarized in Table 0.3. The full text of and rationales for the statements can be found in Chapter 4.

Table 0.3. Summary of good practice statements

	Good practice statements
BC/EC	1. Make systematic measurements of black carbon and/or elemental carbon. Such measurements should not replace or reduce existing monitoring of those pollutants for which guidelines currently exist. 2. Undertake the production of emission inventories, exposure assessments and source apportionment for BC/EC. 3. Take measures to reduce BC/EC emissions from within the relevant jurisdiction and, where appropriate, develop standards (or targets) for ambient BC/EC concentrations.
UFP	1. Quantify ambient UFP in terms of PNC for a size range with a lower limit of ≤ 10 nm and no restriction on the upper limit. 2. Expand the common air quality monitoring strategy by integrating UFP monitoring into the existing air quality monitoring. Include size-segregated real-time PNC measurements at selected air monitoring stations in addition to and simultaneously with other airborne pollutants and characteristics of PM. 3. Distinguish between low and high PNC to guide decisions on the priorities of UFP source emission control. Low PNC can be considered < 1 000 particles/cm³ (24-hour mean). High PNC can be considered > 10 000 particles/cm³ (24-hour mean) or 20 000 particles/cm³ (1-hour mean). 4. Utilize emerging science and technology to advance approaches to the assessment of exposure to UFP for their application in epidemiological studies and UFP management.
SDS	1. Maintain suitable air quality management and dust forecasting programmes. These should include early warning systems and short-term air pollution action plans to alert the population to stay indoors and take personal measures to minimize exposure and subsequent short-term health effects during SDS incidents with high levels of PM. 2. Maintain suitable air quality monitoring programmes and reporting procedures, including source apportionment activities to quantify and characterize PM composition and the percentage contribution of SDS to the overall ambient concentration of PM. This will enable local authorities to target local PM emissions from anthropogenic and natural sources for reduction. 3. Conduct epidemiological studies, including those addressing the long-term effects of SDS, and research activities aimed at better understanding the toxicity of the different types of PM. Such studies are especially recommended for areas where there is a lack of sufficient knowledge and information about the health risk due to frequent exposure to SDS. 4. Implement wind erosion control through the carefully planned expansion of green spaces that considers and is adjusted to the contextual ecosystem conditions. This calls for regional collaboration among countries in the regions affected by SDS to combat desertification and carefully manage green areas. 5. Clean the streets in those urban areas characterized by a relatively high population density and low rainfall to prevent resuspension by road traffic as a short-term measure after intense SDS episodes with high dust deposition rates.

PNC: particle number concentration.

The settings to which these guidelines apply

The present guidelines are applicable to both outdoor and indoor environments globally. Thus, they cover all settings where people spend time. However, as in previous editions, these guidelines do not cover occupational settings, owing to the specific characteristics of the relevant exposures and risk reduction policies and to potential differences in population susceptibility of the adult workforce in comparison with the general population.

What these guidelines do not address

These guidelines do not include recommendations about pollutant mixtures or the combined effects of pollutant exposures. In everyday life, people are exposed to a mixture of air pollutants that varies in space and time. WHO acknowledges the need to develop comprehensive models to quantify the effects of multiple exposures on human health. However, as the main body of evidence on air quality and health still focuses on the impact of single markers of ambient air pollution on the risk of adverse health outcomes, the current guidelines provide recommendations for each air pollutant individually. Achievement of the AQG levels for all these pollutants is necessary to minimize the health risk of the exposure.

Furthermore, these guidelines do not address specific recommendations on policies and interventions because these are largely context specific: what might be effective in one setting might not work in another. Lastly, individual-level interventions, such as the use of personal respiratory protection (e.g. masks, respirators, air purifiers) or behavioural measures, are addressed in another document, *Personal interventions and risk communication on air pollution* (WHO, 2020a).

Target audience

The WHO global air quality guidelines aim to protect populations from the adverse effects of air pollution. They are designed to serve as a global reference for assessing whether, and how much, exposure of a population (including particularly vulnerable and/or susceptible subgroups) to various levels of the considered air pollutants results in health concerns. The guidelines are a critical tool for the following three main groups of users:

- policy-makers, lawmakers and technical experts operating at the local, national and international levels who are responsible for developing and implementing regulations and standards for air quality, air pollution control, urban planning and other policy areas;

- national and local authorities and nongovernmental organizations, civil society organizations and advocacy groups, such as patients, citizen groups, industrial stakeholders and environmental organizations; and
- academics, health and environmental impact assessment practitioners, and researchers in the broad field of air pollution.

These groups are the targets of the information, education and communication strategies outlined in Chapter 5. The strategies, and the tools to implement them, will be essential to ensure that these global guidelines are widely disseminated and considered in policy and planning decisions. In addition, these groups are addressed in Chapter 6, on implementation of the guidelines. This includes the aspects involved in developing air quality standards based on the recommendations and general risk management principles, which are built on decades of experience.

Implementation of the guidelines

While achievement of the AQG levels should be the ultimate goal of actions to implement the guidelines, this might be a difficult task for many countries and regions struggling with high air pollution levels. Therefore, gradual progress in improving air quality, marked by the achievement of interim targets, should be considered a critical indicator of improving health conditions for populations. Key institutional and technical tools supported by human capacity-building are necessary to achieve this goal. Implementation of the guidelines requires the existence and operation of air pollution monitoring systems; public access to air quality data; legally binding, globally harmonized air quality standards; and air quality management systems. Policy decisions to set priorities for action will profit from the health risk assessment of air pollution.

While actions to reduce air pollution require cooperation among various sectors and stakeholders, health sector involvement is crucial for raising awareness of the impacts of air pollution on health and, thus, the economy, and for ensuring that protecting health strongly figures in policy discussions. Monitoring and evaluation are equally crucial to ensure that guidelines are implemented; they are addressed in Chapter 7.

Currently, the accumulated evidence is sufficient to justify actions to reduce population exposure to key air pollutants, not only in particular countries or regions but on a global scale. Nevertheless, uncertainties and knowledge gaps remain. Future research (discussed in Chapter 8) will further strengthen the scientific evidence base for making decisions on clean air policy worldwide.

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Introduction

The WHO air quality guidelines were last published in 2006: *Air quality guidelines – global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide* (hereafter referred to as *Global update 2005*) (WHO Regional Office for Europe, 2006). Since they were issued, air pollution has become recognized as the single biggest environmental threat to human health based on its notable contribution to disease burden. This is particularly true for PM (both $PM_{2.5}$, i.e. particles with an aerodynamic diameter equal to or less than 2.5 μm, and PM_{10}, i.e. particles with an aerodynamic diameter of equal to or less than 10 μm). However, other commonly measured air pollutants such as ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and carbon monoxide (CO) are also of concern, as are other components of air pollution.

The burden of disease associated with both ambient and household air pollution exposure is large and growing. The growth is partly due to increases in exposures in low- and middle-income countries,[3] but is in part also due to the rapidly increasing prevalence of NCDs worldwide as a result of population ageing and lifestyle changes. Air pollution especially increases morbidity and mortality from the noncommunicable cardiovascular and respiratory diseases that are the major causes of global mortality; it also increases the disease burden from lower respiratory tract infections and preterm birth and other causes of death in children and infants, which remain a major cause of the disease burden in low- and middle-income countries. Although air quality has improved gradually in high-income countries in the past decades, pollutant concentrations still exceed the levels published in *Global update 2005* for several pollutants in many areas. Air quality has generally deteriorated in most low- and middle-income countries, in step with large-scale urbanization and economic development that has largely relied on the burning of fossil fuels. Disparities in air pollution exposure are, therefore, increasing worldwide.

Science advances and, since the 2005 air quality guidelines were established, many new studies have continued to document the adverse health effects of air pollution. During this time, enormous advances have also occurred in measuring levels and trends in ground-level air pollution concentrations. In particular, the use of satellite remote sensing instruments in combination with advanced chemical transport models and ground-based measurements has substantially improved the understanding of worldwide pollution levels and trends. Studies conducted in low- and middle-income countries where concentrations are high are of great importance; however, equally important are studies in very clean areas, which answer important questions on the effects of low-level exposures and the evaluation of thresholds.

[3] Country income groupings of low, lower-middle, upper-middle and high are determined by the World Bank based on gross national income per capita (World Bank, 2021).

These studies provide critical information on the benefits that might be expected if air pollution levels were reduced worldwide. In view of these many advances, revision of *Global update 2005* was both timely and necessary. This revision benefited from thousands of new studies and from following the rigorous process for developing guidelines outlined in the *WHO handbook for guideline development, 2nd edition* (WHO, 2014a).

Global update 2005 has had a significant impact on abatement policies all over the world. Its publication led to the first universal frame of reference. In various ways, the air quality guidelines have stimulated authorities and civil society alike to increase efforts to control harmful air pollution exposures. Major challenges still exist, however, and it is hoped that this update of the WHO air quality guidelines will continue to inspire and guide pollution reduction policies all over the world.

1.1 Objectives of the guidelines

The overall objective of these guidelines is to offer quantitative health-based recommendations for air quality, expressed as long- or short-term concentrations of a number of key air pollutants. Exceedance of the air quality guideline levels (hereafter referred to as AQG levels) is associated with important risks to public health. These guidelines are not legally binding standards; however, they do provide countries with an evidence-informed tool, which they can use to inform legislation and policy. In addition, the air quality guidelines will be a key component to support air quality policies globally and the development of standards, clean air policies and other tools for air quality management. Ultimately, the goal of these guidelines is to provide guidance to help reduce levels of air pollutants in order to decrease the enormous worldwide health burden resulting from exposure to air pollution.

Specifically, the objectives of these guidelines are the following.

- Provide evidence-informed recommendations in the form of AQG levels, including an indication of the shape of the concentration–response function (CRF) in relation to critical health outcomes, for $PM_{2.5}$, PM_{10}, nitrogen dioxide, ozone, sulfur dioxide and carbon monoxide for relevant averaging time periods. These pollutants were chosen in the process described in section 2.3 because of their worldwide importance. This choice does not imply that other air pollutants are irrelevant.
- Provide interim targets to guide reduction efforts towards the ultimate and timely achievement of the AQG levels for those countries that substantially exceed the AQG levels.

- Provide qualitative statements on good practices for the management of certain types of PM – that is, BC/EC, UFP and particles originating from SDS – for which the available information is insufficient to derive AQG levels but indicates risk.

1.2 Target audience

The WHO guidelines to protect populations from the adverse effects of air pollution are designed to serve as a global reference for an audience of different groups of end-users, including those involved in policy-making, research and advocacy. Broadly, three main groups can be identified:

- policy-makers, lawmakers and technical experts at the local, national and international levels who are responsible for developing and implementing regulations and standards for air quality, air pollution control, urban planning and other policy areas;
- national and local authorities and nongovernmental organizations, civil society organizations and advocacy groups, such as patients, citizen groups, industrial stakeholders and environmental organizations; and
- academics, health and environmental impact assessment practitioners and researchers in the broad field of air pollution.

1.3 Background and rationale for updated guidelines

An update of the global WHO air quality guidelines was required for several reasons. More than 15 years have passed since the publication of *Global update 2005* and in the intervening years knowledge about the exposure of human populations, the adverse health effects of this exposure and the public health threat that it poses has seen a marked increase. Insight into global concentrations of some pollutants such as PM, ozone and nitrogen dioxide has increased dramatically (section 1.3.1). This is also true for insights in sources of emissions (section 1.3.2) and in the contribution of air pollutants to the global burden of disease (section 1.3.3). Much has been learned about the importance of addressing health inequities related to air pollution and of protecting vulnerable groups in society (section 1.3.4). Enormous advances have occurred since the early 2000s in measuring levels and trends in ground-level air pollution concentrations, and section 1.3.5 provides a summary of some major trends and achievements. Finally, there have been significant advances in the worldwide adoption of the air quality guidelines presented in *Global update 2005* (section 1.3.6), and mitigating air pollution has become more central in WHO and UN activities related to achieving the UN SDGs (section 1.3.7).

1.3.1 Global concentrations and trends

Measurement of air pollutant concentrations at fixed-location monitoring sites has been the traditional approach used for air quality management, for assessment of trends and to estimate exposure for epidemiological analyses. However, despite growth in the numbers of monitoring locations globally, even for the most commonly monitored pollutants, coverage is inadequate – that is, it is often restricted to major cities – to accurately estimate exposure in the many different places where people live. There are two major gaps.

The first is a lack of monitoring in many countries of the world and inadequate monitoring in rural areas or outside of major cities in many countries. Although there is increasing coverage of PM monitoring, coverage for other pollutants such as ozone, nitrogen dioxide and sulfur dioxide is less extensive. The second gap relates to inadequate monitoring to characterize the spatial variation in specific air pollutants within cities. In particular, this holds for concentrations of pollutants such as nitrogen dioxide and black carbon and UFP (diameter of ≤ 0.1 µm; or broader quasi-UFP, as discussed in section 4.3 on UFP), which may vary by an order of magnitude over just a few hundred metres (Karner, Eisinger & Niemeier, 2010). Since 2010, there has been a dramatic improvement in the combination of satellite data retrievals and chemical transport models with land-use information and ground measurements to estimate concentrations globally, which have been used to address the first gap (Shaddick et al., 2018; Brauer et al., 2012, 2016; Larkin et al., 2017; de Hoogh et al., 2016; Novotny et al., 2011; Hystad et al., 2011; Knibbs et al., 2014; Chang et al., 2019). To address the second gap, land-use regression models (Hoek et al., 2008) have been used increasingly – these models capture within-city variability, as discussed for example for UFP (Morawska et al., 2008), and have been scaled up to the global context for nitrogen dioxide (Larkin et al., 2017).

Although in many countries, regional and local authorities maintain accessible databases of air quality measurements, the only global databases are the WHO Global Ambient Air Quality Database and OpenAQ. The WHO Global Ambient Air Quality Database provides information on the annual average concentrations of PM_{10} and $PM_{2.5}$ for specific cities based on available measurements (including averages from multiple monitors within a single city, where these are available) (WHO, 2021a). OpenAQ is a non-profit-making effort to maintain an open-source database of aggregated current and archived air quality data gathered in real time from government agencies (OpenAQ, 2021). Despite the progress made in monitoring and in data access, many publicly funded agencies still do not provide easy access to data.

Exposure to air pollutants is heavily dependent on their ambient concentrations. Ambient $PM_{2.5}$ concentrations vary substantially between and within regions of the world. Importantly, more than 90% of the global population in 2019 lived in areas where concentrations exceeded the 2005 WHO air quality guideline of 10 μg/m^3. In 2019 annual population-weighted $PM_{2.5}$ concentrations were highest in the WHO South-East Asia Region, followed by the WHO Eastern Mediterranean Region. Elevated concentrations were also observed in some western African countries, largely due to the impact of Saharan dust. Windblown desert dust sometimes contributes to very high exposures to coarse particles larger than 2.5 μm or10 μm in diameter. This is a prominent issue in many arid areas in the Middle East, northern Africa, the Gobi desert and elsewhere.

Many of the countries with the lowest national $PM_{2.5}$ exposure levels were either in the WHO Region of the Americas or parts of the WHO European Region. Population-weighted $PM_{2.5}$ concentrations averaged 7 μg/m^3 or less in these countries. Trends in $PM_{2.5}$ indicate a relatively stable population-weighted global mean concentration, which reflects both decreases in exposure in the WHO European Region, the WHO Region of the Americas and the WHO Western Pacific Region but increases elsewhere.

Population-weighted ozone concentrations vary less dramatically than is the case for $PM_{2.5}$, for example ranging from 30–50 μg/m^3, mostly in small island nations, to 120–140 μg/m^3 in Asia and the Middle East. Among the world's most populous countries in southern Asia, population-weighted seasonal ozone concentrations range up to approximately 130 μg/m^3. Concentrations in African mega-cities are also likely to be high but there is still comparatively little documentation.

Trends in ozone at a regional scale show little change over time, although decreases within North America and Europe and increases in the Middle East and much of Asia are apparent.

The patterns of ambient nitrogen dioxide concentrations are quite different from those of $PM_{2.5}$ and ozone, with the highest population-weighted concentrations in eastern Asia, the Middle East, North America and much of Europe, reflecting mobile sources (Larkin et al., 2017; Achakulwisut et al., 2019). In addition, nitrogen dioxide displays a distinct urban–rural gradient, with higher concentrations in more densely populated urban areas. This pattern contrasts distinctly from that of ozone, which displays higher concentrations downwind of urban areas, and $PM_{2.5}$, which is more homogeneous regionally due to its longer atmospheric lifetime and diversity of (urban, rural and regional) sources. Trends in population-weighted nitrogen dioxide concentrations (for 1992–2012) indicated

sharp decreases (-4.7%/year) in high-income North American countries and somewhat lesser decreases in western Europe (-2.5%/year) and high-income Asia–Pacific countries (-2.1%/year). In contrast, population-weighted nitrogen dioxide concentrations increased dramatically during this period in eastern Asia at a rate of 6.7%/year. Judging from satellite observations, concentrations in Africa seem to be generally low, with some evidence of increases in northern Africa and stable or slightly decreasing levels elsewhere (Geddes et al., 2016). However, there are few actual monitoring data on small-scale spatial variability within mega-cities in Africa.

1.3.2 Sources of emissions and exposure

Air pollution originates from numerous sources of emission, both natural and anthropogenic, with the latter becoming globally dominant since the beginning of industrialization. The process of combustion is the greatest contributor to air pollution, in particular, the combustion of fossil fuels and biomass to generate energy. In indoor environments, the use of polluting fuels in unvented heating and cooking stoves, tobacco combustion and combustion for other purposes, such as cultural or religious practices are also important. Fossil and biomass fuel burning for domestic heating is also an important source of outdoor air pollution in many parts of the world.

Outdoor combustion sources include land, air and water transportation; industry and power generation; and biomass burning, which includes controlled and uncontrolled forest and savannah fires and agricultural waste burning, as well as waste burning in urban areas. Other sources and processes contributing to outdoor pollution are the resuspension of surface dust and construction activities. Long-range atmospheric transport of pollutants from distant sources contributes to local pollution, particularly urban air pollution. Some of the pollutants are emitted directly by combustion sources as primary pollutants (with elemental carbon as the main constituent of PM), and some are formed in the air as secondary pollutants (such as nitrates, sulfates and organic carbon) through complex physicochemical processes involving gaseous precursors originating from combustion sources, agriculture (ammonia), other anthropogenic processes and natural processes such as biogenic emissions.

Comprehensive reviews of sources and concentrations of major outdoor air pollutants have been published by the United States Environmental Protection Agency (US EPA) (2010, 2016, 2017, 2019a, 2020). The European Environment Agency (EEA) every year produces a comprehensive report on air quality in Europe; the latest one from 2020 (EEA, 2020).

In indoor environments, pollution is also generated by combustion sources, mainly cooking and heating with polluting fuels such as coal, wood or dung; and using candles, incense and kerosene lamps (e.g. for light or religious practices). Tobacco smoking is also a significant source of indoor pollution. Non-combustion sources and processes also have a significant impact on indoor air pollution, particularly those that generate volatile and semi-volatile organic compounds (VOCs) and/or ozone. These include the renovation of houses, usage of consumer products (e.g. cleaning products and insecticides) and operation of electric devices such as laser printers. Dust resuspension due to human movement is another significant source in some indoor environments, particularly in schools. However, indoor air pollution is generated not only from indoor sources but also from outdoor air pollutants that are brought indoors in the processes of ventilation and penetration through the building envelope. In indoor environments without indoor sources of pollution, pollutants from outdoors are the main cause of indoor air pollution. Exposure is then further influenced by indoor decay, which is very fast for substances such as ozone (which is very reactive) and very slow for substances such as carbon monoxide (which is fairly inert).

Airborne pollutants originating from the sources and processes listed above include PM (measured as $PM_{2.5}$, PM_{10} and UFP), gaseous pollutants (including ammonia (NH_3), carbon monoxide, nitrogen dioxide, sulfur dioxide and ozone) and organic air pollutants. PM is partly formed in the atmosphere through chemical reactions that produce inorganic nitrates and sulfates, as well as organic compounds summarized as organic carbon. Other airborne pollutants not discussed in this document include radon and its decay products, and biological agents. WHO has developed dedicated air quality guidelines for these and for other selected pollutants, dampness and mould, and household fuel combustion (WHO, 2014b; WHO Regional Office for Europe, 2009, 2010).

The spatial and temporal concentration of pollutants in outdoor air varies according to the spatial distribution of the sources and their pattern of operation (e.g. daily or seasonal), the characteristics of the pollutants and their dynamics (dispersion, deposition, interaction with other pollutants), and meteorological conditions. In urban environments, some pollutants are distributed more homogeneously than others; for example, $PM_{2.5}$ concentration has much less spatial variation compared with the concentration of UFP or gases directly emitted by local combustion sources. Importantly, spatial variation determines to what extent ambient concentrations measured at a single fixed site reflect the outdoor concentrations at other sites in the area. Temporal variation is a very important feature of ambient air pollution.

Emissions often have specific and predictable temporal patterns (e.g. weekdays versus weekends). Most importantly, however, meteorological conditions are very strong determinants of temporal variations, and can have far larger effects than the temporal variation in emission alone. Epidemiological research of short-term health effects capitalizes on these short-term temporal variations in ambient concentrations. It offers opportunities to investigate whether temporally varying markers of health, including the number of adverse health events, correlate with the temporal variation in ambient concentrations of pollutants.

In indoor environments, concentrations of pollutants originating from outdoor air are influenced by their outdoor spatiotemporal patterns of concentration and, in particular, by the proximity of the building to outdoor sources (e.g. busy roads). Furthermore, indoor pollution concentrations depend on the amount of air pollution penetrating from outdoors; this is dependent on the penetration fraction, the ventilation rate and the decay rate. The penetration coefficient varies for different particle size fractions and is highest for $PM_{2.5}$. Finally, indoor pollution concentrations depend on the temporal pattern of operation of outdoor sources (e.g. traffic) but also on indoor sources (e.g. the daily cycle of cooking) and the decay process (in the case of highly reactive gases such as ozone).

People are exposed to air pollution in all the microenvironments in which they spend time, and the exposure puts them at risk. A microenvironment is defined as a three-dimensional space in which the pollutant level is uniform at some specified time. Exposure is a product of the pollutant concentration and the time over which a person is in contact with that pollutant. Assessment of exposure constitutes an element of risk assessment that is schematically represented as a chain of events from emissions through air pollution concentrations, population exposure, and body burden and pollutant dose at the organ or cellular level, to health risk.

In some locations, pollutant concentrations are low but the overall contribution to the exposure is high because of the longer time spent there (e.g. at home); in other locations, pollutant concentrations are very high (e.g. at traffic hot spots), and even short periods of time spent at such locations result in high exposures. When concentration varies with time, the time-averaged concentration is used for exposure calculation. For health risk assessment, exposures are defined on different time domains as (i) lifetime exposure, which is the sum of exposures that occurred in different environments – this is particularly important for carcinogenic pollutants; (ii) long-term exposure, measured as a mean of one or several years; and (iii) short-term exposure, measured over minutes to days.

Considering indoor exposures is important because people spend most of their time in various indoor environments, including home, workplace, school and commuting (where the microenvironment is a bus, car or train). Indoors is also where exposure predominantly occurs for vulnerable population groups, as sick and older people may not venture outside much. Although the exposures occur indoors, they are caused by both outdoor and indoor sources of emissions, since outdoor pollutants penetrate indoors, as discussed above.

The most accurate assessment of the risk caused by total air pollution would be based on the assessment of each individual's personal exposure, which would require pollution measurements in each microenvironment in which the individual spends time and an accurate account of the time spent there (time–activity diary). Yet, the most accurate assessment of exposure to ambient outdoor pollution – which is subject to clean air policy-making – may not necessarily be the measurement of personal exposure, unless the measured indicator of pollution is clearly and solely of outdoor origin. Presently it is not possible to measure all of the relevant pollutants in all microenvironments for each individual; therefore, the approach to exposure assessment is pragmatically based on the purpose of the assessment. For example, for studies on the long-term impact of outdoor air pollution (chronic effects), data are typically sourced from a limited number of monitors operating in some central outdoor locations. This has been shown to effectively represent population exposure to outdoor pollutants that are distributed more homogeneously, such as $PM_{2.5}$ or ozone. More complicated is exposure assessment for studies on the acute effects of air pollution (such as mortality or hospital admissions), where spatiotemporal variations in pollution need to be taken into account. However, for many pollutants, daily concentrations are often very highly correlated temporally across rather large regions and, thus, temporal variation may be well captured by single monitors.

Advanced methods of exposure assessment are available, including not only ground base monitoring of pollution but also the use of satellite observations and various modelling tools such as chemical transport models and land-use regression models. Those modelling approaches have overcome some of the former limitations of reliance on only a few monitoring stations to describe population exposure in space and time.

1.3.3 Disease and economic burden

Air pollution is the leading environmental risk factor globally. WHO estimates show that around 7 million deaths, mainly from noncommunicable diseases, are attributable to the joint effects of ambient and household air pollution (WHO, 2018).

Similar global assessments of ambient air pollution alone suggest between 4 million and 9 million deaths annually and hundreds of millions of lost years of healthy life, with the greatest attributable disease burden seen in low- and middle-income countries (Burnett et al., 2018; GBD 2019 Risk Factors Collaborators, 2020; Vohra et al., 2021; WHO, 2018). To date, strong evidence shows causal relationships between $PM_{2.5}$ air pollution exposure and all-cause mortality, as well as acute lower respiratory infections, chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD), lung cancer and stroke (Cohen et al., 2017; WHO, 2018). A growing body of evidence also suggests causal relationships for type II diabetes and impacts on neonatal mortality from low birth weight and short gestation (GBD 2019 Risk Factors Collaborators, 2020). Air pollution exposure may increase the incidence of and mortality from a larger number of diseases than those currently considered, such as Alzheimer's and other neurological diseases (Peters et al., 2019). The burden of disease attributable to air pollution is now estimated to be competing with other major global health risks such as unhealthy diet and tobacco smoking, and was in the top five out of 87 risk factors in the global assessment (GBD 2019 Risk Factors Collaborators, 2020).

At the time of publishing these guidelines, global burden estimates are limited to $PM_{2.5}$ and ozone. Other common pollutants such as nitrogen dioxide and sulfur dioxide are not yet included and, therefore, these figures based on exposure to $PM_{2.5}$ and ozone are likely to underestimate the full health toll from ambient air pollution. For example, an analysis of the disease burden attributable to nitrogen dioxide on one outcome, incident paediatric asthma, indicated that nitrogen dioxide pollution was responsible for 13% of the burden (Achakulwisut et al., 2019). With a spatial pattern quite different than that for $PM_{2.5}$, exposure to nitrogen dioxide resulted in a comparatively high burden in many high-income countries.

Air pollution also leads to health-related economic impacts. Such impacts arise via two major pathways. The first, human health costs, are those related to the incidence of disease and mortality and are estimated by a willingness-to-pay approach. The second is due to lost labour productivity. In 2013 the World Bank estimated a global economic impact of US$ 143 billion in lost labour income and of US$ 3.55 trillion in welfare losses from exposure to $PM_{2.5}$ (World Bank, 2016). The welfare losses ranged from an equivalent of 1% of gross domestic product in low-income countries to 5% in high-income countries not within the Organisation of Economic Co-operation and Development. Apart from the health-related burden, air pollution causes additional economic costs such as through its impact on agricultural crops or through damage to buildings and infrastructure. In addition, there are costs associated with air pollution-related climate change and environmental degradation.

Although some uncertainty surrounding the exact disease burden remains (discussed in Chapter 8), it is clear that the global burden of disease associated with air pollution takes a massive toll on human health and the economy worldwide: exposure to air pollution is estimated to cause millions of deaths and lost years of healthy life, as well as a loss of trillions of dollars annually. Air pollution is now recognized as the single largest environmental threat to human health and well-being.

1.3.4 Inequities and vulnerable and susceptible groups

As already discussed, air pollution from both ambient sources and household use of polluting fuels is a recognized threat to human health, even at low exposures, and causes increased mortality and morbidity worldwide.

This burden of disease is unevenly distributed, often disproportionately affecting the most vulnerable and susceptible populations. The impact of air pollution can be seen on vulnerable individuals with greater exposure levels and susceptible individuals with chronic conditions (such as asthma, COPD, diabetes, heart failure and IHD), as well as children and pregnant women.

According to WHO, health equity is the "the absence of unfair and avoidable or remediable differences in health among population groups defined socially, economically, demographically or geographically" (WHO, 2020b). Health inequities, therefore, involve more than inequality with respect to health determinants, access to the resources needed to improve and maintain health, and health outcomes. They also entail a failure to avoid or overcome inequalities that infringe on fairness and human rights norms.

The fact that this burden of disease and mortality is unevenly distributed also impedes reduction of inequities and progress towards achieving full human rights and the UN SDGs. Global efforts to reduce pollution levels will have a positive impact on lowering inequity (Universal Declaration of Human Rights, Art. 1 and Art. 2) and will promote the right of life and security by ensuring safe and healthy environments (as stated in Art. 3) (UN, 1948).

Successful interventions are feasible, effective and compatible with economic growth. However, only a few studies have looked at equity in health when evaluating intervention delivery. In general, interventions that aim to reduce air pollution in urban areas have a positive impact on air quality and mortality rates, but the documented effect on equity is less straightforward. There is no evidence on whether applied air pollution reduction interventions have reduced health inequalities, since results from studies published to date have been mixed and

not all interventions have had a positive distribution of health benefits. Indeed, depending on the health outcome(s) under study and intervention type/study design (simulations of air pollution concentrations or real interventions), more vulnerable groups such as older persons and deprived households were found to benefit more, equally or less than their socially better-off counterparts. For an in-depth review of published studies until the early 2010s, see Benmarhnia et al. (2014).

The largest inequities in air pollution exposure occur on the global rather than the local scale. Indeed, countries with policy-driven improvements in air quality have often seen particularly steep declines in pollution at hot spots since the 1990s, whereas declines have been gradual in regions with already good air quality. However, on a global scale, the steep decline in pollution in the vast majority of high-income countries is paralleled by an unprecedented increase in low- and middle-income countries. As documented by Zhang et al. (2017), the model of globalized movements of goods with inequities in emission and air quality standards contributes to inequity in air quality (UNEP, 2020). Weak policies in low- and middle-income countries allow pollution from the production of goods that are ultimately consumed in part in high-income countries.

1.3.5 Progress on scientific evidence

There has been tremendous progress in the scientific understanding of the health effects of air pollution since the early 2000s.

First of all, health effects of air pollution have now been studied in most WHO regions; in contrast, almost all evidence underpinning *Global update 2005* came from studies in Europe and North America. This is especially true for studies of short-term effects on mortality and morbidity (Chen et al., 2017; Yang J et al., 2020). However, quite a few studies of long-term effects have now also been reported, especially from Asia and Oceania. These studies have generally found relationships between air pollutants and ill-health that are qualitatively similar to those in high-income countries, although the CRFs are sometimes quantitatively different, with less steep relationships at high than at low concentrations (Yang X et al., 2020; Hanigan et al., 2019).

Secondly, air pollution has now been implicated in the development or worsening of several health conditions not considered in previous research. These include, among others, asthma, diabetes, reproductive outcomes and several neurocognitive end-points (Yang B-Y et al., 2020; Paul et al., 2019) (Thurston et al., 2017).

Thirdly, many studies have tried to identify which sources and/or physicochemical characteristics of airborne PM contribute most greatly to toxicity. This is a challenging area of research, given the great heterogeneity of airborne particles, and a definitive set of particle characteristics has yet to be identified. However, in its 2013 review of the evidence (WHO Regional Office for Europe, 2013a), WHO did point out that a focus on primary combustion particles, secondary inorganic aerosols and secondary organic aerosols was warranted (Thurston et al., 2016b; US EPA, 2019a; Lippmann et al., 2013; Vedal et al., 2013).

Lastly, investigators have learned to collaborate on an unprecedented scale. Prior to 2005, there were few examples of multicentre studies in the domain of time-series studies investigating the short-term effects of air pollution; two notable examples are the Air Pollution and Health, a European Approach (APHEA) studies in Europe and the National Morbidity and Mortality Air Pollution Study (NMMAPS) in the United States of America. These were followed after 2005 by the Air Pollution and Health: A European And North American Approach (APHENA) study across Europe, Canada and United States (Samoli et al., 2008); the ESCALA (Estudio de Salud y Contaminación del Aire en Latinoamérica) study in Latin America (Romieu et al., 2012); and the Public Health and Air Pollution in Asia (PAPA) study in Asia (Wong et al., 2008) – all studies of short-term effects. A remarkable culmination is the Multi-Country Multi-City (MCC) Collaborative Research Network (Chen et al., 2021; Liu et al., 2019; Meng et al., 2021; Vicedo-Cabrera et al., 2020), which combines multiyear data from 652 cities across the world in a single joint analysis of the short-term effects of $PM_{2.5}$, ozone, nitrogen dioxide and carbon monoxide, among other studies. Large collaborations have also emerged in studies of long-term effects such as the European Study of Cohorts for Air Pollution Effects (ESCAPE), which includes data from 36 different cohorts (Beelen et al., 2014). Another example is the Global Exposure Mortality Model (GEMM), which includes data from 41 cohorts from 16 countries across the globe (Burnett et al., 2018). Finally, an ongoing collaboration is studying the long-term health effects of low levels of air pollution in Europe (HEI, 2021), Canada and the United States (Brauer et al., 2019; Dominici et al., 2019).

Collectively, these studies have considerably strengthened the evidence for health effects of air pollution by increasing study power and using highly standardized preplanned methods of data collection, analyses and reporting (Brauer et al., 2019; Di et al., 2017a).

Methods of assessing exposure to air pollution have become much more refined. In 2005 the annual air quality guideline for $PM_{2.5}$ was largely based on results from two studies, the Harvard Six Cities study (Dockery et al., 1993) and the

American Cancer Society Cancer Prevention Study II (Pope et al., 2002). In these studies, exposure to $PM_{2.5}$ was assessed from one or a few monitoring sites per city. In addition, advanced chemical transport models, land-use regression models, satellite observations and much more detailed ground-level monitoring have formed the basis for very detailed assessment of exposure to $PM_{2.5}$ (as well as other pollutants) at very fine temporal and spatial scales. This has been useful not only for population studies of health effects but also for estimating the worldwide health impact of air pollution (Hammer et al., 2020; de Hoogh et al., 2018).

These new methods of exposure assessment have facilitated studies of nationwide populations, not only those living in cities but also those living in rural areas where air pollution monitoring is sparse or even absent. Often, these nationwide studies make use of administrative databases, which have increasingly become automated. These include death registers, disease registers, census data and population statistics. Such studies have the advantage of often including large populations of millions or even tens of millions of subjects. In addition, the data included are often more representative of underlying populations than regular cohort studies. A disadvantage of such databases is that they usually do not contain much information on potential confounding and modifying factors such as smoking and diet. However, innovative solutions have been developed to deal with this (e.g. survey results in Medicare and indirect adjustment for covariates in Canadian census studies) (Crouse et al., 2015; Cesaroni et al., 2013). Such databases usually also lack information from biological markers and specimens and, thus, cannot shed light on biological pathways to explain the observed associations.

Advances in statistical analyses techniques and conceptualization of causal modelling in epidemiology have produced new insights into the robustness of epidemiological associations between air pollutants and health effects. Machine learning techniques are increasingly being applied to explain patterns in complex exposure patterns. Most recently, large collaborative studies of the so-called exposome (defined as the totality of exposure individuals experience over their lives and how these exposures affect health) have started in an attempt to understand the effects of lifelong exposures to complex environmental factors on the development of health and disease throughout the life course. In such studies, air pollution is regularly included as one of several sets of complex environmental exposures and is combined with individual data, ranging from the molecular, genetic or cellular level up to the level of social, cultural and lifestyle data (Vrijheid et al., 2020).

Decision-makers have increasingly asked for reliable estimates of the burden of disease caused by air pollution as input for cost–benefit analyses of policy alternatives and as a basis for risk communication. Since 2005, major steps forward have been taken, especially by WHO and the Global Burden of Disease (GBD) project. An innovative, integrated exposure–response function was developed, integrating insights from studies on outdoor air pollution, on the health effects of indoor exposure to household air pollution from solid fuel combustion and environmental tobacco smoke, and on active smoking (Burnett et al., 2014). The integrated exposure–response function formed the basis for the first-ever truly global burden of disease estimate from exposure to $PM_{2.5}$, ozone and household air pollution from solid fuel burning, published in 2012 (Lim et al., 2012). These estimates used the global exposure estimates mentioned in section 1.3.1 and worldwide data on mortality and morbidity. They have been updated several times as new exposure estimates became available, and the integrated exposure–response function was updated based on new study findings (Cohen et al., 2017). The latest version no longer includes studies on active smoking, for instance (GBD 2019 Risk Factors Collaborators, 2020). Widely available software tools, such as WHO AirQ+ (WHO Regional Office for Europe, 2021a) or the US EPA's Environmental Benefits Mapping and Analysis Program – Community Edition (BenMAP-CE) (US EPA, 2021) facilitate similar analysis on a local (city, region, country) level.

Decision-makers have also sought evidence that measures to reduce air pollution actually produce health benefits. So-called accountability research (i.e. assessment of the effectiveness of interventions) addresses the consequences of policy interventions. An early example is a study from Dublin suggesting that a ban on coal burning led to reduced mortality (Clancy et al., 2002; Dockery et al., 2013). A nationwide study from the United States found that life expectancy increased most in areas where fine particle concentrations decreased the most (Pope, Ezzati & Dockery, 2009). A research programme on this subject, developed by the United States-based Health Effects Institute (HEI), showed promise, as well as pitfalls (Boogaard et al., 2017), while a Cochrane review on interventions to reduce ambient air pollution and their effects on health concluded that more research is needed in this area to reduce uncertainty (Burns et al., 2019).

Another issue of great interest to decision-makers is the that the co-benefits of policies aimed at reducing greenhouse gases may also have adverse direct or indirect health effects (e.g. methane, a powerful greenhouse gas and an ozone precursor) or, conversely, that policies aimed at reducing health-relevant air pollutants (such as black carbon) may also have climate forcing capabilities.

1.3.6 Adoption of the 2005 air quality guidelines worldwide

The first two editions of the air quality guidelines in 1987 and 2000 were successful in providing guidance, mostly to European countries, and provided the basis for the European Union (EU) legislation on air quality. *Global update 2005* was intended to be relevant to the diverse conditions within all WHO regions.

Evidence-informed guidance on air quality and associated health effects is necessary so that countries can use this information in standard setting and in providing information to the public. In 2012 a review of the processes followed to establish national ambient air quality standards (AAQS) for PM_{10} and sulfur dioxide (24-hour average) in the period 2007–2008 concluded that WHO air quality guidelines were the resource used most often to establish or revise national standards by the relevant authorities (Vahlsing & Smith, 2012). At that time, 91% of the countries that responded to a survey planned on using *Global update 2005* for future revision of their AAQS; however, this information was only available for 96 countries. In collaboration with WHO, the Swiss Tropical and Public Health Institute (Swiss TPH) has compiled information on the existence of legally binding AAQS for all UN Member States for PM ($PM_{2.5}$, PM_{10} and other relevant types), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide for different averaging times (both long and short term) (Kutlar Joss et al., 2017; WHO, 2021b). This unique update of the current state of AAQS worldwide provides a useful insight into the degree to which the 2005 air quality guidelines and interim targets are used as a basis for legally binding and non-binding AAQS. Information was identified for over 170 countries in the different WHO regions, of which 53 did not define any standards (see Table 1.1). In general, standards for short-term exposure were set more often than annual limit values. Levels varied greatly by country and by air pollutant.

Daily mean standards for PM_{10} and sulfur dioxide (averaging time ≤ 24 hours) and 1-hour maximum values for nitrogen dioxide were most often defined. Although compliance with WHO air quality guidelines was rather low, it was generally higher for short-term than for long-term standards. Among all countries with standards for 24-hour averaging times for $PM_{2.5}$ and PM_{10}, 21% and 46% met the air quality guidelines, respectively. In contrast, only seven countries (2%) adopted the WHO annual mean air quality guidelines for PM_{10} and $PM_{2.5}$. In case of sulfur dioxide (24 hours), only 7% of countries were in line with the air quality guidelines and 16% aligned their standard with the 1-hour guidelines for ozone. Adoption rates were higher for nitrogen dioxide, sulfur dioxide (10-minute averaging time) and carbon monoxide.

In addition, in the EU, WHO guidelines are referenced in the Ambient Air Quality Directive (European Parliament & Council of the European Union, 2008),

and several countries use/will use WHO air quality guidelines and/or interim targets within existing and forthcoming legislation.

Analysis of the level of adoption of WHO air quality guidelines (see Table 1.1) shows that many countries have guidelines or standards for at least one air pollutant; however, there are many countries without standards or where information is lacking. The gap between the WHO air quality guidelines and the levels adopted in national regulations reflects the policy-making process. Whereas the WHO guidelines are evidence-informed, health-oriented recommendations, the process of developing legally binding regulations is driven by national policy-makers and the willingness to set environmental standards. This process involves different actors and may be influenced by a range of considerations.

Table 1.1. Adoption of WHO air quality guidelines in different regions

WHO region	Countries in the region *(n)*	Countries with standards for at least one pollutant and averaging time		Countries without standards		Countries with no information	
		n	%	*n*	%	*n*	%
African Region	47	17	36	21	45	9	19
Region of the Americas	35	20	57	13	37	2	6
South-East Asian Region	11	7	64	3	27	1	9
European Region	53	50	94	2	4	1	2
Eastern Mediterranean Region	21	11	52	1	5	9	43
Western Pacific Region	27	12	44	13	48	2	7
Total	194	117	60	53	27	24	12

Source: Kutlar Joss et al. (2017).

The difficulty of attaining the air quality guidelines for PM and other pollutants was recognized in *Global update 2005*, and a series of interim targets were set to provide milestones for countries on the way to achieving the air quality guidelines. Interim targets were defined as air pollutant levels that are higher than the air quality guidelines, but which authorities in highly polluted areas can

use to develop pollution reduction policies that are achievable within realistic time frames. The interim targets should be regarded as steps towards ultimately achieving air quality guidelines in the future, rather than as end targets. The number and numerical values of the interim targets are pollutant specific and they are justified in the relevant sections of Chapter 3.

1.3.7 Air pollution and health in the global agenda

World Health Assembly resolution and road map

In May 2015 the Sixty-eighth World Health Assembly adopted resolution WHA68.8, *Health and the environment: addressing the health impact of air pollution*, which was endorsed by 194 WHO Member States (WHO, 2015). This resolution stated the need to redouble the efforts of Member States and WHO to protect populations from the health risks posed by air pollution. Member States were urged to raise public and stakeholder awareness on the impacts of air pollution on health; provide measures to reduce or avoid exposure; facilitate relevant research; develop policy dialogue, strengthen multisectoral cooperation at national, regional and international levels; and take effective steps to reduce health inequities related to air pollution.

Specifically, the resolution recognized the role of the WHO air quality guidelines, for both ambient and indoor air quality, in providing guidance and recommendations for clean air that protect human health. It requested the Director-General to strengthen WHO capacities in the field of air pollution and health through further development and regular updating of the WHO air quality guidelines to facilitate effective and efficient decision-making, and to provide support and guidance to Member States in their efficient implementation. A road map for implementation of this resolution on air pollution and health was presented at the Sixty-ninth World Health Assembly and approved by Member States (WHO, 2016a).

UN Sustainable Development Agenda and other UN processes

The WHO air quality guidelines support the strategic priorities for NCDs (UN, 2018a), as well as those established in the 2030 Agenda for Sustainable Development, which was adopted at the United Nations Sustainable Development Summit in 2015 (UN, 2015). These priorities emphasize the need to strengthen national capacities to reduce modifiable risk factors, including air pollution, for NCDs and to accelerate countries' responses for their prevention and control. The 17 SDGs contained in the Agenda present an indicator framework for global monitoring and include 169 specific associated targets (UN Statistics Division, 2020).

These, in turn, are divided into indicators, thereby providing a tool for quantitative assessment of achievement towards meeting the goals. This update of the WHO air quality guidelines provides evidence-informed benchmarks on the health impacts of air pollution, and will help assess the following air pollution-related SDG indicators to inform the health trends associated with exposure to air pollution:

- Indicator 3.9.1: Mortality rate attributed to household and ambient air pollution
- Indicator 7.1.2: Percentage of population with primary reliance on clean fuels and technology
- Indicator 11.6.2: Annual mean levels of fine PM (population-weighted).

The health impacts of air pollution are a main driver for action by the environment sector. The UN Environment Assembly adopted the following three resolutions on the topic.

- Resolution 1/7 from the United Nations Environment Programme (UNEP), adopted at its first session in 2014 on Strengthening the role of the United Nations Environment Programme in promoting air quality, highlights the effects of air pollution, especially from a perspective of sustainable development. In particular, it encourages governments to take cross-sectoral action to improve air quality and formulate action plans while establishing (and implementing) nationally determined air quality and emissions standards, taking into account relevant information (e.g. WHO guidelines) (UNEP, 2014).
- Additionally, the UN Environment Assembly presented a resolution, at its second session in 2016, requesting the Executive Director to engage with all relevant UN entities to promote a coordinated approach to combating the challenges of SDS globally by supporting Member States in the identification of relevant data and information gaps, best policy measures, and actions to address the problem and by inviting them to intensify monitoring data collection and knowledge sharing on all relevant aspects of SDS, including their impact on ecosystems and on human health and well-being (UNEP, 2016a).
- Finally, the resolution on Preventing and reducing air pollution to improve air quality globally calls for Member States to take action across sectors to reduce all forms of air pollution. Among its recommendations, the resolution urges Member States to:

    > consider joining or cooperating with, as appropriate, relevant global initiatives such as the Climate and Clean Air Coalition and the Global Methane Initiative; [and] facilitate action to reduce air pollution in urban and rural areas including by encouraging cities and local governments to consider participating in, as appropriate, the BreatheLife campaign (UNEP, 2018).

Lastly, a report from 2019 from the UN Special Rapporteur on the Issue of Human Rights Obligations Relating to the Enjoyment of a Safe, Clean, Healthy and Sustainable Environment highlighted the different state obligations in relation to the right to breathe clean air, as well as the specific obligation to protect people and groups in vulnerable situations (UN, 2019a). The Special Rapporteur focused on the right to breathe clean air as one of its components and describes the negative impact of air pollution on the enjoyment of many human rights, in particular the right to life and the right to health, especially by vulnerable groups. The Special Rapporteur identified several good practices implemented worldwide that have helped to improve air quality; offered a number of recommendations to Member States for actions they should consider as part of a national air quality action plan; and urged businesses, in order to fulfil their responsibility in this regard, to contribute to and support efforts to reduce air pollution.

1.4 WHO guidelines relating to air quality

WHO air quality guidelines have been widely used as a reference tool to help decision-makers across the world in setting standards and goals for air quality management. Since the mid-1980s, WHO has coordinated the development of several editions of air quality guidelines for both ambient and indoor air quality. Although the methodologies used and the requirements needed to produce them have evolved over time, these guidelines remain in essence manuals aiming to provide evidence-informed recommendations in the form of air quality guidelines for different averaging times (WHO Regional Office for Europe, 2017).

Since 2009, WHO has issued a separate series of guidelines for indoor air quality, which provide recommendations on biological contaminants of indoor air, selected air pollutants typically measured in indoor settings, and household fuel combustion.

Air quality guidelines for Europe (1987)

The first volume of the air quality guidelines created the initial framework for the scientific rationale for the series. The expert panel formulated guidelines for 28 air pollutants on exposure in both outdoor and indoor environments. In specific cases (e.g. mercury), a guideline level was formulated for indoor settings only. For 19 noncarcinogenic pollutants, recommendations were provided as guideline values using the toxicological concepts of the lowest/no observed adverse effect level and protection factors. In contrast, ranges were provided for cadmium, lead, PM (expressed as black smoke), ozone and sulfur dioxide , with a recommendation to use gravimetric methods for measuring particles.

Because of the impossibility of identifying no-effect levels of exposure, the panel recommended unit risk factors for carcinogenic (genotoxic) pollutants (WHO Regional Office for Europe, 1987).

Air quality guidelines for Europe. second edition (2000)

In response to strengthening of the evidence during the 1990s, the revised air quality guidelines were published in the year 2000. A total of 35 air pollutants were evaluated, including the pollutants covered in the first edition, the additional organic pollutants butadiene, polychlorinated biphenyls and polychlorinated dibenzodioxins/dibenzofurans, and three indoor air pollutants (anthropogenic vitreous fibres, radon and second-hand tobacco smoke). As in the first edition, guidelines were presented in the form of levels/ranges for noncarcinogenic pollutants and as unit risk factors for carcinogenic substances. In contrast, the ozone guideline was formulated as a level and a CRF, whereas the PM guidelines were presented as a CRF alone, this time separately from sulfur dioxide. To aid implementation, a specific chapter was devoted to air quality management and translation of the guidelines into binding standards (WHO Regional Office for Europe, 2000a).

Air quality guidelines – global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide (2006)

Global update 2005 provided numerical guideline values for the classical pollutants – PM, ozone, nitrogen dioxide and sulfur dioxide – based on a comprehensive review of all available evidence at the time. Air quality guidelines for PM were presented for the first time, while the nitrogen dioxide levels from previous editions were retained. In addition, the concept of interim targets as "incremental steps in progressive reduction of air pollution" was introduced and used for PM, ozone and sulfur dioxide. Acknowledging that exposure to these pollutants occurs in both outdoor and indoor settings, the guideline levels were meant to apply in all environments, including indoors in households, schools and vehicles. However, the guideline panel recognized the significance of indoor air pollution as a stand-alone risk factor that needed different management approaches to those employed for outdoor air pollution. Therefore, a specific chapter was dedicated to indoor air quality, including a framework for the future development of WHO indoor air quality guidelines (WHO Regional Office for Europe, 2006).

WHO guidelines for indoor air quality: dampness and mould (2009)

This first volume of the series aimed to raise awareness and assist users in identifying and mitigating the health hazards related to biological contamination in all indoor settings. The guidelines included a comprehensive assessment of the evidence on the adverse health effects associated with

dampness and biological agents such as bacteria, mould and fungi. The guideline panel concluded that the most relevant health outcomes of concern were respiratory and immunological, including asthma and allergies. Given a lack of exposure–response relationships, recommendations were formulated as indicators of health risk, such as the persistence of dampness or presence of mould, rather than numerical levels. The guideline panel recommended the prevention/reduction of such indicators on interior surfaces and building structures as an overarching principle that users could follow to manage risks through specific measures (WHO Regional Office for Europe, 2009).

WHO guidelines for indoor air quality: selected pollutants (2010)

The second volume of the series provided recommendations for nine air pollutants either as numerical levels or unit risks, prioritized according to their presence in potentially harmful concentrations indoors and the availability of data for risk assessment. Thus, comprehensive monographs were prepared for benzene, carbon monoxide, formaldehyde, naphthalene, nitrogen dioxide, polycyclic aromatic hydrocarbons, radon, trichloroethylene and tetrachloroethylene. Guidelines for indoor PM were not formulated, since PM had been covered in *Global update 2005,* which was intended for all environments. Although the evidence on indoor nitrogen dioxide was re-evaluated, guideline levels remained the same as before due to a lack of new evidence suggesting a threshold of effect. In addition, some general measures to reduce exposure indoors were proposed, such as controlling sources of emission, ensuring proper ventilation, using low-emission materials and, switching to cleaner fuels and technologies for indoor combustion (WHO Regional Office for Europe, 2010).

WHO guidelines for indoor air quality: household fuel combustion (2014)

Building on previous guidelines for PM and carbon monoxide, modelling and extensive reviews, the latest volume in the series offered recommendations related to household fuel combustion. Using a new WHO guideline development approach, as outlined in the *WHO handbook for guideline development, 2nd edition* (WHO, 2014a), the guideline panel set emission rate targets for $PM_{2.5}$ and carbon monoxide from household fuels combustion, discouraged the use of kerosene and unprocessed coal, and provided guidance for transition to the sustained adoption of clean fuels (e.g. liquefied petroleum gas) and technologies. In addition, risks related to the use of conventional fuels were highlighted, including burns, poisoning, house fires and those related to fuel-wood collection. As overarching principles, the guidelines highlight the importance of reducing outdoor air pollution to achieve indoor air quality guidelines, and of addressing all main household energy end uses to maximize health (WHO, 2014b).

2

Guideline development process

2.1 Introduction

WHO guideline development follows a rigorous process and involves several groups of individuals with well-defined roles, responsibilities and tasks (WHO, 2014a). The process involves the following main steps:

1. formulation of the scope and key questions of the guidelines (section 2.3);
2. systematic review of the relevant evidence (section 2.4);
3. assessment of the certainty level of the body of evidence resulting from systematic reviews (section 2.4.4);
4. formulation of the air quality guideline (AQG) levels (section 2.5); and
5. formulation of other supporting guidance (section 2.5.3).

Throughout the whole process, the principles of the GRADE approach were followed (Schünemann et al., 2013).

The WHO steering group was primarily involved in initiating, structuring and executing the guideline development process; the guideline development group (GDG), composed of leading experts and stakeholders, was mainly responsible for determining the scope of the guidelines and formulating AQG levels and other guidance; the systematic review team conducted the systematic reviews of evidence; and the external review group (ERG) provided input and peer review, as needed. The WHO Guidelines Review Committee reviewed and approved the guideline document prior to publication.

The process of developing this update of the air quality guidelines started in 2016. Following WHO procedures, the WHO Regional Office for Europe's European Centre for Environment and Health in Bonn, Germany obtained planning approval and established the WHO steering group, the GDG, the systematic review team and the ERG.

Several meetings of the GDG were held in Bonn throughout the guideline development process. During the first meeting of the GDG in September 2016, GDG members helped define the scope of the guidelines, prioritized air pollutants and critical health outcomes, formulated the key questions to be addressed and set a timeline for completion of the work.

In March 2018 and June 2019, the GDG and the systematic review team met to discuss the preliminary results of the methods adaptation work and systematic reviews of evidence. Revision and publication of the systematic reviews of evidence was completed in mid-2020. In February and June 2020, the GDG finalized the AQG levels and other elements of guidance.

The external consultation of the draft guideline document took place in November and December 2020 through an online survey. In January 2021, the GDG met to address the comments from the external consultation of the draft guideline document.

Throughout the guideline development process, several ad hoc working groups were established to address specific (methodological) issues. Composed of subject matter and methodological experts, these groups worked through remote meetings and contributed within the adapted approaches for systematic review and guideline development to the air quality and health domain.

The following sections describe the groups of experts involved in, and the different steps of, the guideline development process.

2.2 Groups involved in and general procedures of guideline development

The development of WHO guidelines is carried out by several groups of people with defined roles and responsibilities. These are the WHO steering group, the GDG, the systematic review team and the ERG comprising WHO staff members, external experts and stakeholders. In addition, the process was supported by an external guideline methodologist with expertise in systematic review and certainty assessment methods, and other external consultants, including experts in risk of bias (RoB) assessment and environmental epidemiology (shown in Annex 1, Tables A1.1–A1.7).

2.2.1 WHO steering group

The WHO steering group is composed of a limited number of WHO staff with extensive work experience at technical level in the area of air quality and health, who were recruited from all relevant departments, centres and WHO regional offices. Members of this group provided input during the different stages of planning, selection of members of the other groups, reviewing evidence, formulating draft recommendations and guidance, and overseeing peer review. The complete list of members of the WHO steering group can be found in Annex 1, Table A1.1.

2.2.2 Guideline development group

The GDG included subject matter experts who were convened to appraise the evidence and formulate recommendations and related guidance. The group was selected by the WHO steering group, as informed by the results of a survey of WHO expert networks, with the aim to cover the technical skills, perspectives and geographical representation needed in a global guideline development process.

The GDG assisted in determining the scope of the guidelines, chose the critical health outcomes and defined the key review questions. Members of the GDG contributed to drafting the guideline document and responded to peer reviewers. Details of the members of the GDG and their specific roles, affiliations and areas of expertise are listed in Annex 1, Table A1.2.

2.2.3 Methodological working groups

Members of this GDG also worked with the guideline methodologist, a RoB methodologist and other experts in ad hoc working groups to adapt the methods of systematic review and guideline development to the specific field of air quality and health. In particular, the following working groups were formed:

- Working Group on Risk of Bias Assessment;
- Working Group on Certainty of Evidence Assessment;
- Working Group on Derivation of Air Quality Guideline Levels and Interim Targets; and
- Working Groups on Good Practice Statements.

The external methodologists are listed in Annex 1, Table A1.4, and members of the working groups are listed in Annex 1, Table A1.7.

2.2.4 Systematic review team

The systematic review team consisted of experts in environmental and clinical epidemiology, who were commissioned by WHO to conduct the systematic reviews informing the recommendations. The team also provided input into the adaptation of systematic review methods and tools. The GDG and WHO steering group identified the members of the systematic review team based on their publications in the field and their expertise. Members of the systematic review team are listed in Annex 1, Table A1.3.

2.2.5 External review group

The ERG included technical experts and representatives from stakeholders such as patient organizations, environmental advocacy groups, industry associations and scientific societies. Members were identified among networks of excellence, WHO collaborating centres and partner groups such as Cochrane, with support from the GDG and online searches.

Based on several considerations (expertise, sex, geographical representation), about 100 individual experts from 38 countries and territories across all WHO regions were identified and invited to participate in the ERG. Of these, 65 experts provided input at different stages of the guideline development process, as needed.

In particular, they provided information on specific topics, assessed and translated scientific papers, peer-reviewed the evidence base, and/or commented on the draft guideline document. Likewise, an inclusive mapping exercise took place of stakeholder organizations from all WHO regions, working at either regional or global level. Of the 100 identified organizations, 72 were invited to be members of the ERG. Ultimately, 14 organizations participated in the external consultation of the draft guideline document and provided comments that were all addressed by the GDG and WHO steering group. The individual experts and stakeholder organizations are listed in Annex 1, Table A1.5 and Table A1.6, respectively.

2.2.6 Management of conflicts of interest

Conflicts of interest – with or without bias – can undermine the credibility of a guideline; hence, their appropriate management is crucial in WHO guideline development. The members of the GDG as well as the other experts involved in the guideline development process were asked to complete declaration of interest forms. In addition, all experts received briefings about the types of conflicts of interest (financial, intellectual/academic and non-academic). Declarations from all experts were collected and managed according to the relevant WHO procedures. No experts had to be excluded from their respective roles. Further information about the process for identifying, managing and reporting conflicts of interest can be found in the *WHO handbook for guideline development, 2nd edition* (WHO, 2014a). A summary of declared conflicts of interest is presented in Annex 2.

2.2.7 Decision-making during the process

The members of the GDG agreed to make decisions by consensus, through discussions moderated by the appointed GDG co-chairs. In (very rare) cases where consensus was not possible, informal voting was employed. The view of the majority (90% or more of the GDG members, as a result of the discussions to reach agreement in the group) was implemented in developing the guidelines.

Decisions in the ad hoc working groups were made in the same way among the participating GDG members, the external guideline methodologist and/or other external experts. Consensus could not be reached among the GDG members and the methodologist on one aspect of the certainty of evidence assessment. This was about whether upgrades of the evidence certainty should be allowed in case of downgrades: the GDG members thought so, but the methodologist did not. The view of the majority (in this case, the complete GDG) was taken. The methodologist made the first proposals on derivation of AQG levels and interim targets but did not participate in the phase of final formulation of recommendations. The GDG, supported by a technical consultant (Annex 1, Table A1.7), concluded this work.

The members of the systematic review team conducted the systematic reviews independently, with regular interaction with the working groups and the GDG to ensure that the most important needs of the GDG were addressed appropriately. One member of the systematic review team served as liaison with the GDG and supported the methodological work on AQG levels and interim targets.

2.2.8 Document preparation and external review

The guideline document was drafted in a stepwise manner following the guideline development process. The GDG identified the background and other relevant supporting information early in the preliminary phase. In their second meeting, the WHO steering group and GDG decided on the table of contents, and several of their members started drafting specific sections. At a later stage, a designated technical editor worked towards ensuring consistency and logical flow.

The guideline document went through several rounds of extensive internal and external review. In particular, the external consultation of the draft document was managed through an online survey targeting 71 members of the ERG (48 provided comments and were acknowledged). As prescribed, the procedure focused on the identification of missing data, unclear information, factual errors and issues related to implementation, but not on changing the recommendations. The GDG and WHO steering group considered all comments provided during this external consultation and revised the guideline document where appropriate.

2.3 Determining the scope of the guidelines and formulation of review questions

Determining the scope of the guidelines involved the selection of air pollutants to be considered, as well as the critical health outcomes for each in relation to durations and scale of exposure. This was a multistep procedure in which experts evaluated the strength of the evidence for the pollutants; the causality of pollutant–outcome pairs; and other considerations such as the severity of health outcomes, burden of disease, expected increases in exposure and policy considerations.

The present guidelines are applicable to both outdoor and indoor environments. Thus, they cover all settings in which people spend a significant portion of their time. This has been the case since the publication of the first edition of the guidelines in 1987 and was reinforced in *Global update 2005* and the 2010 guidelines for indoor air quality.

It is important to note that AQG levels recommended in previous WHO air quality guidelines for pollutants or averaging times not re-evaluated in this update

remain valid, including those for the short averaging times for nitrogen dioxide, sulfur dioxide and carbon monoxide included in the *2005 Global update* and indoor air quality guidelines from 2010. The reader is referred to previous volumes of air quality guidelines (WHO Regional Office for Europe, 1987, 2000a, 2010) for the other pollutants not covered in this update. As in previous volumes, the guidelines do not cover occupational settings, due to the specific characteristics of the relevant exposures and the potential differences in population susceptibility of the adult workforce in comparison with the general population.

Furthermore, the guidelines do not include recommendations about any kind of multiple exposures. In everyday life, people are often exposed to a mixture of air pollutants at the same time. WHO acknowledges the need to develop comprehensive models to quantify the effects of multiple exposures on human health. However, as the main body of evidence on air quality and health still focuses on the impact of single air pollutants on health outcomes, the current guidelines provide recommendations for each air pollutant individually.

The GDG also decided not to formulate specific recommendations on population-wide interventions because these are largely context specific: what might be effective in one setting might not work in another. Instead, general risk management principles, based on decades of experience, are summarized in Chapter 6, on implementation of the guidelines. In addition, individual-level interventions, such as the use of personal respiratory protection (e.g. masks, respirators), air purifiers and behavioural measures, are not addressed here but in a report from a separate WHO consultation (WHO, 2020a).

2.3.1 Preliminary consultation

Following the conclusions from the Review of evidence on health aspects of air pollution (REVIHAAP) project (WHO Regional Office for Europe, 2013a), WHO organized an expert consultation in Bonn in September–October 2015 as a first step for this update of the air quality guidelines. The objective was to gather expert opinion and guidance in order to identify and discuss the latest available evidence on health effects of air pollutants and interventions to reduce exposure to air pollution for the purpose of informing this update of the air quality guidelines.

Twenty-eight participants – representing a wide array of expertise and geographical locations – attended the consultation, which included not only a review of the available scientific evidence on a number of ambient air pollutants but also methodological issues and the implications of exposure and intervention studies. Experts recommended that a focus of these guidelines on pollutant-

specific risk assessment was still appropriate and prioritized 32 air pollutants according to four categories to reflect their relative importance in the context of updating the air quality guidelines. Since reviewing the evidence systematically for all air pollutants was infeasible considering the available resources, experts suggested prioritizing the pollutants $PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide for this update. This advice was based on the large body of new health-related evidence that had been published since *Global update 2005* (WHO Regional Office for Europe, 2016a).

2.3.2 Selection of priority pollutants

The final selection of air pollutants took place in September 2016, during the first meeting of the GDG. Prior to the meeting, WHO surveyed GDG members on the final list of air pollutants to be included in this update of the air quality guidelines. The air pollutants identified in the global expert consultation, together with a number of different health outcomes, were included in the survey. In the ensuing discussion, the GDG decided to develop AQG levels for PM_{10}, $PM_{2.5}$, nitrogen dioxide, ozone, sulfur dioxide and carbon monoxide in relation to health outcomes critical for decision-making and for relevant averaging times.

For PM types such as BC/EC and UFP, the GDG agreed that AQG levels for these pollutants could not be formulated owing to the absence of clear quantitative evidence on independent health effects. However, the results of reviews of evidence conducted by other groups would be examined in order to reach a better-informed decision about whether recommendations should be formulated and in which form. Likewise, for SDS, the GDG agreed that any recommendation would likely be qualitative in nature and geared towards guiding countries in moving towards mitigation and adaptation measures.

Following presentations by invited experts, the GDG, at its third meeting, decided to include guidance on BC/EC, UFP and SDS in the form of good practice statements.

2.3.3 Prioritization of health outcomes

In order to define the pollutant–outcome pairs that would be systematically reviewed to inform the formulation of AQG levels, the GDG developed a prioritization framework based on the considerations outlined in Box 2.1.

Box 2.1. Health outcome prioritization framework

- Evidence on causality for a health outcome would be considered first, according to the latest determination (causal or likely causal) from the Health Canada, the International Agency for Research on Cancer, US EPA or other available integrated science assessments. As mandated by the Clean Air Act, the US EPA periodically reviews all scientific evidence about the health effects of so-called criteria pollutants, including all five pollutants considered in this report. These Integrated Science Assessments (ISAs) include a structured analysis of all evidence – including from toxicology – that supports a classification of a specific effect being causal, likely causal, suggestive of a causal relationship, inadequate to infer a causal relationship or not likely to be a causal relationship. For details, see Owens et al. (2017). These classifications have been used in support of identification of the relevant pollutant–outcome associations addressed in this document.
- Where causality is not determined to be proven or likely (e.g. suggestive causality), the precautionary principle would be used when determining which additional most-severe health outcomes could be included. These outcomes would be based on other considerations such as contribution to burden of disease (e.g. prevalence of disease, disability weight), policy implications and expected increase in exposure to a pollutant in the future.
- Causality determination would supersede the severity of a health outcome but, in some cases, two (or more) different health outcomes might be systematically evaluated for the same pollutant (e.g. one with a causal or likely causal link to the pollutant, and another health outcome for which the evidence is suggestive only but which is very severe or prevalent in the population). Severity of disease would be informed by considerations proposed by the latest update of the joint European Respiratory Society and American Thoracic Society policy statement on health effects from air pollution (fatality, persistence of effect, susceptible groups and medical/functional significance, including loss of autonomy and reduced quality of life) (Thurston et al., 2017).
- Lastly, as health outcomes can be assessed in various ways in studies, the specific health outcome measure(s) would be identified, based on evidence and the expert judgement of the GDG, to be used for quantitative health risk assessment in the guidelines.

By applying the prioritization framework, the GDG identified the following critical health outcomes associated with the selected air pollutants:

- all-cause (non-accidental) mortality[4] (hereafter referred to as all-cause mortality);
- cause-specific mortality, as per the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), 2016 version (WHO, 2016b): cardiovascular (ICD-10 codes I00–I99), lung cancer (ICD-10 codes C30–C39) and respiratory (ICD-10 codes J00–J99);
- hospital admissions and emergency room visits related to asthma (ICD-10 code J45); and
- hospital admissions and emergency room visits related to IHD (ICD-10 codes I20–I25; ultimately restricted to myocardial infarction, ICD-10 codes I21–I22).[5]

The pollutant–outcome pairs that were included comprise those for which there is broad scientific consensus regarding the causal nature of the reported relationships; others were chosen based on the strength of the epidemiological evidence.

Table 2.1 gives an overview of the different considerations included in the prioritization process. This table was adapted from the document resulting from the population, exposure, comparator, outcome and study design (PECOS) process (see section 2.3.4) finalized in November 2016.

Since then, it was decided to include one more pollutant–outcome pair: the association between exposure to short-term sulfur dioxide and all-cause and respiratory mortality. This was done to provide continuity with *Global update 2005*, as explained below.

The GDG recognizes that associations for many more pollutant–outcome pairs have been reported and reviewed in the literature. It would be practically impossible, given the resources available for the current guideline update, to include all of these for consideration and review.

[4] In an epidemiological study of air quality and health, all-cause mortality (ICD-10 code A00–Z99) refers to all deaths, and non-accidental mortality (ICD-10 code A00–R99) includes all deaths with the exception of deaths due to accidents, murder, suicide, etc. Although all-cause mortality includes accidental deaths, the proportion of deaths causes by accidents, etc. is typically small (< 10%) in comparison with the other causes of death.

[5] The systematic review by Lee et al. (2020) focused on myocardial infarction (ICD-10 codes I21–I22) as the only IHD outcome because it is not possible to establish the precise time of onset of other IHD outcomes. Further, other conditions within the spectrum of IHD are routinely managed in outpatient settings rather than in the emergency room/department or hospital wards.

The GDG, however, sees no grounds for assuming that the AQG levels, as derived in Chapter 3, would be very different if more outcomes would have been considered for the pollutants that were included. Obviously, this does not apply to those pollutants that were not considered at all in the current update. A draft version of this document has been reviewed by a large number of experts and stakeholder organizations, and no examples have been provided that would change this assessment.

The GDG also emphasizes that there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating air pollution to human health. However, comprehensive evaluations by authoritative bodies such the Committee on the Medical Effects of Air Pollutants (COMEAP) in the United Kingdom, Health Canada and the US EPA were taken into account in the development of the AQG levels.

Information about all the specific pollutant–outcome pairs reviewed can be found in the systematic reviews of evidence available in a virtual special issue of *Environment International* entitled *Update of the WHO global air quality guidelines: systematic reviews* (Whaley et al., 2021).

Table 2.1. Air pollutants and health outcomes proposed for systematic review in the guideline development process[a]

LONG-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
$PM_{2.5}$ and PM_{10}	Total, cardiopulmonary and lung cancer mortality	• All-cause mortality • Cardiovascular mortality (all, cerebrovascular, IHD) • Respiratory mortality (any, COPD, acute lower respiratory infections) • Lung cancer mortality	**CAUSALITY DETERMINATION (REFERENCE)** **$PM_{2.5}$** • Causal for cardiovascular and respiratory mortality (US EPA, 2009) • Causal for total and cardiovascular mortality (Health Canada, 2013) **PM** • Causal for total mortality in relation to PM (Health Canada, 2013) • Group 1[b] lung cancer for PM (Straif et al., 2013) • Likely causal for lung cancer mortality in relation to PM (Health Canada, 2013) **SUPPORTING CONSIDERATIONS** **PM_{10}** • Health outcome supported by evidence from PM_{10} and $PM_{2.5}$ **OTHER RELEVANT CAUSAL DETERMINATIONS (REFERENCE)** **$PM_{2.5}$** • Likely causal for respiratory effects (US EPA, 2009) • Likely causal for respiratory effects (Health Canada, 2013)

Table 2.1 contd

LONG-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
O_3	No long-term guideline provided	• All-cause mortality • Respiratory mortality	**CAUSALITY DETERMINATION (REFERENCE)** • Suggestive causality for mortality (US EPA, 2013) • Suggestive causality for respiratory mortality (Health Canada, 2013) **SUPPORTING CONSIDERATIONS** • Severity of health outcome, burden of disease • Precautionary principle from expected increase of this pollutant due to climate change (policy implications and end-user perspectives) **OTHER RELEVANT CAUSAL DETERMINATIONS (REFERENCE)** • Likely causal for respiratory effects (US EPA, 2013) • Suggestive causality for respiratory effects (Health Canada, 2013)

Table 2.1 contd

LONG-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
NO_2	Respiratory effects in children	• All-cause mortality • Respiratory mortality	**CAUSALITY DETERMINATION (REFERENCE)** • Suggestive causality for total mortality (US EPA, 2016)) • Suggestive causality for total mortality (Health Canada, 2016a)) **SUPPORTING CONSIDERATIONS** • Severity of health outcome, burden of disease • Recent studies show associations with respiratory mortality, consistent with likely causality for respiratory effects (see other causal determinations below) • The causal determination of US EPA for mortality is suggestive, in the light of the limited number of studies properly addressing confounding by other transport-related air pollutants • The causal determination of US EPA of likely causal for respiratory effects (see other causal determinations below) takes into account respiratory mortality **OTHER RELEVANT CAUSAL DETERMINATIONS (REFERENCE)** • Likely causal for respiratory effects (US EPA, 2016) • Likely causal for respiratory effects (Health Canada, 2016a)

Table 2.1 contd

SHORT-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
CO	COHb levels of below 2% in nonsmokers' blood (also protective for long-term exposure) (WHO Regional Office for Europe, 2000a, 2010)	• Hospital admissions and emergency room visits related to IHD[c]	**CAUSALITY DETERMINATION (REFERENCE)** • Likely causal for cardiovascular effects (US EPA, 2010) • Likely causal for cardiovascular effects (Health Canada, 2010) **SUPPORTING CONSIDERATIONS** • Consistent with WHO indoor air quality guidelines (WHO Regional Office for Europe, 2010) using COHb levels linked to IHD[c]-related symptoms (e.g. ST-segment changes, reduced time to exercise-induced angina) • IHD[c] appears to be the most consistent outcome from cardiovascular effects associated with short-term CO exposure in epidemiological studies (US EPA, 2010)
$PM_{2.5}$ and PM_{10}	COHb levels of below 2% in nonsmokers' blood (also protective for long-term exposure) (WHO Regional Office for Europe, 2000a, 2010)	• All-cause mortality • Cardiovascular mortality • Respiratory mortality	**CAUSALITY DETERMINATION (REFERENCE)** **$PM_{2.5}$** • Causal for all-cause, cardiovascular and respiratory mortality (US EPA, 2009) • Causal for all-cause, respiratory and cardiovascular mortality (Health Canada, 2013)

Table 2.1 contd

SHORT-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
$PM_{2.5}$ and PM_{10} (contd)			**PM (any size fraction)** • Causal for all-cause mortality (Health Canada, 2013) **SUPPORTING CONSIDERATIONS** • Cardiovascular and respiratory mortality also considered in causal determination of respiratory/cardiovascular effects (US EPA, 2009) (see other relevant causal determinations) • PM_{10}, supported by evidence from $PM_{2.5}$ **OTHER RELEVANT CAUSAL DETERMINATIONS ($PM_{2.5}$) (REFERENCE)** • Likely causal for respiratory effects (US EPA, 2009) • Causal for cardiovascular effects (US EPA, 2009) • Causal for respiratory effects (Health Canada, 2013) • Causal for cardiovascular effects (Health Canada, 2013)

Table 2.1 contd

SHORT-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
O_3	Daily mortality	• Hospital admissions and emergency room visits related to asthma • All-cause mortality	**CAUSALITY DETERMINATION (REFERENCE)** • Causal for respiratory effects (US EPA, 2013) • Causal for respiratory effects (Health Canada, 2013) • Likely causal for total mortality (US EPA, 2013) • Likely causal for total mortality (Health Canada, 2013) **SUPPORTING CONSIDERATIONS** • Stronger causal determination for respiratory effects than for mortality outcomes (see other relevant causal determinations below) • Experimental studies demonstrate decreases in lung function at exposures as low as 60–70 ppb O_3 in young healthy adults. Equally strong evidence demonstrates associations of ambient O_3 with asthma hospital admissions and emergency room visits, including for at-risk subpopulations (e.g. children, people with asthma or other pre-existing diseases), who cannot ethically be included in experimental studies

Table 2.1 contd

SHORT-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
O_3 (contd)			• Mortality also included because of the severity of health outcome, number of exposed individuals and precautionary principle (expected future increase of this pollutant due to climate change, with policy and end-user implications). On the other hand, studies on mortality might target other subgroups of the population such as older people **OTHER RELEVANT CAUSAL DETERMINATIONS (REFERENCE)** • Likely causal for cardiovascular effects (US EPA, 2013) • Suggestive causality for cardiovascular effects (Health Canada, 2013) • Likely causal for cardiopulmonary mortality (Health Canada, 2013)

Table 2.1 contd

SHORT-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
NO_2	Bronchial responsiveness in asthmatics	• Hospital admissions and emergency room visits related to asthma • All-cause mortality	**CAUSALITY DETERMINATION (REFERENCE)** • Causal for respiratory effects (US EPA, 2016) • Causal for respiratory effects (Health Canada, 2016a) • Likely causal for total mortality (Health Canada, 2016a) • Suggestive causality for total mortality (US EPA, 2016) **SUPPORTING CONSIDERATIONS** • Stronger causal determination for respiratory effects than for mortality outcomes (see other relevant causal determinations below) • Both Health Canada and US EPA causality assessments for respiratory effects are very recent (2016); limited new evidence might have accumulated since

Table 2.1 contd

SHORT-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
NO_2 (contd)			• Strongest evidence for relationships of short-term NO_2 exposure with respiratory effects is for asthma exacerbations. More uncertainty exists with independent effect of short-term NO_2 exposure on non-asthma respiratory effects due to less consistent evidence across scientific disciplines and limited evidence to support biological plausibility. Additionally, studies of short-term NO_2 exposure with asthma hospital admissions and emergency room visits include at-risk subpopulations (e.g. children, people with asthma or other pre-existing diseases) who cannot ethically be included in experimental studies • Mortality is also included because of severity of health outcome and number of exposed individuals. On the other hand, studies on mortality might target other subgroups of the population such as older people

Table 2.1 contd

SHORT-TERM EXPOSURE

Pollutant	Health outcomes used in *Global update 2005*	Health outcomes selected for updating in the 2021 air quality guidelines	Justification for health outcome selection
SO_2	All-age mortality and childhood respiratory disease	• Hospital admissions and emergency room visits related to asthma • All-cause mortality[d] • Respiratory mortality[d]	**CAUSALITY DETERMINATION (REFERENCE)** • Causal for respiratory effects (US EPA, 2015) • Causal in adults for respiratory effects (Health Canada, 2016b) **SUPPORTING CONSIDERATIONS** • Experimental studies demonstrate lung function decrements and respiratory symptoms at very short-term exposures • (i.e. 5–10 minutes) to SO_2 in adults with asthma. Studies of hospital admissions and emergency room visits related to asthma, including evidence from at-risk subpopulations (e.g. children, people with asthma or other pre-existing diseases) who cannot ethically be included in experimental studies, report positive associations with shortterm SO_2 exposures, particularly for children

COHb: carboxyhaemoglobin; ppb: parts per billion.
[a] This table was adapted from the document resulting from the PECOS process (see section 2.3.4) finalized in November 2016.
[b] Group 1 means carcinogenic to humans.
[c] Ultimately restricted to myocardial infarction (ICD-10 codes I21 and I22).
[d] In the second GDG meeting held in 2018, the GDG agreed to include the pollutant–outcome pairs SO_2–all-cause mortality and SO_2–respiratory mortality.

In the second GDG meeting in March 2018, the question was raised of why a systematic review of short-term associations between sulfur dioxide and all-cause mortality would be needed in addition to the reviews on PM, ozone and nitrogen dioxide. It was suggested to also review SO_2 and mortality to ensure continuity with the previous *Global update 2005*. If a new review is not feasible, the GDG suggested formulating clear justification as to why mortality attributed to SO_2 is not considered. It was subsequently decided to commission a separate review on short-term associations between sulfur dioxide and all-cause as well as respiratory mortality, to be conducted by the team that had already conducted the review on short-term associations of PM, ozone and nitrogen dioxide with mortality. Therefore, the latest US EPA ISA of causality for this association is mentioned below.

In 2017 the latest US EPA ISA on sulfur oxides was published (US EPA, 2017). This did not change the assessment noted in Table 2.1 of a causal relationship between short-term sulfur dioxide concentrations and respiratory effects. The association between short-term sulfur dioxide concentrations and total mortality was deemed to be suggestive of a causal relationship. This association was not considered by the GDG in 2016, but was added at a later stage, as previously mentioned. Therefore, the causality assessment is not reported in Table 2.1.

The US EPA published an updated ISA of PM in 2019 (US EPA, 2019a). The causality determinations for long- and short-term PM effects on mortality and on respiratory and cardiovascular morbidity were the same as those in the 2009 ISA (US EPA, 2009), which was quoted in Table 2.1.

The US EPA published an updated ISA of ozone in 2020 (US EPA, 2020). The causality determinations for ozone effects on respiratory morbidity were the same as those in the 2009 ISA, which was quoted in Table 2.1. For short-term mortality and for cardiovascular morbidity, the evidence was changed from likely causal to suggestive of a causal relationship, in part because new human exposure studies such as the Multicenter Ozone Study in oldEr Subjects (MOSES) study did not clearly demonstrate the cardiovascular effects of ozone (Frampton et al., 2017; Rich et al., 2020). Other reasons quoted were the lack of control for co-pollutants in epidemiological studies and uncertainty about the short-term effects of ozone on cardiovascular emergency room and hospital admissions.

Although the US EPA ISA was published in 2020, the literature on long- and short-term effects of ozone has grown since then. Chapter 3 includes five new studies on the long-term effects of ozone on mortality and one very large

worldwide multicity study on the short-term effects of ozone on mortality, which have provided further evidence of the short- and long-term effects on total and respiratory mortality. The reader is referred to section 3.4 for further details.

The nitrogen dioxide causality assessments shown in Table 2.1 are based on reviews published in 2016. Since then, COMEAP published a report in 2018 entitled *Associations of long-term average concentrations of nitrogen dioxide with mortality*, which is somewhat more supportive of a causal role of long-term nitrogen dioxide in increasing all non-accidental mortality, especially respiratory mortality (PHE, 2018). The 2016 EPA ISA classified the relationship between short-term nitrogen dioxide and respiratory effects as causal and the relationship between long-term nitrogen dioxide and respiratory effects as likely causal. A footnote to the causality determination defined the health outcome as "[a] n array of outcomes is evaluated as part of a broad health effects category: physiological measures (e.g. airway responsiveness), clinical outcomes (e.g. hospital admissions), cause-specific mortality". This suggests the causality determinations also extend to respiratory mortality, although the further detailed assessments in the ISA provide some qualifications for the separate health effects that were evaluated (US EPA, 2016). A 2018 review by the German Environment Agency (in German, with a summary in English) also supports a role for long-term nitrogen dioxide in causing cardiovascular mortality (Schneider et al., 2018).

The GDG notes that one review has specifically investigated how sensitive the associations between long-term nitrogen dioxide concentrations and mortality were to adjustment for different PM metrics (Faustini, Rapp & Forastiere, 2014). Associations with nitrogen dioxide were found to be generally robust.

Since 2016, no authoritative reviews have been published on short-term associations between carbon monoxide and hospital admissions for myocardial infarction.

2.3.4 Formulation of review questions

As per the WHO procedure of developing guidelines (WHO, 2014a), key questions to guide the review of evidence are best developed using the population, intervention, comparator and outcome format.

However, in environmental health risk guidelines such as the WHO air quality guidelines, recommendations are typically given in the form of numerical concentration values to prevent adverse health effects from exposure to environmental pollutants (so-called AQG levels). Typically, the best available evidence from human studies in this field consists mostly, if not exclusively,

of observational studies, as opposed to (randomized) controlled trials. Therefore – and as raised by several expert guideline development methodologists dealing with environmental risk guidelines (Collaboration for Environmental Evidence, 2013) – the use of a slightly adapted formulation of the traditional population, intervention, comparator and outcome question was used: a PECOS question. The intervention (I) term was replaced by an exposure (E) term, reflecting the concentration in ambient air of the particular air pollutant under consideration; also, an S was added to define study designs to be considered in evaluating the evidence, resulting in a PECOS question: population, exposure, comparator, outcome and study design (Table 2.2).

The GDG proposed the following PECOS questions (Box 2.2), which were later adapted to the health outcome and specific type of studies relevant for each pollutant and time average (short- or long-term exposure) considered in the updated guidelines.

Box 2.2. Generic PECOS question for long- and short-term exposures

Long-term exposures

In any population, including subgroups of susceptible adults and children (P), what is the increase in risk of health outcome x (O) per unit increase (C) in μg/m³ of long-term exposure (in the order of months to years) to ambient[a] concentration of air pollutant y (E), observed in studies relevant for the health outcome and exposure duration of interest (S)? In these studies, what is the lowest concentration that produces a measurable increase in risk?

Short-term exposures

In any population, including subgroups of susceptible adults and children (P), what is the increase in risk of health outcome x (O) per unit increase (C) in μg/m³ of short-term exposure (in the order of hours to days) to ambienta concentration of air pollutant y (E), observed in studies relevant for the health outcome and exposure duration of interest (S)? In these studies, what is the lowest concentration that produces a measurable increase in risk?

[a] Ambient refers to both outdoor and indoor environments.

These PECOS questions were designed to retrieve the epidemiological evidence necessary to develop updated AQG levels and inform the shape of the CRF for the different pollutant–outcome pairs.

For the specific purpose of updating the WHO air quality guidelines, the PECOS terms were defined as follows (Table 2.2).

Table 2.2. Elements of a PECOS question

Element	Explanation
Population	The general population, all age groups, from developed and developing countries, living both in urban and in rural areas exposed on a daily basis to the pollutant of interest through ambient air (understood as encompassing exposure in both outdoor and indoor environments), and not exclusively in occupational settings or as a result of indoor exposure alone. Population subgroups that are vulnerable to the effects of air pollution would be included, such as those with specific pre-existing health conditions (e.g. respiratory or cardiovascular diseases), pregnant women, newborns, children or older people. Whenever applicable, the considered health effect of exposure to the pollutant of interest in these vulnerable subgroups of the population would be assessed separately
Exposure	Exposure to air pollutants from any source, measured as long term (months to years) or short term (hours to days)
Comparator	Exposure to the lowest levels of air pollutants from any source, measured as long- (months to years) or short-term (hours to days)
Outcome	Health outcome(s) upon which the AQG levels are developed for each air pollutant considered in the guidelines
Study design	Type of studies evaluated, such as cohort and case–control studies (long term) and time-series, case-crossover and panel studies (short term)

2.4 Systematic review of the evidence

To address the PECOS questions posed by the GDG, a preliminary search of the relevant literature was conducted to identify available systematic reviews and meta-analyses on air quality and health. Based on an overview that assessed the quality of reviews in the field (Sheehan et al., 2016), it was decided that

included peer-reviewed articles that were of sufficient quality and addressed the formulated PECOS would serve as a starting point for most systematic reviews. Missing elements (e.g. specific assessments or syntheses) would be extracted anew and searches updated to the latest possible date within the process.

Selected members of the systematic review team, who were mostly identified through the above procedure, reviewed and synthesized all the relevant epidemiological literature in the area of air quality and health, following the principles outlined in the *WHO handbook for guideline development*, *2nd edition* (WHO, 2014a) and guidance provided from methodologists and experts in the discipline.

The instruments needed to assess the RoB for individual studies included in the reviews and the overall certainty of evidence across studies were adapted to better reflect the particularities of the air quality and health field.

PECOS questions were formulated for each of the major pollutant–outcome pairs and relevant averaging times. When the same health outcomes and averaging times were assessed, various air pollutants were grouped under the same systematic review, resulting in six systematic reviews.

All systematic reviews followed a common protocol prepared according to the provisions set out by the *WHO handbook for guideline development, 2nd edition* (WHO, 2014a) and later fine-tuned in relation to the specific exposure–outcome averaging time combinations that each review aimed to address.

The protocols for each systematic review are registered on PROSPERO, an international register of systematic reviews, maintained by the University of York (NIHR, 2021).

Furthermore, all systematic reviews used in the derivation of AQG levels are publicly available in a special issue of the journal *Environment International* (Whaley et al., 2021), which are also summarized in Annex 3.

- Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis (Chen & Hoek, 2020).
- Long-term exposure to NO_2 and O_3 and all-cause and respiratory mortality: a systematic review and meta-analysis (Huangfu & Atkinson, 2020).
- Short-term exposure to particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) and all-cause and cause-specific mortality: systematic review and meta-analysis (Orellano et al., 2020).

- Short-term exposure to sulfur dioxide (SO_2) and all-cause and respiratory mortality: a systematic review and meta-analysis (Orellano, Reynoso & Quaranta, 2021).
- Short-term exposure to ozone, nitrogen dioxide, and sulfur dioxide and emergency room visits and hospital admissions due to asthma: a systematic review and meta-analysis (Zheng et al., 2021).
- Short-term exposure to carbon monoxide and myocardial infarction: a systematic review and meta-analysis (Lee et al., 2020).

The core systematic reviews of adverse health effects were commissioned to address the PECOS questions. To ensure and confirm that no relevant studies in indoor settings had been missed in these reviews (none had been identified in the searches, based on the selected pollutant–outcome pairs), complementary searches were also conducted. In addition, several reviews and analyses were conducted in the context of this update of the guidelines. These included work on the health effects of exposure to particles originating from SDS, the burden of disease attributable to air pollution, the effectiveness of individual-level interventions and the cost–effectiveness of air quality interventions. Relevant review work conducted by other groups was closely monitored (e.g. on the health effects of BC/EC and UFP).[6]

2.4.1 Identification and retrieval of evidence

Based on the PECOS questions, a list of inclusion and exclusion criteria were defined for each systematic review and later fine-tuned by the systematic review team (Table 2.3 and Table 2.4).

Because most of the systematic reviews were based on peer-reviewed papers, the original search strategies were revised to reflect any additional eligibility criteria to ensure that all papers addressing the PECOS questions were identified.

Specific search strategies using both free text and controlled vocabulary terms were run for each database. More details can be found in the systematic reviews published in *Environment International* (Whaley et al., 2021).

All efforts were made to include all relevant papers published, which entailed searching a considerable number of literature sources, the inclusion of papers in languages other than English and the use of time frames spanning from database inception to late 2018.

[6] With the exception of the review and analysis performed by Evangelopoulos et al. (2020) and the review by Fussell & Kelly (2021), none of the reviews conducted in the context of the update of the guidelines have yet been published.

Table 2.3. Generic eligibility criteria for systematic reviews of long-term exposures

PECOS	Inclusion	Exclusion
Population	▪ General human population (including subgroups at risk: children, pregnant women, older people and patients with particular conditions) of all ages, living in developed and developing areas, both urban and rural. No geographical restrictions ▪ Exposure to the pollutant of interest predominantly via inhalation through ambient air (this covers exposures in both outdoor and indoor environments)	▪ Exposure to the pollutant of interest in occupational settings or as a result of indoor exposure exclusively
Exposure	▪ Long-term exposure (in the order of months to years) to ambient air $PM_{2.5}$, PM_{10}, O_3 and NO_2 expressed in a concentration unit ($\mu g/m^3$, ppb) ▪ For the NO_2 systematic review, NO_x studies may be included	▪ Less than 1 year of data available ▪ No exclusion criteria applied based on adjustment for co-pollutants
Comparator	▪ Exposure to lowest levels of the air pollutant of interest in the same or a control population	–
Outcome	▪ Health outcomes selected in relation to long-term exposure include (ICD-10 codes (version 2016)): all-cause mortality and cause-specific mortality, including cardiovascular (I00–I99), lung cancer (C30–C39) and respiratory (J00–J99)	–
Study design	▪ Human epidemiological studies such as: - prospective and retrospective studies - cohort studies - case–control and nested case–control studies ▪ Published (or accepted for publication, i.e. in press) studies in peer-reviewed indexed journals in any language (abstract in English language) and grey literature, where relevant.	▪ Qualitative studies ▪ Studies without individual-level data, that is, fully group-level (ecological) covariates ▪ Studies where no original data were analysed ▪ Reviews and methodological papers ▪ Non-human studies (in vivo, in vitro, other)

ppb: parts per billion.

Table 2.4. Generic eligibility criteria for systematic reviews of short-term exposures

PECOS	Inclusion	Exclusion
Population	▪ General human population (including subgroups at risk: children, pregnant women, older people, and patients with particular conditions) of all ages, living in developed and developing areas, both urban and rural. No geographical restrictions ▪ Exposure to the pollutant of interest predominantly via inhalation through ambient air (this covers exposures in both outdoor and indoor environments)	▪ Exposure to the pollutant of interest in occupational settings or as a result of indoor exposure exclusively
Exposure	▪ Short-term exposure (in the order of hours to 7 days) to ambient air $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2 and CO, from any source expressed in a concentration unit ($\mu g/m^3$, ppb) ▪ For NO_2 systematic review, NO_x studies may be included	▪ No exclusion criteria were applied based on adjustment for co-pollutants
Comparator	▪ Exposure to lowest levels of the air pollutant of interest in the same or a control population	–
Outcome	▪ Health outcomes selected for short-term exposure include (ICD-10 codes (version 2016)): all-cause mortality and cause-specific mortality, including cardiovascular (I00–I99) and respiratory (J00–J99), and hospital admissions and emergency room visits related to asthma (J45–J46) and myocardial infarction (I21–I22)	–
Study design	▪ Human epidemiological studies such as: - time-series studies - case-crossover studies - panel studies ▪ Published (or accepted for publication, i.e. in press) studies in peer-reviewed indexed journals in any language (abstract in English language) and grey literature, where relevant	▪ Qualitative studies ▪ Studies without individual-level data, that is, fully group-level (ecological) covariates ▪ Reviews and methodological papers ▪ Non-human studies (in vivo, in vitro, other) ▪ Studies with geographical and temporal overlap during meta-analysis

ppb: parts per billion.

For each of the systematic reviews, two reviewers independently screened titles and abstracts of papers identified with the systematic search and identified those that could be excluded based on the eligibility criteria. The full texts of the remaining articles were independently reassessed by two reviewers to ensure that all eligibility criteria were met. Disagreements among reviewers were resolved by discussion or through consultation with a third reviewer. The reasons for excluding articles were recorded. In addition, references of identified relevant articles (and reviews/guidelines, where relevant) were scanned to identify additional papers matching the PECOS question. The resulting list of papers was circulated with the systematic review team and the GDG to identify any potentially relevant missing studies (published or in press). Lastly, papers identified through the peer review process were incorporated as appropriate, either quantitatively or qualitatively, as feasible.

Two reviewers extracted all relevant data needed for the process using pre-defined forms. Key data included the elements defined by PECOS and declared conflicts of interest, as well as the data necessary to conduct RoB assessments (e.g. confounding factors) and to derive the AQG levels (i.e. for onset of the CRF: 5th–95th percentiles of population exposure, mean/median, and minimum and maximum pollutant concentrations; for shape of the CRF: methods and results of authors' assessments). Where necessary data were missing, the systematic review team obtained them from the authors of the primary studies or calculated them.

2.4.2 RoB assessment of individual studies

To assess RoB for individual studies, a specific instrument was developed by a working group composed of GDG members and methodologists. Based on a review of existing tools, the group agreed to take into account six key domains (confounding, selection bias, exposure assessment, outcome measurement, missing data, selective reporting), each including several subdomains or signalling questions. Judgement options included high, moderate and low RoB. The group also prepared guidance notes to assist the systematic review team in performing the task, including a list of critical and additional potential confounders to consider when making judgements about confounding and key information on the particularities of exposure assessment in the field. To avoid carrying forward the ratings from one domain to the others, the working group considered that an overall judgement of bias at the study level was not appropriate: instead, subgroup analyses were suggested per RoB domain across studies. This approach was considered more suited to identify which particular type of bias had an impact on the pooled effect size, as well as its direction and magnitude (Morgan et al., 2019).

A detailed description of the instrument is available in a dedicated publication (WHO Regional Office for Europe, 2020).

2.4.3 Synthesis of evidence

Meta-analyses were conducted to obtain summary pooled estimates of the risk for an adverse health outcome per unit increase in exposure to a given air pollutant. When three or more studies were identified for the same pollutant and health outcome, a quantitative synthesis was performed. Otherwise, the effect estimates were described qualitatively. Overall, statistical analyses were performed according to the *Guidelines for application of meta-analysis in environmental epidemiology* (Blair et al., 1995), the *Cochrane handbook for systematic reviews of interventions* (Higgins & Green, 2011) or other authoritative guidance. The approach used was the inverse variance method, assuming a linear concentration–response relationship.

When exposure metrics differed among studies, the data were transformed to the same metric, generally the relative risk (RR).

Although no dose–response meta-analytic techniques were employed to assess the shape of the CRF, potential deviations from linearity were assessed by other means, for example, by stratifying by mean pollutant concentrations or qualitatively evaluating the determinations and judgements made by study authors.

Because of differences in populations and pollution composition across populations, it was decided that estimates were to be pooled by means of a random-effects meta-analysis (maximum likelihood approach). Several measures of statistical heterogeneity were calculated, including *I-squared* and *tau-squared*. If considerable heterogeneity was present, attempts were made to explain the source of heterogeneity by subgroup analysis, meta-regression or sensitivity analysis (only possible if enough studies were available).

Other sensitivity analyses included those needed to inform the judgements on RoB, large magnitude of effect size and publication bias within the certainty of evidence approach. Lastly, additional sensitivity analyses were conducted to explore the impact of multipollutant models, conflicts of interest of study authors, population characteristics or lag patterns, where appropriate.

2.4.4 Grading of the certainty of the overall body of evidence

Evaluation of the certainty of evidence is foundational for systematic review, with a focus on the validity and precision of effect estimates. In the clinical realm, evidence-informed review has become the starting point for establishing

guidelines for clinical practice, including guidance for therapeutics and diagnostics. Much of the evidence considered in the clinical context comes from randomized controlled trials, where exposures are assigned at random by the investigator to provide some degree of assurance that potential confounders and effect modifiers, both known and unknown, are balanced across treatment groups. In the clinical context, evidence may also come from observational studies, including cohort and case–control studies, case series and other data resources. Given the strength of the randomized controlled trial design for ensuring comparability of treatment and control groups, a hierarchy of evidence sources has been established in which randomized controlled trials (providing the strongest evidence) have the highest ranking and lower rankings are given to other sources.

The GRADE approach has been adopted as the basis for evidence review in support of WHO guidelines (Schünemann et al., 2013; WHO, 2014a). GRADE was implemented for the purpose of evaluating evidence in support of formulation of clinical guidelines and, as such, it divided studies into randomized and non-randomized designs and ranked randomized studies as higher-quality evidence.

The initial certainty level of evidence was determined by the type of study, with randomized controlled trials starting at high certainty and non-randomized studies starting at low certainty. Thereafter, five domains were assessed for downgrading the certainty of the evidence resulting from randomized and non-randomized studies, and three domains were assessed for upgrading the certainty of evidence from non-randomized studies alone (Box 2.3).

Consistent with the standard approach, the certainty of the effect estimate was graded as high, moderate, low or very low. The ratings were subsequently used to select the risk functions used to derive AQG levels.

With the extension of GRADE to topics for which evidence derives largely or totally from observational studies, there are areas for which evidence from randomized designs is not available and decision-making, of necessity, draws on other evidence. For environmental agents, the evidence foundation is diverse and with very few exceptions does not involve a randomized exposure (e.g. air cleaner with filter versus air cleaner without filter). The human evidence is observational, coming from population-level studies (time-series studies, geospatial analyses, cohort studies, case–control studies and cross-sectional studies). A further issue that arises with environmental agents is identifying and summarizing the evidence derived from toxicological studies, in vivo animal bioassays and in vitro work addressing mechanisms.

Box 2.3. GRADE domains

Domains assessed for downgrading the certainty of evidence by one or two levels

- Limitations or RoB in all studies that constitute the body of evidence
- Indirectness of evidence in the studies
- Inconsistency of results between studies
- Imprecision of the pooled effect estimate
- Publication bias detected in the body of evidence.

Domains assessed for upgrading the certainty of evidence by one level

- Large magnitude of the pooled effect estimate
- All plausible confounding shifting the pooled effect estimate towards the null
- Existence of a concentration–response gradient.

Source: adapted from WHO (2014a).

Recognizing these complexities, different groups have made efforts to adapt GRADE for the assessment of evidence on exposures, but limitations were still under discussion at the time of developing these guidelines (National Research Council, 2014; Morgan et al., 2016; Saracci, 2017; Steenland et al., 2020). In this context, a working group was convened to adjust the standard GRADE approach to the field of air quality and health. The current adaptation was not aimed to assess causality through an examination of all the relevant streams of research (Woodruff & Sutton, 2011), but instead aimed to rate how certain one can be that the "true" estimate of the association between an air pollutant and an adverse health effect lies within a particular range (Hultcrantz et al., 2017).

The working group decided to start the rating for air pollution observational studies at moderate rather than high certainty evidence because of the risk of unmeasured confounding in observational research. From this level, the certainty of the evidence was then downgraded or upgraded based on several criteria per GRADE domain.

In addition, the working group recognized the need for taking a more nuanced view of the evidence, as well as for incorporating the following additional criteria to complement or replace existing guidance:

- calculation of an 80% prediction interval, to help assess heterogeneity in conjunction with the 95% confidence interval (CI) (IntHout et al., 2016);
- calculation of the sample size needed for a study based on a specific RR and CI, to help guide judgements about imprecision (Rothman & Greenland, 2018);
- estimation of the extent to which confounding may influence a pooled effect size using the *E-value,* to facilitate judgements for large magnitude of effect size (Mathur & VanderWeele, 2020); and
- additional approaches to help assess publication bias, such as a subgroup analysis of multicentre studies compared with single-city studies in case of evidence based on time-series studies, an analysis of differences in effect estimates from earlier versus later studies, and a comparison with published results of attempts to quantify the magnitude of bias.

A detailed description of the adaptation of GRADE is provided in the supplementary materials of the articles published in the special issue of *Environment International* (WHO Global Air Quality Guidelines Working Group on Certainty of Evidence Assessment, 2020).

2.5 From evidence to recommendations

The GDG decided that the recommendations (AQG levels) would be primarily based on epidemiological evidence. The GDG discussed how to account for contextual factors in formulating the AQG levels. Given the very large variability in exposures, socioeconomic conditions and other policy considerations across the world, the GDG concluded that retaining and enhancing the widely adopted interim targets from the previous guidelines would be a more useful instrument to assist end-users in implementing the recommendations. Contextual factors should instead be considered during the policy-making process at national, regional or local level, as discussed in Chapters 1 and 6 of this document. The recommendations were based on the certainty of evidence judgements alone, whereby low/very low certainty would prevent the GDG from formulating a recommendation for an AQG level. See, however, the caveats about this in sections 2.5.1 and 2.5.2.

Furthermore, two additional elements of guidance are offered in these guidelines. These elements differ from the recommendations in that they are not derived from systematic reviews of evidence of adverse health effects from air pollution.

Instead, they are based on an expert assessment of several types of evidence that included their utility to support end-users in their efforts to improve air quality. These elements of guidance are interim targets and good practice statements. Interim targets are air pollutant levels that are higher than the AQG levels, but which authorities in highly polluted areas can use to develop pollution reduction policies that are achievable within realistic time frames. The interim targets should be regarded as steps towards ultimately achieving AQG levels in the future, rather than as end targets. The number and numerical values of the interim targets are pollutant specific, and they are justified in the relevant sections of Chapter 3.

Contextual factors also did not play a direct role in the formulation of this guidance, although some considerations were described in a qualitative manner where relevant (e.g. burden of disease in relation to interim targets, resource considerations in relation to some good practice statements).

The following sections provide a detailed description of the approaches used by the GDG to formulate the recommendations and the additional guidance.

2.5.1 Formulation of long-term AQG levels

2.5.1.1 Definition

Long-term AQG levels are developed to provide advice to end-users to reduce the adverse effects of long-term exposure to air pollutants and, thereby, reducing associated disease and mortality.

Health outcomes in the current process are restricted to all-cause and respiratory mortality ($PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide). In addition, cardiovascular and lung cancer mortality are considered for some pollutants ($PM_{2.5}$, PM_{10}).

A long-term AQG level is defined as the lowest exposure level of an air pollutant above which the GDG is confident that there is an increase in adverse health effects. Confidence refers primarily to the adapted GRADE qualification confirming that there is high or moderate certainty evidence for an association between a specific pollutant and a specific health outcome. The GRADE certainty rating is based on eight criteria (discussed later in this section). The GDG also took into account additional considerations, including causality determinations.

In principle, AQG levels were developed only for pollutant–outcome pairs with at least moderate certainty data. The GDG recognizes that, following the precautionary principle, conditional recommendations could be considered where the certainty of the evidence is less than moderate.

This would be the case, for instance, when exposure is widespread and the effect on population health is severe. However, as will become evident in Chapter 3, there was at least moderate certainty evidence to support long- and short-term AQG levels for all pollutants considered.

This approach avoids consideration about what level of exposure should be considered safe, given that the available evidence cannot currently identify levels of exposure that are risk free for any of the pollutant–outcome pairs considered in this document. Moreover, the approach also avoids defining a so-called accepted level of risk, which would violate clean air acts or directives in countries where adverse health effects of air pollution are not accepted.[7] It also avoids making inferences for exposure levels below those for which there is solid evidence. The challenge is then to find the lowest level of exposure for which the GDG is still confident that there is at least moderate certainty evidence for adverse health effects. Note that this also requires some consideration of what is an adverse health effect. As a reference for this, the GDG used the latest update of the joint European Respiratory Society and American Thoracic Society policy statement on "what constitutes an adverse health effect of air pollution" (Thurston et al., 2017).

The systematic reviews commissioned by WHO formed the starting point for the body of evidence on which an AQG level is based and, therefore, underpin these guidelines. The systematic reviews each provide a summary estimate of the RR derived from the included meta-analyses for each pair of air pollutant and adverse health effect, a 95% CI for this estimate and a GRADE qualification for the certainty of the evidence. In principle, the GDG used this estimate for guideline derivation only if the 95% CI from a random-effects meta-analysis did not include an RR of 1. However, as air pollution has no known health benefits, the GDG decided in specific, well-argued cases to deviate from this principle.

2.5.1.2 Procedure

To find the lowest level of long-term exposure for which the GDG would be confident of an adverse health effect, a dedicated working group developed a procedure for each pollutant–outcome pair, based on the following eight steps (Table 2.5).

7 For example, the US National Ambient Air Quality Standards are based on the Clean Air Act, which stipulates: "National primary ambient air quality standards, prescribed under subsection (a) shall be ambient air quality standards the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health" (42 U.S.C. 7409(a)).

Table 2.5. Eight steps in formulation of long-term AQG levels

Step	Description
Step 1	Assess RR estimates and, when available, CRF for each critical health outcome per pollutant as provided by the systematic review. In its first meeting in 2016, based on an initial survey, the GDG decided that the following health outcomes are critical (depending on air pollutant): (i) all-cause mortality (or all, natural-cause mortality, excluding accidental deaths); (ii) respiratory mortality; (iii) cardiovascular mortality, associated with both long- and short-term exposures; (iv) short-term, day-to-day variations in hospital admissions and emergency room visits related to asthma; and (v) myocardial infarction. The GDG recommends AQG levels for all pollutant–outcome pairs identified in 2016 except for those associations not meeting at least moderate levels of certainty. This includes pairs with different likelihoods of causality, according to authoritative reviews by COMEAP, Health Canada, International Agency for Research on Cancer, US EPA and others
Step 2	Determine the lowest level of exposure measured in the studies included in the systematic review or in the subset of studies in the systematic review that estimate risk at this lowest level. For individual studies that used statistical models to evaluate the shape of the CRF, ensure that the lowest level of exposure is associated with a monotonic increase of the CRF curve
Step 3	Determine the minimal relevant increase in health outcomes
Step 4	Determine the starting point for AQG level determination as the long-term concentration of pollutant from which the minimal relevant amount of the health outcome will result
Step 5	Compare the AQG levels for a specific pollutant across critical health outcomes. Take as the final AQG level the lowest AQG level found for any of the critical health outcomes
Step 6	Assess the certainty of the evidence at low levels of exposure. The adapted GRADE assessment is for the entire body of evidence, not the subset of studies conducted at the lowest exposure levels. The evidence provided by these latter studies needs to be discussed, starting from the RoB assessment that was conducted at individual study level
Step 7	Consider new relevant evidence not included in the systematic reviews in a qualitative or, where possible, quantitative manner
Step 8	Reconsider causality of associations between pollutants and outcomes, taking into account whether or not associations have been classified as causal or likely causal in recent reviews by COMEAP, Health Canada, US EPA, WHO or other authoritative bodies

Each of the eight steps is discussed below.

Step 1. The GDG used the meta-analytic effect estimate that results from the systematic review and the assessment of the certainty of the evidence that underpins this effect estimate according to GRADE. In principle, effect estimates are only used if the 95% CI does not include an RR of 1 in the random-effects meta-analysis of the relevant body of evidence for a specific exposure–outcome pair. In addition, they are only used when underpinned by moderate to high certainty evidence. This is because there would be little confidence in an AQG level based on a non-significant meta-analytic effect estimate or on an effect estimate for which there is only low-certainty evidence.

The GDG recognized that the probability value (*P* value) generated by a test of statistical significance is a continuous measure and that even a statistically non-significant result may be more consistent with a real increased risk than with the null. Therefore, in cases of borderline significance or where significance is restricted to major subgroups, the GDG decided whether or not to proceed with guideline development, regardless of the overall statistical significance. It was noted that in the meta-analyses of the systematic reviews, statistical significance was based on two-sided tests. As the air pollutants under consideration have no known health benefits, this indicated that careful consideration was necessary for any meta-analytic random-effects effect estimate with a two-sided *P* value of less than 0.10.

It is important to realize that the adapted GRADE assessments apply to the whole body of evidence or to some part thereof based on, for example, a selection of studies at low or moderate RoB. No separate GRADE assessments were carried out for the – necessarily smaller number of – studies providing information at the lowest levels of exposure. GRADE assessments for a small number of studies are less robust. Key elements of GRADE such as RoB can be assessed for a smaller number of studies, and this was done where applicable.

Step 2. Since the effect estimates examined in the systematic reviews were generally evaluated using linear models and existing evidence generally supports a linear or supralinear, no-threshold relationship for the pollutant–outcome pairs, there must be a procedure to determine the lowest level of observed (measured or modelled) exposure that is sufficiently underpinned with evidence and can, therefore, be used.

Pragmatically, the GDG used as a starting point the 5th percentile of the exposure distributions from at least a few studies with the lowest levels of exposure (see below).

The rationale was that below the 5th percentile of an exposure distribution, where data density tends to be sparse, there is typically little confidence in the shape of the CRF. This is evident, for example, from the CIs of splines reported in a number of relevant papers. Confidence depends on the study size. When there are no studies with narrow CIs for effect estimates down to the 5th percentile of the exposure distribution, a higher percentile can be chosen as a starting point.

One would hesitate to use the 5th percentile of just one study, but the bodies of evidence considered for AQG level derivation varied considerably in terms of the numbers of studies included in the meta-analyses. In each case, the GDG made a pragmatic choice of studies to include.

Step 3. Next, the GDG determined what amount or increase in mortality or other outcome above the lowest level would be considered a relevant increase. This is an a priori decision based on a judgement by the GDG. The GDG decided to use zero as a baseline when reviewing studies (i.e. any increase of the adverse health risk from the lowest long-term concentration – as defined in step 2 – would be considered relevant). A zero increase represents a figure that comes closest to the ideal of having an AQG level that is based on health arguments only. With a positive slope of the CRF at this lowest exposure level, any increase in exposure will result in a non-zero risk increase. See below, however, for a discussion of what zero means in practical terms, and how that differs for the derivation of long- and short-term AQG levels.

Step 4. The lowest level – the mean of a number of observed 5th percentile concentrations, as defined in step 2 – of measurement is the point above which the GDG assumed (with some confidence) that an increase in risk occurs. Since the GDG decided not to allow any increase in the adverse health risk from the lowest level measured, this is then the starting point for derivation of the AQG level.

Step 5. The GDG established an AQG level for all critical health outcomes associated with a specific pollutant following steps 1–4. Of these, the lowest AQG level is recommended as the WHO AQG level for that pollutant. This will prevent the possibility that, for example, using an AQG level based on all-cause mortality would still allow a substantial amount of asthma to occur. For example, if the AQG level for asthma were lower than the all-cause mortality level, the AQG level based on the asthma outcome would be taken as the WHO AQG level.

Step 6. No separate GRADE assessments were carried out for the relatively few studies reporting the lowest levels of exposure since GRADE was applied to the whole body of evidence and not to single studies.

Nevertheless, a critical discussion was warranted on the merits of studies reporting the lowest exposure levels. This discussion started from an assessment of the RoB, which was conducted at the individual study level. If a study that found a low exposure level was deemed to be at high RoB, then it was excluded from consideration unless the GDG had sound reasons to disagree with this assessment in the relevant systematic review. The GDG also considered whether studies conducted at the lowest exposure levels continued to show increased RRs.

Step 7. The systematic reviews concluded their literature searches in early autumn of 2018. Since then, several relevant studies have been published. The GDG considered new evidence up to the meeting in June 2020 – after verifying that it met the same standards for inclusion as the studies already included.

Step 8. The GDG reconsidered causality of associations for all pollutant–outcome pairs. However, as all pollutant–outcome pairs were considered worthy of further consideration at the start of the process in 2016, such considerations generally did not prevent recommendations of an AQG level whenever the epidemiological evidence was considered to be of moderate or high certainty.

Specifically, the GDG referred to the causality assessments shown in Table 2.1, which formed the basis of the current AQG level development process. The assessment was updated, when necessary, to include newer evaluations published since 2016. These updates are all discussed at the end of section 2.3.3.

The steps outlined above produce a rounded integer value as a starting point for AQG level development. This starting point is not equivalent to a threshold of no effect: it is merely a level below which there is less certainty about the existence of an effect. Where there was no threshold, the starting point level was associated with some effect on health. The magnitude of this effect could be estimated from the meta-analytic effect estimate from the systematic review by assuming that, in the absence of a threshold, any level of exposure increases risk. It was useful to do this as a benchmark for comparing the starting points for long-term AQG levels between the pollutants $PM_{2.5}$, PM_{10}, ozone and nitrogen dioxide. It also provided a benchmark for comparing estimated health effects between long- and short-term AQG levels for the same pollutant.

2.5.2 Formulation of short-term AQG levels

There are fundamental differences between AQG levels for short-term and long-term exposures. For long-term exposures, AQG levels are derived based on the lowest long-term exposures that are, with at least moderate certainty, associated with adverse health effects.

Such guidelines are typically expressed as annual averages. Daily and hourly concentrations vary around the annual average, often in a lognormal distribution. If short-term AQG levels are derived based on lowest short-term exposures that are – with at least moderate certainty – associated with adverse health effects, then much lower values are obtained than those determined for long-term AQG levels. (The caveat about evidence of less than moderate certainty expressed in section 2.5.1 also applies here.) Importantly, the short-term variation in air pollution concentrations is largely driven by meteorology, which cannot be controlled. Short-term guidelines are typically defined as a high percentile of the distribution of daily values, for example the 98th or 99th percentiles equivalent to seven or three days a year exceeding this value (i.e. exceedance days). The rationale for choosing a high percentile and not the maximum is that the maximum of daily values for a given year is a less stable statistic than the high percentiles.

For locations in which concentrations are below the annual mean AQG level, days with such high daily mean concentrations will be rare and a large proportion of days will have concentrations below the annual mean AQG level. Thus, the health burden related to a few days with higher concentrations corresponds to a very small fraction of the total air pollution-related burden.

In contrast, the long-term variation in air pollution concentrations is largely driven by spatial variation in air pollution sources and emissions, which can be controlled, although control for some sources such as desert dust, pose unique and much more considerable challenges. Typically, the magnitude of the health effects associated with variations in long-term exposure is larger, per mass unit, than the magnitude of the health effects associated with short-term variations. As a consequence, long-term AQG levels for most health outcomes are more health protective than short-term AQG levels. In such instances, the long-term AQG level is used to derive a short-term AQG level whenever the same health effect is considered (e.g. mortality) for both long- and short-term exposures.

According to this line of reasoning, all eight steps outlined for long-term AQG level development remain valid for short-term AQG level development, except for step 3: defining the minimal relevant increase in health outcomes.

2.5.2.1 Procedure

In keeping with established practice, as a starting point, short-term AQG levels were considered by the GDG as the 99th percentiles of daily concentrations empirically observed in distributions with a mean equal to the long-term AQG level, for pollutant–outcome pairs for which a long-term AQG level is also being recommended. This is the case for all-cause mortality and $PM_{2.5}$, PM_{10}, ozone and

nitrogen dioxide. It is also the case for cause-specific mortality and $PM_{2.5}$ and PM_{10}. The GDG evaluated the percentage of excess daily deaths expected from the meta-analytic linear short-term effect estimate to occur at a day at the 99th percentile of the distribution of daily, 24-hour average concentrations, compared with a day at the annual mean guideline concentration.

In the cases of sulfur dioxide and all-cause mortality and hospital admissions and emergency room visits related to asthma and of carbon monoxide and myocardial infarction, no long-term AQG levels were recommended and there are no long-term AQG levels from 2005. The same approach as described at the beginning of step 2 was followed, by evaluating the percentage of excess daily deaths expected from the meta-analytic linear effect estimate to occur at the 99th percentile, relative to a specified and justified low concentration. The rationale for the long-term reference concentrations of sulfur dioxide and carbon monoxide is discussed in Chapter 3.

Once the starting point for the short-term AQG level was calculated, it was rounded to the nearest integer value.

The rationale for having short-term AQG levels next to long-term AQG levels for the same pollutant is based on the need to provide air quality managers, health-care providers, vulnerable patients and the general population with tools to communicate health risks and short-term emission controls. The GDG notes that there is substantial evidence that some susceptible groups may be harmed by short-term elevations of some pollutants: those with asthma, coronary heart disease, COPD and other chronic conditions and diseases. Overall, these susceptible groups represent a substantial proportion of the population in many countries.

The rationale for having short-term AQG levels in the absence of long-term AQG levels is typically based on documented acute elevation of risk over timescales of minutes to one or a few days.

More detailed advice to policy-makers and air quality managers is provided in Chapter 6 of these guidelines.

In this protocol a distinction is made between three different scenarios (Table 2.6).

Scenario 1. In the first scenario, internally consistent long- and short-term AQG levels is desired, and the argument is that meeting the long-term AQG level protects against serious short-term effects on mortality. This can be shown for PM, nitrogen dioxide and ozone.

Table 2.6. Scenarios in formulation of short-term AQG levels

Scenario	Description
Scenario 1	Development of a short-term AQG level for a pollutant for which a long-term AQG level for the same outcome was developed (e.g. all-cause mortality)
Scenario 2	Development of a short-term AQG level for a pollutant for which a long-term AQG level was developed for another outcome (e.g. hospital admissions and emergency room visits related to asthma versus all-cause mortality)
Scenario 3	Development of a short-term AQG level for a pollutant for which no long-term AQG level was developed

First, for $PM_{2.5}$ and all-cause mortality, in *Global update 2005* the annual mean air quality guideline is 10 μg/m³ and the short-term 99th percentile 24-hour average air quality guideline is 25 μg/m³ so the ratio between short-term and long-term guideline values was 2.5. At the time, this ratio was not empirically underpinned; the ratio was simply said to be 2.5, with some recognition that it may vary from place to place and from time to time. There is now a very large database – including the 652 cities from the Liu et al. (2019) paper – to document the ratios between higher percentiles of the distributions of 24-hour average concentrations and the annual means.

The GDG recommends using the same ratio everywhere for the purpose of deriving a 24-hour average AQG level. The primary motivation is that short-term effect estimates for $PM_{2.5}$ and all-cause mortality do not significantly vary between different regions of the world. (Note that there are differences in effect estimates depending on $PM_{2.5}$ level, but that is not important when deriving AQG levels for relatively low short-term concentrations; it is important when quantifying the health burdens associated with the higher interim target levels.)

The database from the MCC Collaborative Research Network (A. Gasparrini, London School of Hygiene and Tropical Medicine, unpublished data, 23 June 2020) has descriptive data on long time series of daily average $PM_{2.5}$ and PM_{10} concentrations from 384 and 480 cities, respectively. The ratio of the 99th percentile of the daily average concentrations to the multiyear mean is 3.05 for $PM_{2.5}$, 2.85 for PM_{10}, 2.34 for nitrogen dioxide (398 cities), 2.05 for ozone (244 cities), 3.90 for sulfur dioxide (396 cities) and 2.97 for carbon monoxide (349 cities).

Based on this database, the Network has published a series of articles, which are published as open access (Chen et al., 2021; Liu et al., 2019; Meng et al., 2021; Vicedo-Cabrera et al., 2020). When considering long- and short-term AQG levels for ozone, the GDG realized that long-term AQG levels could be based on the mean peak-season ozone levels, which have a different relationship to the 99th percentile of the daily distributions than the annual means.

As an example, the GDG recommended setting the long-term AQG level for $PM_{2.5}$ at 5 μg/m³, and if a ratio of 3 were used to calculate the corresponding 99th percentile of daily means, a 24-hour AQG level of 15 μg/m³ would be derived. All the recommendations can be found in Chapter 3.

Scenario 2. In the second scenario, there may be long-term AQG levels for nitrogen dioxide and ozone based on effect estimates for respiratory mortality, and short-term AQG levels based on effect estimates for all-cause mortality only. For $PM_{2.5}$ and PM_{10}, there are long- and short-term effect estimates for all-cause mortality as well as a number of cause-specific mortalities. In most cases, these are from the same studies, so there are no serious differences between the 5th percentiles of PM in the lowest-level studies for natural-cause and cause-specific mortality. If there are differences, the expectation is that in the smaller numbers of cause-specific mortality studies the 5th percentiles of the concentration distributions are more likely to be higher than lower, compared with the all-cause mortality studies. The general pattern is that effect estimates for both long- and short-term cause-specific mortality are somewhat bigger than those for all-cause mortality. This is always true for $PM_{2.5}$; the picture for PM_{10} is a bit more mixed. Nevertheless, these patterns do not lead to different conclusions for AQG level derivation based on all-cause mortality as compared with AQG levels based on cause-specific mortality. This again assumes that the 5th percentiles from the lowest-level studies are not lower for cause-specific mortality studies than for all-cause mortality studies.

There will be short-term AQG levels for ozone, nitrogen dioxide and sulfur dioxide and hospital admissions and emergency room visits related to asthma, and for carbon monoxide and hospital admissions and emergency room visits related to myocardial infarction. The GDG recommends (for ozone and nitrogen dioxide) to start from the long-term AQG level based on mortality, look at the internally consistent short-term AQG level for mortality and then quantify the effect on hospital admissions and emergency room visits related to asthma at that level. Here, too, data from the Liu et al. (2019) collaboration provide insight into the ratios between 99th percentiles and annual means for ozone as well as for nitrogen dioxide.

A judgement on whether one or the other effect should drive the short-term AQG level is then needed, with potential consequences for consistency between long- and short-term AQG levels. As mentioned before, for ozone and nitrogen dioxide, only short-term CRFs for all-cause mortality are available. Therefore, comparisons (as outlined for PM above) are not always possible.

Scenario 3. Lastly, in the third scenario, a short-term AQG level needs to be derived for a pollutant for which no long-term AQG level is being developed.

A case in point is sulfur dioxide, for which there are systematic reviews of short-term 24-hour associations with all-cause and respiratory mortality and asthma hospital admissions and emergency room visits.

For carbon monoxide, there is a 24-hour AQG level based on the systematic review of associations between 24-hour mean carbon monoxide concentrations and hospital admissions and emergency room visits due to myocardial infarction, which can then be compared with the air quality guideline of 7 mg/m³ for carbon monoxide indoors (WHO, 2014b) and the shorter-term AQG levels as well.

To develop an AQG level for a particular pollutant–outcome pair, the GDG examined external evidence for causality of the pollutant–outcome association. Causality judgements were part of the process that produced the PECOS questions for the current process (Table 2.1).

In the case of hospital admissions and emergency room visits related to asthma and myocardial infarction, further adaptations were needed to compare visits/admissions to deaths. The GDG specified short-term AQG levels for hospital admissions and emergency room visits related to asthma or myocardial infarction based on quantification of the expected increase in such visits/admissions at the proposed short-term AQG level. This recognizes that the health burden related to a few days (three to four per year when using 99th percentiles) with higher concentrations corresponds to a very small fraction of the total air pollution-related burden.

2.5.3 Formulation of interim targets and good practice statements

2.5.3.1 Interim targets

Interim targets were introduced in *Global update 2005* as additional integral elements of guidance, designed to complement the WHO air quality guidelines.

Interim targets may be defined as air pollutant concentrations associated with a

specific decrease in health risk that serve as "incremental steps in progressive reduction of air pollution [...] intended for use in areas where pollution is high" (WHO Regional Office for Europe, 2006). As stated in *Global update 2005,* "countries may find these interim targets helpful in gauging progress over time in the difficult process of steadily reducing population exposures [to air pollution]".

Moreover, interim targets "aim to promote a shift from high air pollutant concentrations, with acute and serious health consequences, to lower concentrations"(WHO Regional Office for Europe, 2006), in line with the AQG levels. Further:

> [i]f these [interim] targets were to be achieved, one could expect significant reductions in risks for acute and chronic human health effects from air pollution. Progress towards the guideline values should, however, be the ultimate objective of air quality management and health risk reduction in all areas (WHO Regional Office for Europe, 2006).

The GDG decided that interim targets, and specifically the 2005 interim targets, should be retained in the updated air quality guidelines for two reasons.

- The first is to promote continuous air quality improvement in places with high levels of ambient air pollution with the goal of achieving AQG levels as expeditiously as possible. Interim targets for reduction of air pollution have been shown to be achievable with abatement measures and have practical value in that several countries have standards equal to some of the interim targets (Kutlar Joss et al., 2017). Importantly, interim targets also have been helpful in achieving AQG levels.
- The second is to maintain continuity. Policy-makers, nongovernmental organizations and the scientific community in low- and middle-income countries are already familiar with the 2005 interim targets and have employed them since their introduction 15 years ago. Changing the interim targets at this point would be confusing and unnecessary because the interim target levels are still globally relevant, although the 2005 air quality guideline would be added as an interim target in the event that the AQG level is lowered.

Descriptors for each interim target have been provided to inform decision-makers of the implications of achieving the corresponding air pollutant concentrations. These are the risk descriptors calculated using updated CRFs.

Lastly, the results of simulating a reduction of the 2016 burden of disease attributable to $PM_{2.5}$ to the interim target and the new AQG level are provided in

section 3.9, in order to illustrate the mortality and disability adjusted life-year benefits that could be achieved by expeditiously reducing air pollutant levels (Evangelopoulos et al., 2020).

2.5.3.2 Good practice statements

The *WHO handbook for guideline development, 2nd edition* (WHO, 2014a), provides for the development of good practice statements in certain cases. This occurs when a GDG is confident that a large body of diverse evidence that is difficult to synthesize indicates that the desirable effects of a particular course of action far outweigh its undesirable effects. In other words, when a GDG is confident that implementing a measure would be beneficial with high certainty but when conducting numerous systematic reviews and detailed assessments of evidence would be a poor use of resources (WHO, 2014c).

The evidence considered may be of a diverse nature, including linked or indirect evidence, physical and biochemical properties, ethical principles and human rights conventions (WHO, 2019a). Along these lines, the types of evidence that the GDG may consider in the context of air quality guidelines would also include air quality management principles and good practices implemented by reputable institutions.

The option of developing good practice statements was used to provide much-needed guidance in relation to some specific types of PM identified as critical in the preliminary phase. The GDG chose to closely follow-up major external reviews on BC/EC, UFP and SDS throughout the process. The decision was made to develop good practice statements for these, rather than numerical AQG levels, in the absence of clear quantitative evidence on independent health effects from these pollutants.

3

Recommendations on classical air pollutants

3.1 Introduction

This chapter presents specific recommendations on air quality guideline (AQG) levels for the pollutants $PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide, together with the corresponding interim targets.

In Chapter 2, a detailed protocol was described that was followed to derive AQG levels for the pollutants and averaging times. Chapter 2 also provide the rationales for including the specific pollutant–outcome associations that formed the basis for the recommendations given in this chapter. The averaging times considered were long term (annual mean or, for ozone, highest six-month average) and short term (24 hours). Long-term effects were considered only for all-cause and cause-specific mortality ($PM_{2.5}$, PM_{10}, ozone and nitrogen dioxide). For those, any pollutant-attributed increase in long-term mortality was considered harmful. Short-term effects were considered for all non-accidental and cause-specific mortality ($PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide and sulfur dioxide), for asthma hospital admissions and emergency room visits (ozone, nitrogen dioxide and sulfur dioxide), and for myocardial infarction hospital admissions and emergency room visits (carbon monoxide only). When both long- and short-term AQG levels were considered for a pollutant–outcome pair, preference was given to the long-term AQG level and the short-term AQG level was aligned using empirical data on frequency distributions of 24-hour concentrations. When only short-term AQG levels were considered, analogy with other pollutant–outcome pairs was used.

Information about all the specific pollutant–outcome pairs reviewed can be found in the systematic reviews of evidence available in a special issue of *Environment International* (Whaley et al., 2021).

3.2 $PM_{2.5}$

3.2.1 General description

The general description comes from *Global update 2005*.

> PM in urban and non-urban environments is a complex mixture with components having diverse chemical and physical characteristics. Research on PM and the interpretation of research findings on exposure and risk are complicated by this heterogeneity, and the possibility that the potential of particles to cause injury varies with size and other physical characteristics, chemical composition and source(s). Different characteristics of PM may be relevant to different health effects. Newer research findings continue to highlight this complexity and the dynamic nature of airborne PM, as it is formed either primarily or secondarily

and then continues to undergo chemical and physical transformation in the atmosphere.

Nonetheless, particles are still generally classified by their aerodynamic properties, because these determine transport and removal processes in the air and deposition sites and clearance pathways within the respiratory tract. The aerodynamic diameter is used as the summary indicator of particle size; the aerodynamic diameter corresponds to the size of a unit-density sphere with the same aerodynamic characteristics as the particle of interest. The differences in aerodynamic properties among particles are exploited by many particle sampling techniques (WHO Regional Office for Europe, 2006).

The focus in recent decades has been on particles with aerodynamic diameters of less than or equal to 2.5 μm ($PM_{2.5}$) or 10 μm (PM_{10}).

3.2.2 Recommended AQG level for long-term exposure to $PM_{2.5}$

Based on the methods for deriving an AQG level outlined in the guideline development protocol in Chapter 2, this section provides a recommendation for an annual AQG level for $PM_{2.5}$ that is based on all non-accidental mortality and cause-specific mortality (Table 3.1).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, which is referred to in section 2.4. The review of this pollutant (Chen & Hoek, 2020) was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating ambient particles to human health.

The recommendations in this chapter follow the eight steps outlined in the protocol for AQG level development in Chapter 2 (section 2.5). The tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review on $PM_{2.5}$ and all non-accidental mortality (Chen & Hoek, 2020) reported a meta-analytic effect estimate of RR of 1.08 (95% CI: 1.06–1.09) per 10 μg/m³ $PM_{2.5}$, assuming a linear relationship. The authors found an indication of a supralinear relationship, suggesting a steeper risk increase at lower exposure levels.

The certainty of the evidence was considered high according to GRADE. CRFs were provided by several studies. These are shown in Fig. 3.1, Fig. 3.2, Fig. 3.3 and Fig. 3.4 (which follow a discussion of the eight steps) for the studies with information at low to very low levels of measured exposure (step 2) (Pinault et al., 2016, 2017; Villeneuve et al., 2015; Di et al., 2017a). CRFs were published from four of the six studies with the lowest exposure levels. Two studies did not provide a CRF (Weichenthal et al., 2014; Cakmak et al., 2018). For obvious reasons, the uncertainty in the shape of the CRFs is higher in single than in pooled studies, and higher in small than in large studies. Very large studies such as the study by Di et al. (2017a) provide the best evidence for the shape of the CRF at the low end of the exposure range. These shapes generally show linear relationships down to very low concentrations or somewhat steeper curves at low than at higher concentrations.

Step 2. Determine the lowest level of exposure measured

In 18 of the 25 studies included in the meta-analysis, a 5th percentile of the exposure distribution was reported or could be calculated from the reported mean and standard deviation (Table 3.2). As the concentration distributions are often lognormal, this calculation is not straightforward. Therefore, preference was given to actual reports of the relevant numbers obtained from the published papers or upon request from the study authors. This is indicated in Table 3.2, Table 3.3, Table 3.4 and Table 3.5. The five lowest levels reported or estimated in these studies were 3.0 μg/m³ (Pinault et al., 2016), 3.2 μg/m³ (Cakmak et al., 2018), 3.5 μg/m³ (Pinault et al., 2017), 4.8 μg/m³ (Villeneuve et al., 2015) and 6.7 μg/m³ (Weichenthal et al., 2014). Weichenthal et al. (2014) found no effect. The Villeneuve et al. (2015) study provided no evidence of an effect of $PM_{2.5}$ on all non-accidental mortality below 8 μg/m³. The study by Di et al. (2017a) has the next lowest 5th percentile (7.1 μg/m³) and the study by Hart et al. (2015) the next lowest (7.8 μg/m³). The average $PM_{2.5}$ level across these five studies with the lowest exposure measurements in the systematic review is 4.2 μg/m³. A sensitivity analysis disregarding the Villeneuve et al. (2015) and Weichenthal et al. (2014) studies produced a mean of 4.9 μg/m³ $PM_{2.5}$. The sum of weights in the meta-analysis was > 25%, indicating that these studies were influential in the meta-analysis.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant.

Step 4. Determine the starting point for AQG level determination as the long-term concentration of the pollutant from which the minimal relevant amount of the health outcome will result

The average of the five lowest 5th percentile levels measured in these five studies was the starting point for deriving an AQG level (4.2–4.9 μg/m³ $PM_{2.5}$). The data obtained support a long-term AQG level of no more than 5 μg/m³, based on the association between long-term $PM_{2.5}$ and all non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: cause-specific mortality

The cause-specific mortality outcomes that were investigated all yielded bigger hazard ratios (HRs) for $PM_{2.5}$ compared with the HR for all non-accidental mortality, with an HR of 1.11 (95% CI: 1.09–1.14) for circulatory mortality, 1.10 (95% CI: 1.03–1.18) for non-malignant respiratory mortality and 1.12 (95% CI: 1.07–1.16) for lung cancer mortality. The certainty of the evidence on $PM_{2.5}$ was rated as high for circulatory and lung cancer mortality and moderate for non-malignant respiratory mortality. Starting points for AQG level determination for these other outcomes would be 4.0–4.3 μg/m³ based on the five studies with the lowest 5th percentiles and 4.1–6.2 μg/m³ based on the five studies documenting positive associations (HR > 1) for these three cause-specific mortality end-points (Table 3.3, Table 3.4 and Table 3.5). The data obtained for cause-specific mortality also support a long-term $PM_{2.5}$ AQG level of no more than 5 μg/m³.

Step 6. Assess certainty of the evidence

None of the studies that make up the lowest levels measured in the all-cause mortality studies were considered to have a high RoB; thus, there is no reason to change the AQG level because of low certainty of the evidence in the lowest-level studies.

Step 7. Consider new evidence

Several new studies were published between autumn 2018 and the summer of 2020. They are discussed in the systematic review by Chen & Hoek (2020). When adding the new studies to the meta-analysis, the joint effect estimate for all-cause mortality and $PM_{2.5}$ was exactly the same as for the studies already included (Fig. A7.43 in Chen & Hoek (2020)). therefore, there is no reason to change the assessment based on the newly published studies. Chen & Hoek (2020) also referred to an analysis of a large number of cohort studies from many different areas of the world, showing a near linear association between annual $PM_{2.5}$ and all-cause mortality, defined as mortality from NCD plus lower respiratory illness, over a range of 2.4–80 μg/m³ (Fig. 3.5; published as Fig. 1 in Burnett et al. (2018)).

Step 8. Reconsider causality

All PM–outcome associations were deemed to be causal or likely causal in the 2016 outcome prioritization framework (see section 2.3.3). These judgements have not changed in more recent authoritative assessments. For more details, see Table 2.1 and additional text in section 2.3.3.

The 5th percentile and mean or median of exposure distributions in studies of $PM_{2.5}$ and the all-cause mortality meta-analysis results are indicated in Table 3.2 based on data from the systematic review by Chen & Hoek (2020). Table 3.3, Table 3.4 and Table 3.5 have the same information for studies on circulatory, non-malignant respiratory and lung cancer mortality, respectively.

3.2.2.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

The recommendation is an annual $PM_{2.5}$ AQG level of 5 µg/m³. The GDG recommends maintaining the 2005 interim targets and introducing an interim target 4 at the level of the 2005 air quality guideline, as shown in Table 3.1.

Table 3.1. Recommended annual AQG level and interim targets for $PM_{2.5}$

Recommendation	$PM_{2.5}$ (µg/m³)
Interim target 1	35
Interim target 2	25
Interim target 3	15
Interim target 4	10
AQG level	**5**

If mortality in a population exposed to $PM_{2.5}$ at the AQG level is arbitrarily set to 100, then it will be 124, 116, 108 and 104, respectively, in populations exposed to $PM_{2.5}$ at interim target 1, 2, 3 and 4 levels. These projections are based on the linear HR of 1.08 per 10-µg/m³ increase in $PM_{2.5}$ for all non-accidental mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Table 3.2. Studies on long-term $PM_{2.5}$ exposure and all non-accidental mortality included in the systematic review by Chen & Hoek (2020), ordered by me(di)an concentration

Study	Me(di)an (µg/m³)	SD	P5	P25	HR (95% CI)[a]
Pinault et al. (2016)	5.9	–	3.0[b]	4.2	1.26 (1.19–1.34)
Cakmak et al. (2018)	6.5	2.0	3.2[c]	–	1.16 (1.08–1.25)
Pinault et al. (2017)	7.1	–	3.5[b]	5.4	1.18 (1.15–1.21)
Weichenthal et al. (2014)	9.5	1.7	6.7[c]	–	0.95 (0.76–1.19)
Villeneuve et al. (2015)	9.5	3.5	4.8[b]	–	1.12 (1.05–1.20)
Di et al. (2017a)	11.5	2.9	7.1[b]	9.5	1.08 (1.08–1.09)
Parker, Kravets & Vaidyanathan (2018)	11.8	–	–	10.1	1.03 (0.99–1.08)
Bowe et al. (2018)	11.8	–	7.9[b]	10.2	1.08 (1.03–1.13)
Hart et al. (2015)	12.0	2.8	7.8[b]	10.2	1.13 (1.05–1.22)
Turner et al. (2016)	12.6	2.9	7.8[c]	–	1.07 (1.06–1.09)
Carey et al. (2013)	12.9	1.4	10.6[c]	–	1.11 (0.98–1.26)
Beelen et al. (2014)	13.4	–	7.9[b]	11.3	1.14 (1.03–1.27)
Thurston et al. (2016a)	13.6	3.6	8.9[b]	11.1	1.03 (1.01–1.06)
Hart et al. (2011)	14.1	4.0	7.8[b]	11.8	1.10 (1.02–1.18)
Lepeule et al. (2012)	15.9	–	–	–	1.14 (1.07–1.22)
Bentayeb et al. (2015)	17.0	–	–	–	1.16 (0.98–1.36)
Puett et al. (2011)	17.8	3.4	12.2[c]	–	0.86 (0.72–1.02)
Ostro et al. (2015)	17.9	–	–	13.1	1.01 (0.97–1.05)
Badaloni et al. (2017)	19.6	1.9	16.5[c]	–	1.05 (1.02–1.08)
Enstrom (2005)	23.4	–	–	–	1.01 (0.99–1.03)
Beelen et al. (2008)	28.3	2.1	24.8[c]	–	1.06 (0.97–1.16)
Tseng et al. (2015)	29.6	–	–	–	0.92 (0.72–1.17)
Yin et al. (2017)	40.7	18.6	10.1[c]	–	1.09 (1.08–1.10)
Yang et al. (2018)	42.2	–	–	–	1.06 (1.01–1.10)
McDonnell et al. (2000)	59.2	16.8	31.6[c]	–	1.09 (0.98–1.21)

–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; HR: hazard ratio; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Table 3.3. Studies on long-term $PM_{2.5}$ exposure and circulatory mortality included in the systematic review by Chen & Hoek (2020), ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Pinault et al. (2016)	5.9	–	3.0[b]	4.2	1.19 (1.07–1.31)
Pinault et al. (2017)	7.1	–	3.5[b]	5.4	1.25 (1.19–1.30)
Crouse et al. (2015)	8.9	–	3.5[b]	6.0	1.06 (1.04–1.08)
Weichenthal et al. (2014)	9.5	1.7	6.7[c]	–	1.15 (0.76–1.73)
Villeneuve et al. (2015)	9.5	3.5	3.7[c]	–	1.32 (1.14–1.52)
Dehbi et al. (2017)	9.9	–	–	9.4	1.30 (0.39–4.34)
Parker, Kravets & Vaidyanathan (2018)	11.8	–	–	10.1	1.16 (1.08–1.25)
Turner et al. (2016)	12.6	2.9	7.8[c]	–	1.12 (1.09–1.15)
Carey et al. (2013)	12.9	1.4	10.6[c]	–	1.00 (0.85–1.17)
Vedal et al. (2013)	12.9	2.8	8.3[c]	–	1.31 (0.94–1.83)
Beelen et al. (2014)	13.4	–	7.9[b]	11.3	0.98 (0.83–1.16)
Thurston et al. (2016a)	13.6	3.6	8.9[b]	11.1	1.05 (0.98–1.13)
Hart et al. (2011)	14.1	4.0	7.8[b]	11.8	1.05 (0.93–1.19)
Laden et al. (2006)	–	–	–	–	1.08 (0.79–1.48)
Bentayeb et al. (2015)	17.0	–	–	–	1.21 (0.72–2.04)
Ostro et al. (2015)	17.9	–	–	13.1	1.05 (0.99–1.12)
Badaloni et al. (2017)	19.6	1.9	16.5[c]	–	1.08 (1.03–1.12)
Beelen et al. (2008)	28.3	2.1	24.8[c]	–	1.07 (0.75–1.52)
Tseng et al. (2015)	29.6	–	–	–	0.80 (0.43–1.49)
Yin et al. (2017)	40.7	18.6	10.1[c]	–	1.09 (1.08–1.10)
Yang et al. (2018)	42.2	–	–	–	1.02 (0.93–1.11)

–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Table 3.4. Studies on long-term $PM_{2.5}$ exposure and non-malignant respiratory mortality included in the systematic review by Chen & Hoek (2020), ordered by me(di)an concentration

Study	Me(di)an (µg/m³)	SD	P5	P25	HR (95% CI)[a]
Pinault et al. (2016)	5.9	–	3.0[b]	4.2	1.52 (1.26–1.84)
Pinault et al. (2017)	7.1	–	3.5[b]	5.4	1.22 (1.12–1.32)
Crouse et al. (2015)	8.9	–	3.5[b]	6.0	0.95 (0.91–0.98)
Villeneuve et al. (2015)	9.5	3.5	3.7[c]	–	0.82 (0.61–1.11)
Turner et al. (2016)	12.6	2.9	7.8[c]	–	1.16 (1.10–1.22)
Carey et al. (2013)	12.9	1.4	10.6[c]	–	1.57 (1.30–1.91)
Dimakopoulou et al. (2014)	13.4	–	7.9[b]	11.3	0.79 (0.47–1.34)
Thurston et al. (2016a)	13.6	3.6	8.9[b]	11.1	1.10 (1.05–1.15)
Hart et al. (2011)	14.1	4.0	7.8[b]	11.8	1.18 (0.91–1.53)
Laden et al. (2006)	14.8	–	–	–	1.08 (0.79–1.48)
Bentayeb et al. (2015)	17.0	–	–	–	0.88 (0.57–1.36)
Ostro et al. (2015)	17.9	–	–	13.1	0.99 (0.90–1.09)
Cesaroni et al. (2013)	23.0	4.4	15.8[c]	20.3	1.03 (0.98–1.08)
Beelen et al. (2008)	28.3	2.1	24.8[c]	–	1.04 (0.90–1.21)
Katanoda et al. (2011)	30.5	–	–	–	1.16 (1.04–1.30)
Yang et al. (2018)	42.2	–	–	–	1.11 (1.04–1.19)
McDonnell et al. (2000)	59.2	16.8	31.6[c]	–	1.23 (0.97–1.55)

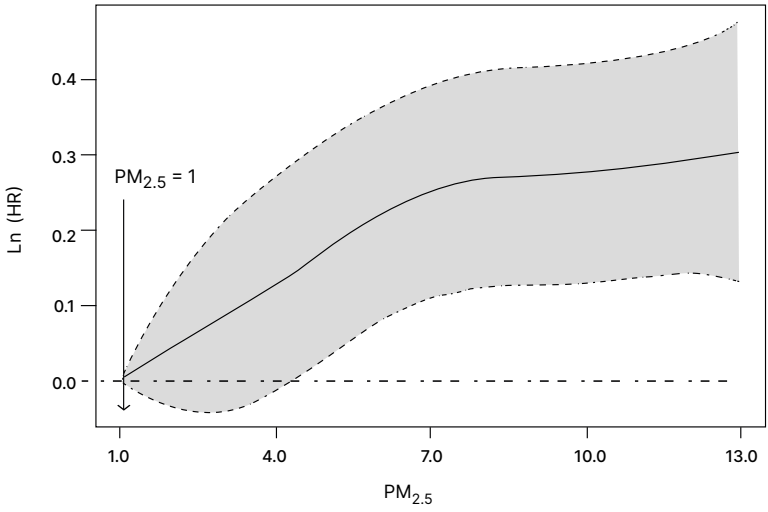
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Table 3.5. Studies on long-term $PM_{2.5}$ exposure and lung cancer mortality included in the systematic review by Chen & Hoek (2020), ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Pinault et al. (2016)	5.9	–	3.0[b]	4.2	1.17 (0.98–1.40)
Cakmak et al. (2018)	6.5	2.0	3.2[c]	–	1.29 (1.06–1.59)
Pinault et al. (2017)	7.1	–	3.5[b]	5.4	1.16 (1.07–1.25)
Weichenthal et al. (2014)	9.5	1.7	6.7[c]	–	0.75 (0.34–1.65)
Villeneuve et al. (2015)	9.5	3.5	3.7[c]	–	0.97 (0.80–1.18)
Turner et al. (2016)	12.6	2.9	7.8[c]	–	1.09 (1.03–1.16)
Carey et al. (2013)	12.9	1.4	10.6[c]	–	1.11 (0.86–1.44)
Hart et al. (2011)	14.1	4	7.8[b]	11.8	1.05 (0.88–1.26)
Lepeule et al. (2012)	15.9	–	–	–	1.37 (1.07–1.75)
Cesaroni et al. (2013)	23.0	4.4	15.8[c]	20.3	1.05 (1.01–1.10)
Beelen et al. (2008)	28.3	2.1	24.8[c]	–	1.06 (0.82–1.38)
Katanoda et al. (2011)	30.5	–	–	–	1.24 (1.12–1.37)
Yin et al. (2017)	40.7	18.6	10.1[c]	–	1.12 (1.09–1.16)
McDonnell et al. (2000)	59.2	16.8	31.6[c]	–	1.39 (0.79–2.46)
Lipsett et al. (2011)	–	–	–	–	0.95 (0.70–1.28)

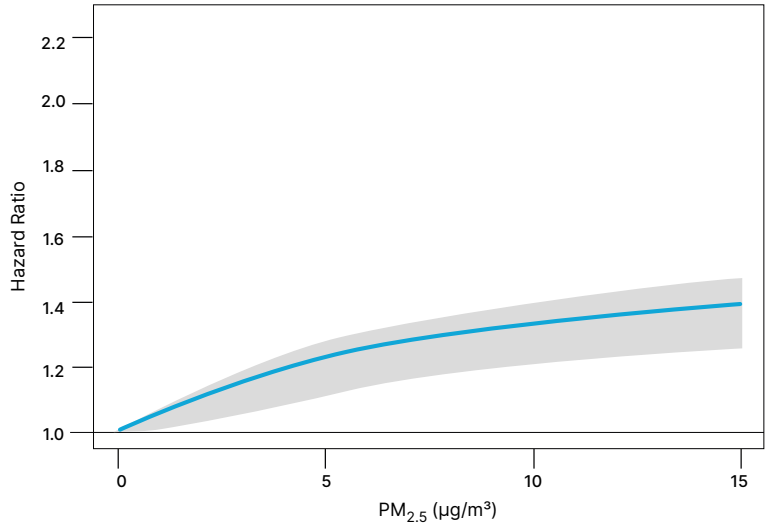
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Fig. 3.1. CRF for long-term $PM_{2.5}$ exposure (µg/m³) and all non-accidental mortality



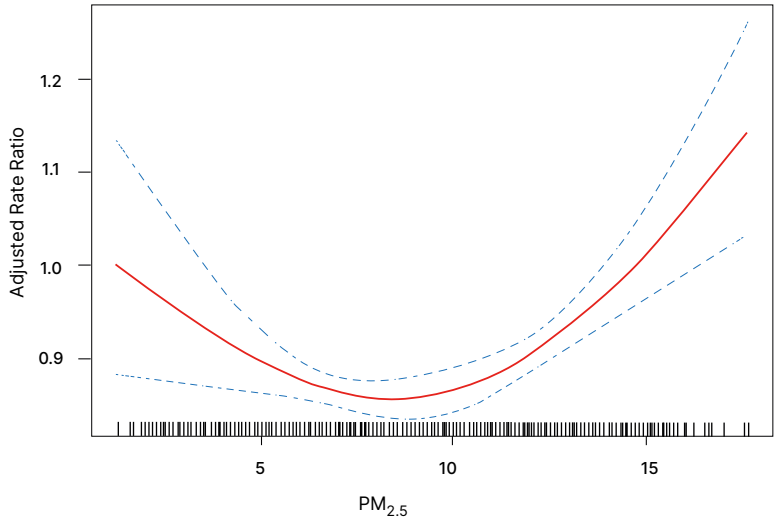
Ln (HR): log HR, with an HR of 1 at a $PM_{2.5}$ concentration of 1 µg/m³.
Source: Pinault et al. (2016).

Fig. 3.2. CRF for long-term $PM_{2.5}$ exposure (µg/m³) and all non-accidental mortality



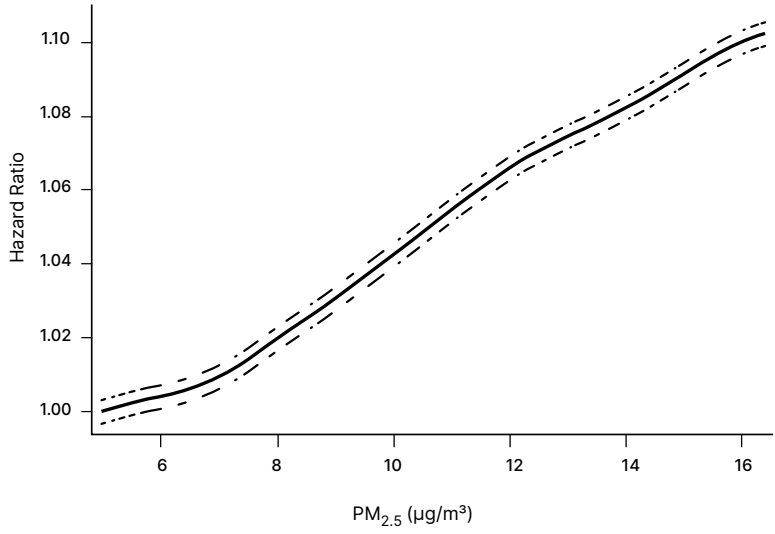
Source: reprinted from Pinault et al. (2017) with permission from Elsevier.

Fig. 3.3. CRF for long-term $PM_{2.5}$ exposure (μg/m³) and all non-accidental mortality



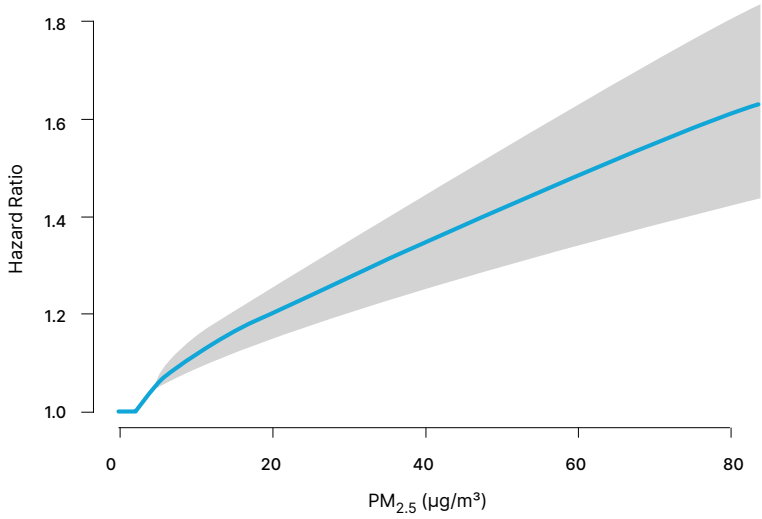
Source: reprinted from Villeneuve et al. (2015) with permission from the publisher. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Fig. 3.4. CRF for long-term $PM_{2.5}$ exposure (μg/m³) and all non-accidental mortality



Source: reprinted from Di et al. (2017a) with permission from the Massachusetts Medical Society. Copyright © 2017 Massachusetts Medical Society.

Fig. 3.5. Association between long-term $PM_{2.5}$ exposure (μg/m³) and mortality from NCDs and lower respiratory illness, as observed in an analysis of data from 41 different cohort studies



Notes: The lowest observed $PM_{2.5}$ concentration was 2.4 μg/m³.
Source: Burnett et al. (2018), Fig. 1.

3.2.3 Recommended AQG level for short-term exposure to $PM_{2.5}$

Based on the methods for deriving an AQG level outlined in the guideline development protocol, this section provides a recommended AQG level for short-term, 24-hour average $PM_{2.5}$ that is based on all-cause non-accidental mortality and cause-specific mortality (Table 3.6).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, as explained in more detail in section 2.4. The review (Orellano et al., 2020) was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating ambient particles to human health.

This section follows the eight steps outlined in the protocol for AQG level development according to scenario 1 for short-term AQG levels (section 2.5.2). Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Orellano et al. (2020) on $PM_{2.5}$ and all-cause non-accidental mortality reported a meta-analytic effect estimate of RR of 1.0065 (95% CI: 1.0044–1.0086) per 10 μg/m³ $PM_{2.5}$, assuming a linear relationship. The certainty of the evidence was considered high according to GRADE. The authors found an indication of a supralinear relationship, suggesting a steeper risk increase at lower exposure levels. CRFs were provided by several studies. Examples show that the associations persist to very low levels of exposure (see Fig. 5A of the original study (Di et al., 2017b) and Fig. 3.6 of this document (taken from Liu et al. (2019)).

Step 2. Determine the lowest level of exposure measured

As discussed in the protocol for deriving AQG levels in section 2.5, the lowest concentrations in time-series studies of the effects of daily variations in air pollution concentrations are often very low. Therefore, the 5th percentiles of these daily distributions cannot be used as starting points for AQG level development. In such cases, the protocol suggests identifying the 99th percentile of common distributions of daily air pollution concentrations corresponding to an average long-term concentration equivalent to the annual AQG level. Thus, it is expected that daily means will be higher than the short-term AQG level not more than three to four times per year once air quality complies with the proposed annual mean AQG level. The proposed annual mean AQG level is 5 μg/m³ for $PM_{2.5}$. Common distributions observed in large numbers of cities around the world (data from Liu et al. (2019)) suggest that the 99th percentiles of daily concentrations are about three times higher than the annual mean $PM_{2.5}$ concentration.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant. For short-term exposures, the linear CRFs from the systematic review by Orellano et al. (2020) were used to calculate the increase in mortality expected on a day with a $PM_{2.5}$ concentration of 15 μg/m³, compared with a day with a $PM_{2.5}$ concentration of 5 μg/m³. With an RR for all non-accidental mortality of 1.0065 per 10 μg/m³, the estimated excess mortality on such a day would be 0.65%. For locations in which concentrations are below the annual mean AQG level, days with such high daily mean concentrations will be rare and most days will have concentrations below the annual mean AQG level. Thus, the health burden related to a few days with higher concentrations corresponds to a very small fraction of the total air pollution-related burden. The GDG notes that at higher concentrations, the CRFs may no longer be linear but sublinear (e.g. see Liu et al. (2019)) so that the excess mortality will be overestimated by using a linear function.

Step 4. Determine the starting point for AQG level determination as the 99th percentile, as mentioned in step 3

The data presented in the previous three steps support a short-term AQG level of no more than 15 µg/m³, based on the association between short-term $PM_{2.5}$ and all-cause non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: cause-specific mortality

The cause-specific mortality outcomes that were investigated all yielded bigger RRs for $PM_{2.5}$ compared with the RR for all-cause mortality, with RRs of 1.0092 (95% CI: 1.0061–1.0123) per 10 µg/m³ for cardiovascular mortality, 1.0073 (95% CI: 1.0029–1.0016) for non-malignant respiratory mortality and 1.0072 (95% CI: 1.0012–1.0132) for cerebrovascular mortality. The certainty of the evidence was rated as high for cardiovascular mortality and moderate for both non-malignant respiratory mortality and cerebrovascular mortality. With these RRs for cause-specific mortality per 10 µg/m³, the estimated excess mortality on such a day would be 0.72–0.92% for $PM_{2.5}$. The same considerations apply as for all-cause non-accidental mortality (as discussed in step 3). The data obtained for cause-specific mortality also support a short-term AQG level of no more than 15 µg/m³ for $PM_{2.5}$.

Step 6. Assess certainty of the evidence

As mentioned in step 1, the certainty of the evidence linking short-term PM concentration variations to short-term mortality variations is high. In addition, as shown in Fig. 5A of Di et al. (2017b), there is evidence that this association persists to very low levels of exposure.

Step 7. Consider new evidence

Several new studies have been published since the autumn of 2018. Only one of these (the 652 cities study by Liu et al. (2019)) is discussed in the systematic review by Orellano et al. (2020). The results of this new, very large study were in line with those of the systematic review. A full search of studies reported since autumn 2018 was not done nor has been reported. As dozens of studies were already included in the systematic review by Orellano et al. (2020) and the Liu et al. (2019) study showed similar results, the GDG does not expect that inclusion of the new studies would change the assessment of the systematic review.

Step 8. Reconsider causality

All PM–outcome associations were deemed to be causal or likely causal in the 2016 outcome prioritization framework (see section 2.3.3). These judgements have not changed in more recent authoritative assessments.

3.2.3.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

The recommendation is a short-term (24-hour) $PM_{2.5}$ AQG level of 15 μg/m³, defined as the 99th percentile (equivalent to 3–4 exceedance days per year) of the annual distribution of 24-hour average concentrations.

The GDG recommends maintaining the 2005 interim targets and introducing an interim target 4 at the level of the 2005 air quality guideline, as shown in Table 3.6.

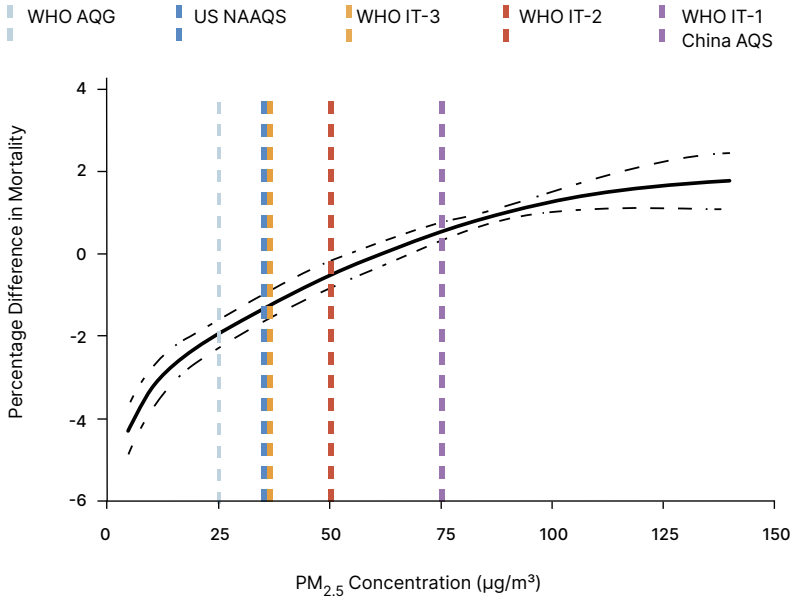
Table 3.6. Recommended short-term (24-hour) AQG level and interim targets for $PM_{2.5}$[a]

Recommendation	$PM_{2.5}$ (μg/m³)
Interim target 1	75
Interim target 2	50
Interim target 3	37.5
Interim target 4	25
AQG level	**15**

[a] Defined as the 99th percentile of the annual distribution of 24-hour average concentrations (equivalent to 3–4 exceedance days per year).

If mortality in a population exposed to $PM_{2.5}$ at the AQG level is arbitrarily set at 100, then it will be 104, 102, 101 and 101, respectively, in populations exposed at $PM_{2.5}$ at interim target 1, 2, 3 and 4 levels. These projections are based on the linear HR of 1.0065 per 10-μg/m³ increase in $PM_{2.5}$ for all non-accidental mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Fig. 3.6. CRF of 24-hour average $PM_{2.5}$ concentrations (μg/m³) and daily all-cause mortality, as observed in a joint analysis of data from 652 cities worldwide[a]



AQG: Air Quality Guidelines; AQS: Air Quality Standard; EU AQD: European Union Air Quality Directive; IT-1: interim target 1; IT-2: interim target 2; IT-3: interim target 3; US NAAQS: United States National Ambient Air Quality Standard.

[a] The y-axis represents the percentage difference from the pooled mean effect on mortality (as derived from the entire range of PM concentrations at each location). Zero on the y-axis represents the pooled mean effect, and the portion of the curve below zero denotes a smaller estimate than the mean effect.

Source: reprinted from Liu et al. (2019) with permission from the Massachusetts Medical Society. Copyright © 2019 Massachusetts Medical Society.

3.3 PM_{10}

3.3.1 Recommended AQG level for long-term exposure to PM_{10}

Based on the methods for deriving an AQG level outlined in the guideline development protocol in Chapter 2, this section provides a recommended AQG level for long-term PM_{10} that is based on non-accidental mortality and cause-specific mortality (Table 3.7).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, as explained in more detail in section 2.4. The review (Chen & Hoek, 2020) was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating ambient particles to human health.

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimate and, when available, CRFs

The systematic review by Chen & Hoek (2020) on PM_{10} and all non-accidental mortality reported a meta-analytic effect estimate of RR = 1.04 (95% CI: 1.03–1.06) per 10 μg/m³ PM_{10}, assuming a linear relationship.

The certainty of the evidence was considered high according to GRADE. Only one study (Fischer et al., 2015) provided a CRF; it concluded that the association between PM_{10} and non-accidental mortality did not deviate significantly from linear (Fig. 3.7).

Step 2. Determine the lowest level of exposure measured

For 13 of the 17 studies included in the meta-analysis, the 5th percentile of the exposure distribution was reported or could be calculated from the reported mean and standard deviation. As the concentration distributions are often lognormal, this calculation is not straightforward. In all cases where a 5th percentile was reported in the paper or obtained from the study authors upon request, the GDG gave preference to that number (see Table 3.8). The five lowest levels reported or estimated in these studies were 13.7 μg/m³ (Beelen et al., 2014), 15.0 μg/m³ (Bentayeb et al., 2015), 15.1 μg/m³ (Puett et al., 2008), 15.9 μg/m³ (Carey et al., 2013) and 16.0 μg/m³ (Hart et al., 2011). The average 5th percentile across the five studies with the lowest concentrations was 15.1 μg/m³. The sum of weights in the meta-analysis was 21% for the lowest five studies, indicating that they made a significant contribution to the effect estimate from the meta-analysis. All of these studies had positive effect estimates with lower confidence limits of 1.00 or more.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant.

Step 4. Determine the starting point for AQG level determination as the long-term concentration of the pollutant from which the minimal relevant amount of the health outcome will result

The average of the five lowest 5th percentile levels measured in these five studies was the starting point for deriving a AQG level: 15.1 μg/m³ PM_{10}.

The data obtained so far support a long-term AQG level of no more than 15 μg/m³, based on the association between long-term PM_{10} and all non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: cause-specific mortality

The RRs estimated by the review of Chen & Hoek (2020) meta-analysis for effects of PM_{10} exposure were 1.06 (95% CI: 1.01–1.10) for IHD, 1.12 (95% CI: 1.06–1.19) for respiratory and 1.08 (95% CI: 1.04–1.13) for lung cancer mortality, all per 10 μg/m³. The certainty of the evidence was considered high for respiratory mortality and lung cancer mortality and moderate for IHD mortality, according to GRADE. For the remaining causes of mortality considered (circulatory, COPD and stroke mortality), the estimates of RR exceeded 1 but with 95% CIs that included 1. Most of the studies addressing cause-specific mortality were based on the same populations as the studies of all non-accidental mortality. For the few studies based on different populations, PM_{10} exposure levels were higher than in those used to derive the starting point for AQG level. Therefore, there is no evidence from cause-specific mortality studies supporting a decrease of the AQG level below that suggested by all non-accidental cause mortality studies.

Step 6. Assess certainty of the evidence

None of the studies that reported the lowest levels measured in the studies of all non-accidental mortality were considered at high RoB; thus, there is no reason to change the AQG level because of low certainty of the evidence in the lowest level studies.

Step 7. Consider new evidence

Two new studies were published between autumn 2018 and the summer of 2020 (Fischer et al., 2020; Hvidtfeldt et al., 2019). They are discussed in Chen & Hoek (2020). The effect estimates for PM_{10} (RR = 1.12 (95% CI: 1.09–1.14) and RR = 1.12 (95% CI: 1.03–1.22) respectively) were higher in those studies than the estimates from the meta-analysis of earlier studies, but the PM_{10} exposure levels were higher than those in the studies selected to support the derivation of the AQG level. Therefore, this new evidence does not change the recommended AQG level for long-term PM_{10} concentrations.

Step 8. Reconsider causality

All PM–outcome associations were deemed to be causal or likely causal in the 2016 outcome prioritization framework (see section 2.3.3). These judgements have not changed in more recent authoritative assessments. For more details, see Table 2.1 in section 2.3.3.

The 5th percentile and mean or median of the exposure distributions in studies on PM_{10} and mortality meta-analysis is indicated in Table 3.8 based on data from the systematic review by Chen & Hoek (2020).

3.3.1.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

The recommendation is an annual PM_{10} AQG level of 15 µg/m³. This is based on an evaluation of the studies on the long-term effects of PM_{10} on mortality only, without taking into consideration that a large proportion of PM_{10} is made up of $PM_{2.5}$. As in most situations $PM_{2.5}$ is about 50–80% of PM_{10} by weight, the annual PM_{10} AQG level of 15 µg/m³ is less protective than the annual AQG level for $PM_{2.5}$. In all situations where both $PM_{2.5}$ and PM_{10} measurements are available, preference should be given to the $PM_{2.5}$ AQG level.

The GDG recommends maintaining the 2005 interim targets and introducing an interim target 4 at the level of the 2005 air quality guideline, as shown in Table 3.7.

Table 3.7. Recommended annual mean AQG level and interim targets for PM_{10}

Recommendation	PM_{10} (µg/m³)
Interim target 1	70
Interim target 2	50
Interim target 3	30
Interim target 4	20
AQG level	**15**

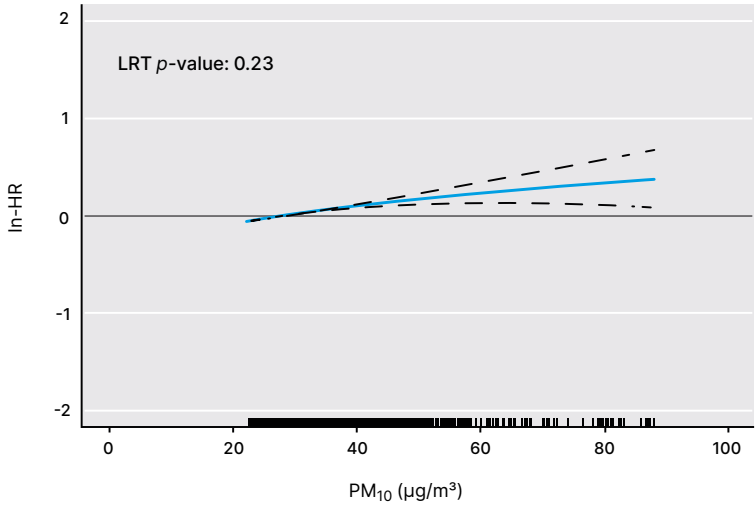
If mortality in a population exposed to PM_{10} at the AQG level were arbitrarily set at 100, then it will be 122, 114, 106 and 102, respectively, in populations exposed to PM_{10} at the interim target 1, 2, 3 and 4 levels. These projections are based on the linear HR of 1.04 per 10-µg/m³ increase in PM_{10} for all non-accidental mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Table 3.8. Studies on long-term PM_{10} exposure and all non-accidental mortality included in the systematic review by Chen & Hoek (2020), ordered by me(di)an concentration

Study	Me(di)an (µg/m³)	SD	P5	P25	HR (95% CI)[a]
Carey et al. (2013)	19.7	2.3	15.9[b]	–	1.07 (1.00–1.14)
Hansell et al. (2016)[c]	20.7	2.5	16.5[b]	–	1.24 (1.15–1.32)
Beelen et al. (2014)	20.9	–	13.7[b]	17.1	1.04 (1.00–1.09)
Puett et al. (2008)	21.6	4.3	15.1[b]	–	1.16 (1.05–1.28)
Bentayeb et al. (2015)	25.0	5.5	15.0[b]	–	1.18 (1.06–1.32)
Hart et al. (2011)	26.8	6.0	16.0[b]	–	1.07 (1.02–1.11)
Puett et al. (2011)	27.9	5.8	19.1[b]	–	0.92 (0.84–0.99)
Dockery et al. (1993)	28.9	–	–	–	1.09 (1.03–1.15)
Fischer et al. (2015)	29.0	–	24.0[b]	–	1.08 (1.07–1.09)
Lipsett et al. (2011)	29.2	9.7	18.2[b]	–	1.00 (0.97–1.04)
Ueda et al. (2012)	34.9	–	–	–	0.98 (0.92–1.04)
Badaloni et al. (2017)	36.6	5.1	28.2[d]	–	1.02 (1.01–1.03)
Heinrich et al. (2013)	43.7	–	–	39.8	1.22 (1.06–1.41)
Abbey et al. (1999)	51.2	16.6	23.9[d]	–	1.01 (0.94–1.08)
Kim, Kim & Kim (2017)	56.0	6.5	45.3[d]	–	1.05 (0.99–1.11)
Zhou et al. (2014)	104.0	–	–	–	1.02 (1.01–1.03)
Chen et al. (2016)	144.0	3.6	–	126.0	1.01 (1.01–1.01)

–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Reported in paper or by authors.
[c] Study classified as having high RoB due to potentially insufficient control for confounding.
[d] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Fig. 3.7. Estimated concentration–response curve for non-accidental mortality and annual PM_{10} exposure (μg/m³)



ln: natural logarithm; LRT: likelihood ratio test.
Note: Solid blue line: estimated concentration–response curve; dashed lines: 95% CIs.
Source: reproduced from Fischer et al. (2015) with the permission of the lead author.

3.3.2 Recommended AQG level for short-term exposure to PM_{10}

Based on the methods for deriving an AQG level outlined in the guideline development protocol in Chapter 2, this section provides a recommended AQG level for short-term, 24-hour average PM_{10} that is based on all-cause non-accidental mortality and cause-specific mortality (Table 3.9).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, as explained in more detail in section 2.4. The review (Orellano et al., 2020) was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating ambient particles to human health.

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Orellano et al. (2020) on PM_{10} and all-cause non-accidental mortality reported a meta-analytic effect estimate of RR = 1.0041 (95% CI: 1.0034–1.0049) per 10 μg/m³ PM_{10}, assuming a linear relationship. The evidence was considered to be of high certainty according to GRADE. The authors found an indication of a supralinear relationship, suggesting a steeper risk increase at lower exposure levels. In contrast to $PM_{2.5}$, no individual studies published graphical representations of CRFs.

Step 2. Determine the lowest level of exposure measured

As discussed in the protocol for deriving AQG levels, the lowest concentrations in time-series studies of effects of daily variations in air pollution concentrations are often very low. Therefore, the 5th percentiles of these daily distributions cannot be used as starting points for AQG level development. In such cases, the protocol suggests identifying the 99th percentile of common distributions of daily air pollution concentrations corresponding to an average long-term concentration equivalent to the annual AQG level. Thus, once the air quality complies with the proposed annual mean AQG level, daily means would be expected to be higher than the short-term AQG level not more than three to four times per year. The proposed annual mean AQG level is 15 μg/m³ for PM_{10}. Common distributions observed in large numbers of cities around the world (data from Liu et al. (2019)) suggest that the 99th percentiles of daily concentrations are about three times higher than the annual mean PM_{10} concentration.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant. For short-term exposures, the CRFs from the systematic review by Orellano et al. (2020) were used to calculate the increase in mortality expected on a day with a PM_{10} concentration of 45 μg/m³ compared with a day with a PM_{10} concentration of 15 μg/m³. With an RR for all-cause mortality of 1.0041 per 10 μg/m³, the estimated excess mortality on such a day would be 1.23%. Under compliance with the annual mean AQG level, days with such high daily mean concentrations will be rare and most days will have concentrations below the annual mean AQG level. Thus, the health burden related to a few days with higher concentrations corresponds to a very small fraction of the total air pollution-related burden.

Step 4. Determine the starting point for AQG level determination as the 99th percentile, as mentioned in step 3

The data obtained support a short-term AQG level of no more than 45 μg/m³, based on the association between short-term PM_{10} and all-cause non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: cause-specific mortality

All cause-specific mortality outcomes that were investigated yielded slightly bigger RRs for PM_{10} compared with the RR for all-cause mortality. The certainty of the evidence was rated as high for cardiovascular mortality and moderate for cerebrovascular mortality and non-malignant respiratory mortality. The data obtained for cause-specific mortality also support a short-term AQG level of no more than 45 μg/m³ for PM_{10}.

Step 6. Assess certainty of the evidence

As mentioned in step 1, the evidence linking short-term PM concentration variations to short-term mortality variations was of high certainty.

Step 7. Consider new evidence

The GDG noted that several new time-series studies, almost all from Asia, were published after the inclusion deadline of September 2018. A full search of studies reported since autumn 2018 was not done or has not been reported. As dozens of studies were already included in the systematic review by Orellano et al. (2020), the GDG did not expect that inclusion of new studies would change the assessment of the systematic review.

Step 8. Reconsider causality

All PM–outcome associations were deemed to be causal or likely causal in the 2016 outcome prioritization framework (see section 2.3.3). These judgements have not changed in more recent authoritative assessments.

3.3.2.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

The recommendation is a short-term (24-hour) PM_{10} AQG level of 45 μg/m³, defined as the 99th percentile (equivalent to three to four exceedance days per year) of the annual distribution of 24-hour average concentrations.

The GDG recommends maintaining the 2005 interim targets and introducing an interim target 4 at the level of the 2005 air quality guideline, as shown in Table 3.9.

Table 3.9. Recommended short-term (24-hour) AQG level and interim targets for PM_{10}[a]

Recommendation	PM_{10} (μg/m³)
Interim target 1	150
Interim target 2	100
Interim target 3	75
Interim target 4	50
AQG level	**45**

[a] Defined as the 99th percentile of the annual distribution of 24-hour average concentrations (equivalent to 3–4 exceedance days per year).

If mortality in a population exposed to PM_{10} at the AQG level is arbitrarily set at 100, then it will be 104, 102, 101 and 100.2, respectively, in populations exposed to PM_{10} at the interim target 1, 2, 3 and 4 levels. These projections are based on the linear HR of 1.0041 per 10-μg/m³ increase in PM_{10} for all non-accidental mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

3.4 Ozone

3.4.1 General description

The general description comes from *Global update 2005*.

> Ozone (O_3) and other photochemical oxidants are pollutants that are not directly emitted by primary sources. Rather, they encompass a group of chemical species formed through a series of complex reactions in the atmosphere driven by the energy transferred to nitrogen dioxide (NO_2) molecules when they absorb light from solar radiation ….
>
> The precursors that contribute most to the formation of oxidant species in polluted atmospheres are nitrogen dioxide and non-methane volatile organic compounds (VOCs), especially unsaturated VOCs. Methane is much less reactive than the other VOCs but is present at much higher concentrations, having risen in concentration over the past 100 years owing to its increasing use as fuel, and is released from rice fields and farm animals. Photochemistry involving methane accounts for much of the rise in ozone over the oceans and remote land areas, from about 30 μg/m³ to about 75 μg/m³ (WHO Regional Office for Europe, 2006).

Conversion factors for ozone: at 20 °C and 1013 hPa, 1 part per million (ppm) = 1.9957 mg/m³ and 1 mg/m³ = 0.5011 ppm.

3.4.2 Recommended AQG level for long-term exposure to ozone

Based on the methods for deriving an AQG level outlined in the guideline development protocol, this section provides an AQG level for long-term, peak-season ozone that is based on all non-accidental mortality and respiratory mortality (Table 3.10).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, as explained in more detail in section 2.4. The review (Huangfu & Atkinson, 2020) was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating ambient ozone to human health.

The long-term AQG level for ozone is linked to the so-called peak-season exposure. Peak season is defined as the six consecutive months of the year with the highest six-month running-average ozone concentration. In regions away from the equator, this period will typically be in the warm season within a single calendar year (northern hemisphere) or spanning two calendar years (southern hemisphere). Close to the equator, such clear seasonal patterns may not be obvious, but a running-average six-month peak season will usually be identifiable from existing monitoring or modelling data.

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Huangfu & Atkinson (2020) on ozone and all non-accidental mortality reported a meta-analytic effect estimate of RR = 1.01 (95% CI: 1.00–1.02) per 10 μg/m³ increase in peak-season average of daily maximum 8-hour mean ozone concentrations, assuming a linear relationship. For ozone, it is customary to calculate daily maximum of 8-hour mean concentrations rather than 24-hour averages because of the strong diurnal variation in ozone concentration. In most of the quoted studies, peak season was defined as the warm season, that is, the warmest five or six months of the year, for example May–September in studies from Canada and April–September in several of the studies from the

United States. The certainty of the evidence was considered moderate according to GRADE. CRFs were provided in one study (Di et al., 2017a), which documented a linear function starting from the 5th percentile of the observed warm-season concentrations of about 60 μg/m³ (Fig. 3.8). From the series of Canadian Census Health and Environment Cohort (CanCHEC) studies, the more recent Cakmak et al. (2018) study was included instead of the earlier study by Crouse et al. (2015), which did document a monotonic dose–response relationship (Fig. 3.9).

Step 2. Determine the lowest level of exposure measured

For all seven studies included in the meta-analysis, a 5th percentile of the exposure distribution was reported or could be calculated from the reported mean and standard deviation. As the concentration distributions are often lognormal, this calculation is not straightforward. Therefore, in most cases it was replaced by actual reports of the relevant numbers obtained from the study authors (for details, see Table 3.11 and Table 3.12). The three lowest 5th percentile concentrations reported or estimated in these studies were the peak-season averages of 55 μg/m³ (Weichenthal, Pinault & Burnett, 2017), 56 μg/m³ (Cakmak et al., 2018) and 68 μg/m³ (Di et al., 2017a). The study by Weichenthal, Pinault & Burnett (2017) was considered in the systematic review to be at high RoB. If this study is ignored, then the next lowest 5th percentile concentration was 68 μg/m³ (Lipsett et al., 2011). The average of the three lowest 5th percentile values is either approximately 60 or 64 μg/m³ (depending on whether or not the study by Weichenthal, Pinault & Burnett (2017) is included). Three of these four studies found statistically significant positive associations between ozone and all non-accidental mortality. The sum of weights of these four studies in the meta-analysis was well over 60%.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant.

Step 4. Determine the starting point for AQG level determination as the long-term concentration of the pollutant from which the minimal relevant amount of the health outcome will result

Thus, the average of the three lowest 5th percentile levels measured in these studies was the starting point for deriving an AQG level: 60 μg/m³ ozone, based on the average concentrations of either 60 μg/m³ or 64 μg/m³. The data obtained support a long-term, peak-season AQG level of no more than 60 μg/m³, based on the association between long-term ozone and all non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: respiratory mortality

The other outcome that was investigated was respiratory mortality, which yielded a bigger RR for peak-season ozone, compared with the RR for all non-accidental mortality, with an RR of 1.02 (95% CI: 0.99–1.05) per 10 μg/m³. The certainty of the evidence, however, was rated low for non-malignant respiratory mortality because the prediction interval of 0.96–1.08 included unity and was exactly twice the meta-analytic 95% CI. For an explanation of the prediction interval, see section 2.4.4. In addition, because none of the studies had explicitly considered the shape of the CRF, no upgrade was applied for dose–response. Table 3.12 shows the findings for non-malignant respiratory mortality. The starting points for AQG level determination for this additional health outcome would not be further supported by including respiratory mortality, although three of the four studies are included in the all non-accidental mortality analysis and the fourth is on the same cohort as all-cause mortality (Crouse et al. (2015) versus Cakmak et al. (2018)). For further discussion, see step 7.

Step 6. Assess certainty of the evidence

The certainty of the evidence was rated as moderate for non-accidental mortality and low for respiratory mortality. One of the studies that made up the lowest levels measured in all non-accidental mortality studies (Weichenthal, Pinault & Burnett, 2017) was considered at high RoB, so the GDG calculated the starting point for AQG level determination with and without that study, as previously mentioned.

Step 7. Consider new evidence

Several new studies were published between autumn 2018 and the summer of 2020. The systematic review discussed these but did not include them in the assessment, so the GDG made its own assessment of these studies. These new studies are largely the same as those identified and included in the revision of the systematic review of long-term PM effects on mortality (Chen & Hoek, 2020). Table 3.13 shows these studies, ordered by mean or median exposure level for all non-accidental mortality. These include two studies from Canada (Brauer et al., 2019; Pappin et al., 2019) and three new studies from the United States (Lefler et al., 2019; Lim et al., 2019; Kazemiparkouhi et al., 2020). Two of the five were administrative database studies with no adjustment (Brauer et al., 2019) or with area-level adjustment (Kazemiparkouhi et al., 2020) for lifestyle factors such as smoking. The other three were cohort studies with adequate information on lifestyle covariates. Adding these studies to the meta-analysis produced an HR of 1.013 (95% CI: 1.002–1.023) for non-accidental mortality. The effect estimate from the systematic review was 1.01 (95% CI: 1.00–1.02; see step 1).

The Kazemiparkouhi et al. (2020) study was based on 1-hour maximum concentrations, not 8-hour maximum concentrations. The 8-hour maximum concentrations usually correlate very highly with the 1-hour maximum concentrations but are 10–40% lower. Therefore, in principle, one would expect effect estimates expressed over the same concentration range to be somewhat higher when using 8-hour maximum concentrations as the denominator. However, a large study from Europe (Gryparis et al., 2004) found no difference in effect estimates based on 1-hour versus 8-hour maximum concentrations and expressed over the same concentration range. Therefore, the GDG did not change the effect estimate from the Kazemiparkouhi et al. (2020) study. Adding these studies to the meta-analysis produced an HR of 1.013 (95% CI: 1.006–1.021) and a prediction interval of 0.997–1.030. For an explanation of the prediction interval, see section 2.4.4. Note that this prediction interval includes unity and is slightly larger than twice the HR 95% CI, so this would justify a downgrade of the certainty of evidence due to inconsistency. As argued before, the GDG finds the evidence of dose–response sufficient for an upgrade of certainty, so that the net result for the association between peak-season ozone and non-accidental mortality would be moderate certainty.

Two cohort studies also reported effect estimates for respiratory mortality (Table 3.14). Adding these studies to the meta-analysis produced an HR for respiratory mortality of 1.023 (95% CI: 1.007–1.038) with a prediction interval of 0.993–1.053. As this prediction interval is less than twice the meta-analytic 95% CI, there is no need to downgrade the certainty of the evidence due to inconsistency. The effect estimate from the systematic review was an RR of 1.02 (95% CI: 0.99–1.05) per 10 μg/m³. In addition, as Fig. 3.10 shows, one of the new studies (Lim et al., 2019) supports a dose–response for respiratory mortality down to slightly less than 60 μg/m³.

The GDG notes that these very recent studies almost doubled the number of studies available for inclusion. If they had been part of the review, the AQG level starting point based on the three lowest 5th percentile values, excluding the studies at high RoB, would be even somewhat lower, at (50 + 56 + 62) / 3 = 56 μg/m³. There is no reason, based on these new findings, to change the proposed long-term AQG level.

Step 8. Reconsider causality

The long-term ozone-outcome associations were deemed to be likely causal (for respiratory effects) or suggestive of being causal (for total mortality) in the 2016 outcome prioritization framework (see section 2.3.3). These judgements were primarily based on the 2013 US EPA ISA of ozone (US EPA, 2013) and a 2013 Health Canada report (Health Canada, 2013). The 2020 EPA ISA (US EPA,

2020) did not change these classifications. As discussed in step 7 and shown in Table 3.13 and Table 3.14, a number of very recent studies have provided further support for associations between long-term ozone concentrations and both total and respiratory mortality.

The 5th percentile and mean or median of exposure distributions in studies in the ozone and mortality meta-analyses are shown in Table 3.11 and Table 3.12 based on data from the systematic review by Huangfu & Atkinson (2020) and in Table 3.13 and Table 3.14 for the new studies that were identified.

3.4.2.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

Interim targets were not specified for long-term ozone in *Global update 2005*. The GDG recommends a peak-season average ozone concentration of 100 μg/m³ as interim target 1, as this is a level already shown to be achievable in many parts of the world. As interim target 2, a concentration of 70 μg/m³ is proposed; this is the threshold in the widely used SOMO35 metric. SOMO35 is the accumulated ozone concentration (daily maximum 8-hour mean) in excess of 35 parts per billion (ppb; equivalent to 70 μg/m³) (EEA, 2020).

The recommendation is a peak season ozone AQG level of 60 μg/m³ (the average of daily maximum 8-hour mean ozone concentrations). The peak season is defined as the six consecutive months of the year with the highest six-month running-average ozone concentration. In regions away from the equator, this period will typically be in the warm season within a single calendar year (northern hemisphere) or spanning two calendar years (southern hemisphere). Close to the equator, such clear seasonal patterns may not be obvious, but a running-average six-month peak season will usually be identifiable from existing monitoring or modelling data.

An interim target 1 of 100 μg/m³ and an interim target 2 of 70 μg/m³ are proposed, as shown in Table 3.10.

If mortality in a population exposed to ozone at the AQG level is arbitrarily set at 100, then it will be 104 and 101, respectively, in populations exposed to ozone at the interim target 1 and 2 levels. These projections are based on the linear HR of 1.01 per 10-μg/m³ increase in ozone of all non-accidental mortality reported in the systematic review. For respiratory mortality, the numbers will be 108 and 102, respectively, at the interim target 1 and 2 levels, based on the linear HR of 1.02 of respiratory mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Table 3.10. Recommended peak season[a] AQG level and interim targets for ozone

Recommendation	O_3 (μg/m³)
Interim target 1	100
Interim target 2	70
AQG level	**60**

[a] Average of daily maximum 8-hour mean O_3 concentration in the six consecutive months with the highest six-month running-average O_3 concentration.

Table 3.11. Studies on peak-season, long-term ozone exposure and all non-accidental mortality included in the systematic review by Huangfu & Atkinson (2020), ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Weichenthal, Pinault & Burnett (2017)[b]	76.6	–	55.2[c]	67.3	1.0290 (1.024–1.033)
Cakmak et al. (2018)	78.4	13.4	56.4[d]	–	1.0400 (1.010–1.070)
Di et al. (2017a)	90.0	14.0	68.0[c]	–	1.0115 (1.011–1.012)
Turner et al. (2016)	94.2	11.8	71.4[c]	88.4	1.0100 (1.010–1.015)
Lipsett et al. (2011)	96.2	17.4	67.6[d]	–	0.9900 (0.990–1.000)
Bentayeb et al. (2015)	101.0	8.5	87.0[d]	–	0.9800 (0.900–1.060)
Lipfert et al. (2006)	173.4	18.6	142.8[d]	–	1.0000 (0.990–1.020)

–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Considered to be at high RoB.
[c] Reported in paper or by authors on request.
[d] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Table 3.12. Studies on peak-season, long-term ozone exposure and respiratory mortality included in the systematic review by Huangfu & Atkinson (2020), ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Weichenthal, Pinault & Burnett (2017)[b]	76.6	–	55.2[c]	67.3	1.020 (1.006–1.035)
Crouse et al. (2015)	78.0	–	56.0[d]	68.6	0.985 (0.975–0.994)
Turner et al. (2016)	94.2	11.8	71.4[c]	88.4	1.05 (1.035–1.060)
Lipsett et al. (2011)	96.2	17.4	67.6[e]	–	1.02 (0.990–1.040)

–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Considered to be at high RoB.
[c] Reported in paper or by authors on request.
[d] Similar distribution assumed as in the paper by Weichenthal, Pinault & Burnett (2017), based on the same CanCHEC cohort.
[e] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Table 3.13. New studies on peak-season, long-term ozone exposure and all non-accidental mortality published since autumn 2018, ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Brauer et al. (2019) – CanCHEC subjects	72.0	15.0	52.3[b]	–	1.036 (1.034–1.036)
Brauer et al. (2019) – CCHS subjects	72.0	15.0	50.0[b]	–	1.025 (1.015–1.035)
Lim et al. (2019)	92.4	15.2	62.3[b]	–	1.000 (0.995–1.005)
Lefler et al. (2019)	94.9	10.6	77.5[c]	–	1.016 (1.010–1.022)
Kazemiparkouhi et al. (2020)	110.0	–	–	100.0	1.006 (1.006–1.007)

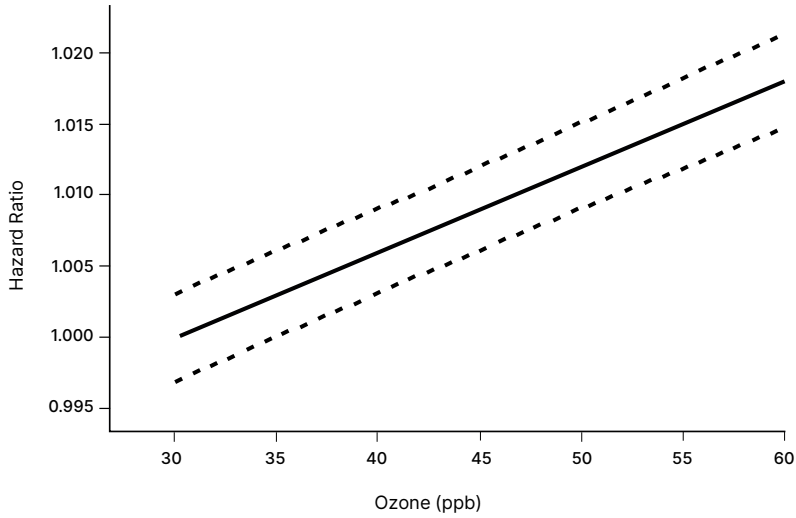
–, data unavailable; CCHS: Canadian Community Health Survey; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Table 3.14. New studies on peak-season, long-term ozone exposure and respiratory mortality published since autumn 2018, ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Lim et al. (2019)	92.4	15.2	62.3[b]	–	1.040 (1.020–1.060)
Kazemiparkouhi et al. (2020)	110.0	–		100.0	1.018 (1.016–1.020)

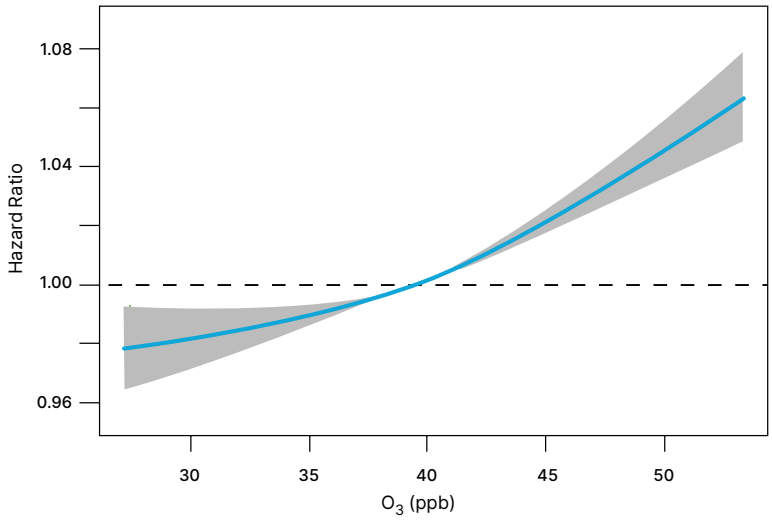
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.

Fig. 3.8. Association between peak-season, long-term ozone exposure (ppb) and all non-accidental mortality[a]



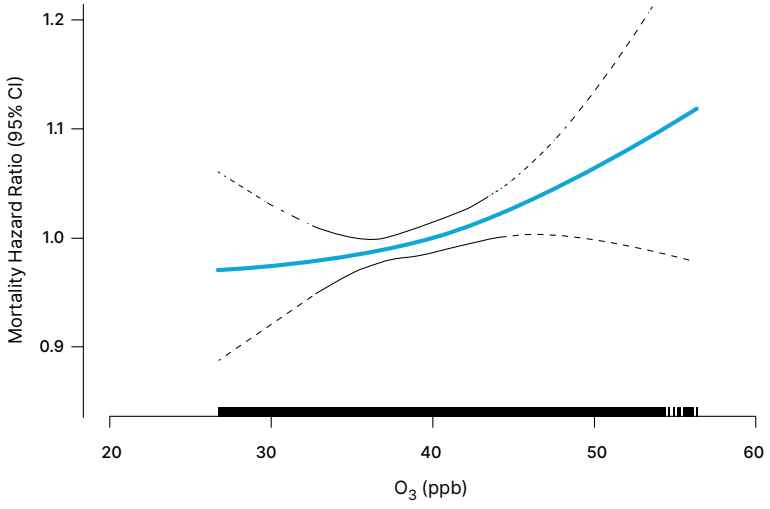
[a] Note that the units for ozone are in ppb; these need to be multiplied by 2 to arrive at concentrations expressed in μg/m³. HR is expressed relative to the 5th percentile of the distribution of ozone concentrations, which was 30 ppb. *Source:* reprinted from Di et al. (2017a) with permission from the Massachusetts Medical Society. Copyright © 2017 Massachusetts Medical Society.

Fig. 3.9 The association between peak-season, long-term ozone exposure (ppb) and all-cause mortality[a]



[a] Note that the units for ozone are in ppb; these need to be multiplied by 2 to arrive at concentrations expressed in μg/m³. HRs are expressed relative to the mean ozone concentration of 39.6 ppb.
Source: reproduced from Crouse et al. (2015) with permission of the lead author.

Fig. 3.10 The association between peak-season, long-term ozone exposure (ppb) and respiratory mortality[a]



[a] Note that the units for ozone are in ppb; these need to be multiplied by 2 to arrive at concentrations expressed in μg/m³. HRs are expressed relative to the mean ozone concentration of 46.2 ppb.
Source: adapted from Lim et al. (2019) with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. All rights reserved. Note that the authors, editors and the American Thoracic Society are not responsible for errors or omissions in adaptations.

3.4.3 Recommended AQG level for short-term exposure to ozone

Based on the methods for deriving an AQG level outlined in the guideline development protocol, this section provides an AQG level for short-term, daily maximum 8-hour average ozone that is based on all-cause non-accidental mortality (Table 3.15).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, as explained in more detail in section 2.4. The review (Orellano et al., 2020), was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating ozone to human health. However, comprehensive evaluations by authoritative bodies such Health Canada, the United Kingdom's Committee on Medical Effects of Air Pollution and US EPA were taken into account in the development of the AQG levels. This was especially relevant when assessing causality of the associations examined in the systematic reviews (see step 8).

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Orellano et al. (2020) on ozone and all-cause non-accidental mortality reported a meta-analytic effect estimate of RR = 1.0043 (95% CI: 1.0034–1.0052) per 10 μg/m³ ozone, assuming a linear relationship. This effect estimate is for 8-hour maximum concentrations. The certainty of the evidence was considered high according to GRADE. CRFs were provided by several studies. Many studies have found that associations persisted at daily levels of 100 μg/m³ ozone or lower. An example is provided in Fig. 5B of the original study (Di et al., 2017b), which was a very large study conducted in the United States of the entire Medicare population. Another example is from the multicity study by Vicedo-Cabrera et al. (2020), which was published after the systematic review search was completed (Fig. 3.11). This was a worldwide study combining evidence from 406 locations in 20 countries.

Step 2. Determine the lowest level of exposure measured

As discussed in the protocol for deriving AQG levels, the lowest concentrations in time-series studies of effects of daily variations in air pollution concentrations are often very low.

Therefore, the 5th percentiles of these daily distributions cannot be used as starting points for AQG level development.

In such cases, the protocol suggests identifying the 99th percentile of common distributions of daily air pollution concentrations corresponding to an average long-term concentration equivalent to the annual AQG level. The proposed long-term AQG level is 60 μg/m³ for ozone, as a warm-season average of daily maximum 8-hour concentrations. Common distributions observed in large numbers of cities around the world (data from Vicedo-Cabrera et al. (2020)) suggest that the 99th percentiles of daily concentrations are on average 2.05 (rounded to 2) times higher than the annual mean ozone concentrations. However, the long-term AQG level for ozone is for a peak-season average, which is always higher than the annual average. Note that the definitions of peak season and warm season vary slightly from study to study, sometimes restricted to the three summer months, sometimes using the (northern hemisphere) May–September period. A study from the United States (Turner et al., 2016) observed an annual mean of modelled daily 8-hour maximum ozone concentrations of 76.4 μg/m³ and a warm-season mean of 94.2 μg/m³ (ratio of 1.23). A very large database from Europe documented a ratio of 1.24 based on actual ozone measurements (de Hoogh et al., 2018). Therefore, using this ratio, the chosen peak-season AQG level of 60 μg/m³ corresponds to an annual mean of 48.7 μg/m³. Calculating the short-term AQG level using a ratio of 2 between the 99th percentile and annual mean produced a value of 120 μg/m³, and dividing that number by the 1.24 ratio of the peak (warm) season to annual average concentrations produced a value of 97 μg/m³, which was rounded up to a proposed short-term AQG level of 100 μg/m³.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant. For short-term exposures, the CRFs from the systematic review by Orellano et al. (2020) were used to calculate the increase in mortality expected on a day with an 8-hour maximum ozone concentration of 100 μg/m³ compared with a day with an 8-hour maximum ozone concentration of 60 μg/m³. With an RR for all-cause mortality of 1.0043 per 10 μg/m³, the estimated excess mortality on such a day would be 1.72%. However, under compliance with the long-term peak-season AQG level, days with concentrations close to 100 μg/m³ will correspond to the far upper tail of the distribution of daily exposures. Most days will have much lower values and almost half will have concentrations below or far below the peak-season AQG level. The health burden related to a few days with higher concentrations corresponds to a very small fraction of the total air pollution-related burden.

Step 4. Determine the starting point for AQG level determination as the 99th percentile, as mentioned in step 3

The data obtained support a short-term AQG level of no more than 100 μg/m³, based on the association between short-term ozone and all-cause non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: cause-specific mortality and asthma hospital admissions and emergency room visits

Studies on short-term associations and cause-specific mortality were not reviewed. However, another systematic review assessed the evidence for associations between ozone and daily hospital and emergency room admissions for asthma (Zheng et al., 2021). The review found an effect estimate of RR = 1.012 (95% CI: 1.008–1.016) per 10 μg/m³, which would produce an excess morbidity of 4.8% for a day at the proposed short-term AQG level of 100 μg/m³ compared with a day at the proposed long-term AQG level of 60 μg/m³. As mentioned in step 3, such days will be rare events under compliance with the peak-season long-term AQG level; thus, the short-term burden due to the few days with higher values is relatively small.

Step 6. Assess certainty of the evidence

As mentioned in step 1, the certainty level is high for evidence linking short-term ozone concentration variations to short-term mortality variations. In addition, as shown in Fig. 5B of Di et al. (2017b) and Fig. 3.11, there is evidence that this association persists to very low levels of exposure.

Step 7. Consider new evidence

Several new studies have been published since autumn 2018. Of note is the very large study conducted by Vicedo-Cabrera et al. (2020). This study reported an effect estimate of RR = 1.0018 (95% CI: 1.0012–1.0024) per 10 μg/m³, which is considerably lower than the RR of 1.0043 reported by Orellano et al. (2020). Whereas this new effect estimate would lower the estimated excess mortality at the proposed short-term AQG level, it would not change the proposed AQG level because this was calculated according to the methods explained in section 2.5.

Step 8. Reconsider causality

The association between short-term ozone concentrations and all-cause mortality was judged as likely causal in the 2016 outcome prioritization framework (see section 2.3.3). This judgement was changed in the US EPA ISA of 2020 to suggestive of a causal relationship. A discussion of these changes is provided in section 2.5 of this report. The relationship between short-term ozone and respiratory effects (including mortality) was classified as causal.

As mentioned in step 7, new results from a very large worldwide study (Vicedo-Cabrera et al., 2020) provide further support for an association between short-term ozone and all-cause mortality. The GDG judged it prudent to propose a short-term AQG level for ozone, also in view of the large proportions of the world population exposed to relatively high ozone concentrations and the prospect that concentrations may go up rather than down as a result of climate change.

3.4.3.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

The recommendation is a short-term daily maximum 8-hour ozone AQG level of 100 µg/m³, defined as the 99th percentile (equivalent to three to four exceedance days per year) of the annual distribution of daily maximum 8-hour average concentrations.

An interim target 1 of 160 µg/m³ is retained from *Global update 2005*. An interim target 2 of 120 µg/m³ is also proposed, as shown in Table 3.15.

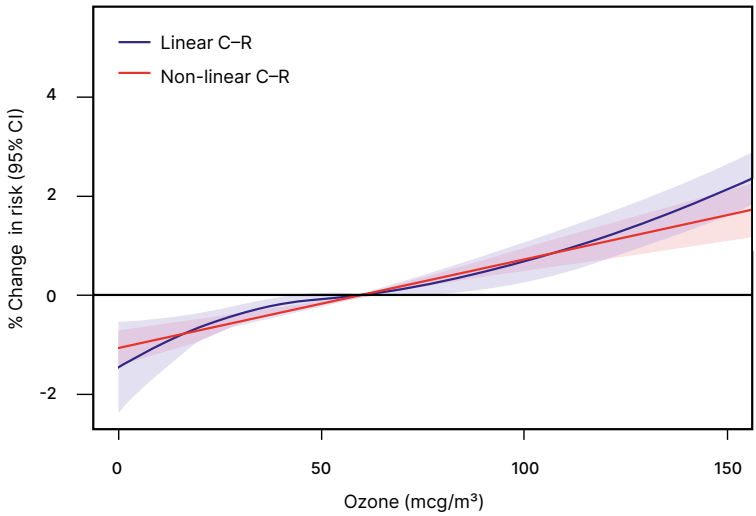
Table 3.15. Recommended short-term (8-hour) daily maximum AQG level and interim targets for ozone[a]

Recommendation	O_3 (µg/m³)
Interim target 1	160
Interim target 2	120
AQG level	**100**

[a] Defined as the 99th percentile of the annual distribution of daily maximum 8-hour average concentrations (equivalent to 3–4 exceedance days per year).

If mortality in a population exposed, on a given day, to ozone at the AQG level is arbitrarily set at 100, then it will be 103 and 101, respectively, in populations exposed, on a given, high pollution day to ozone at the interim target 1 and 2 levels. These projections are based on the linear HR of 1.0043 per 10-µg/m³ increase in ozone for all non-accidental mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Fig. 3.11. Exposure–response curve for 8-hour ozone exposure (μg/m³) and all-cause mortality[a]



C–R: concentration–response.
[a] The change in risk is expressed relative to a mean ozone concentration of about 60 μg/m³.
Source: Vicedo-Cabrera et al. (2020).

3.5 Nitrogen dioxide

3.5.1 General description

The general description comes from *Global update 2005*.

> Many chemical species of nitrogen oxides exist, but the air pollutant species of most interest from the point of view of human health is nitrogen dioxide. Nitrogen dioxide is a reddish brown gas with a characteristic pungent odour. Nitric oxide spontaneously produces the dioxide when exposed to air. Nitrogen dioxide gas is a strong oxidant, and reacts with water to produce nitric acid and nitric oxide.
>
> Nitrogen dioxide is an important atmospheric trace gas not only because of its health effects but also because: (*a*) it absorbs visible solar radiation and contributes to impaired atmospheric visibility; (*b*) it absorbs visible radiation and has a potentially direct role in global climate change; (*c*) it is, along with nitric oxide, a chief regulator of the oxidizing capacity of the free troposphere by controlling the build-up and fate of radical species, including hydroxyl radicals; and (*d*) it plays a critical role in determining ozone concentrations in the troposphere because the photolysis of nitrogen dioxide is the only key initiator of the photochemical formation of ozone, whether in polluted or in non-polluted atmospheres (US EPA, 1993, 1995).

> Nitrogen dioxide is subject to extensive further atmospheric transformations that lead to the formation of strong oxidants that participate in the conversion of nitrogen dioxide to nitric acid and sulfur dioxide to sulfuric acid and subsequent conversions to their ammonium neutralization salts. Thus, through the photochemical reaction sequence initiated by solar-radiation-induced activation of nitrogen dioxide, the newly generated pollutants are an important source of organic, nitrate and sulfate particles currently measured as PM_{10} or $PM_{2.5}$. For these reasons, nitrogen dioxide is a key precursor of a range of secondary pollutants whose effects on human health are well-documented (WHO Regional Office for Europe, 2006).

Conversion factors: at 20 °C and 1013 hPa, 1 ppm = 1.914 mg/m³ and 1 mg/m³ = 0.523 ppm.

3.5.2 Recommended AQG level for long-term exposure to nitrogen dioxide

Based on the methods for deriving an AQG level outlined in the guideline development protocol, this section provides a recommendation for an AQG level for long-term nitrogen dioxide that is based on all non-accidental mortality and cause-specific, respiratory mortality (Table 3.16).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, as explained in more detail in section 2.4. The review (Huangfu & Atkinson, 2020) was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating nitrogen dioxide to human health.

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Huangfu & Atkinson (2020) on nitrogen dioxide and all non-accidental mortality reported a meta-analytic effect estimate of RR = 1.02 (95% CI: 1.01–1.04) per 10 μg/m³ nitrogen dioxide, assuming a linear relationship. The certainty of the evidence was considered moderate according to GRADE. The authors found an indication of a supralinear relationship, suggesting a steeper risk increase at lower exposure levels. CRFs were provided by a few studies.

They are shown in Fig. 3.12 and Fig. 3.13 for those studies with information on low to very low levels of exposure measured (step 2).

Step 2. Determine the lowest level of exposure measured

For 19 of the 24 studies included in the meta-analysis, the 5th percentile of the exposure distribution was reported or could be calculated from the reported mean and standard deviation (Table 3.17). As the concentration distributions are often lognormal, this calculation is not straightforward. Therefore, in most cases it was replaced by actual reports of the relevant numbers obtained from the study authors. The three lowest levels reported or estimated in these studies are -2.7 μg/m³ (Yorifuji et al., 2013) and 4.0 μg/m³ (Bentayeb et al., 2015) (both estimated) and 6.3 μg/m³ (Weichenthal, Pinault & Burnett, 2017). The GDG ignored these three numbers because the first two were a function of very high standard deviations in studies with otherwise not very low mean concentrations. The GDG ignored the third study because it was considered to be at a high RoB (see below). The next five lowest 5th percentile concentrations were 7.3 μg/m³ (Tonne & Wilkinson, 2013), 8.3 μg/m³ in two separate studies (Hart et al., 2011, 2013), 9.6 μg/m³ (Turner et al., 2016) and 10.3 μg/m³ (Carey et al., 2013). The average of these five 5th percentile values was 8.8 μg/m³; all of these studies found positive associations between nitrogen dioxide and all non-accidental mortality, of which three were statistically significant by themselves. The sum of weights in the meta-analysis was > 25%, indicating that these studies made an important contribution to the meta-analysis.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant.

Step 4. Determine the starting point for AQG level determination as the long-term concentration of the pollutant from which the minimal relevant amount of the health outcome will result

Thus, the average of the five lowest 5th percentile levels measured in these five studies was the starting point for deriving an AQG level: 8.8 μg/m³ nitrogen dioxide. The data obtained support a long-term AQG level of no more than 10 μg/m³, based on the association between long-term nitrogen dioxide and all non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: cause-specific mortality

The cause-specific mortality outcomes that were investigated all yielded bigger RRs than the RR for all non-accidental mortality, with RRs of 1.03 (95% CI: 1.01–1.04),

1.03 (95% CI: 1.01–1.05) and 1.06 (95% CI: 1.02–1.10) per 10 μg/m³ for COPD, respiratory and acute lower respiratory infection mortality, respectively. The certainty of the evidence was rated as high for COPD mortality and moderate for non-malignant respiratory mortality and acute lower respiratory infection mortality. Table 3.18 shows the findings for non-malignant respiratory mortality. Starting points for AQG level determination for this additional health outcome would not change the analysis much, as the studies are essentially a large proportion of those in Table 3.17. Therefore, the data obtained for cause-specific mortality also support a long-term AQG level of no more than 10 μg/m³.

Step 6. Assess certainty of the evidence

One of the studies that made up the lowest levels measured in the non-accidental mortality studies (Weichenthal, Pinault & Burnett, 2017) was considered at high RoB, so the GDG did not include that study in further calculations.

Step 7. Consider new evidence

Several new studies were published between autumn 2018 and the summer of 2020. The systematic review did not include these, so the GDG had to make its own overview of these studies. These new studies were largely the same as those identified and included in the revision of the systematic review of long-term PM effects on mortality (Chen & Hoek, 2020). As they were included in the PM review, they are now also discussed in the context of nitrogen dioxide. Table 3.19 shows these studies, ordered by the mean or median exposure level for all non-accidental mortality. These include two studies from Australia (Dirgawati et al., 2019; Hanigan et al., 2019) and two from Canada (Brauer et al., 2019; Pappin et al., 2019), all of which had mean or median nitrogen dioxide levels well below 20 μg/m³. There are two new studies from the United States (Lefler et al., 2019; Eum et al., 2019), one from Denmark (Hvidtfeldt et al., 2019) and one from the Netherlands (Klompmaker et al., 2020). Two of these were administrative database studies with no adjustment (Brauer et al., 2019) or with area-level adjustment (Eum et al., 2019) for lifestyle factors such as smoking. The last three studies also reported effect estimates for respiratory mortality (Table 3.20).

There was no reason, based on these new findings, to change the calculation of the proposed AQG level or the assessment of the certainty of the evidence.

Step 8. Reconsider causality

Most nitrogen dioxide–outcome associations were deemed to be suggestive of being causal or likely causal in the 2016 outcome prioritization framework (see Table 2.1 in section 2.3.3). COMEAP published a report in 2018, Associations of long-term average concentrations of nitrogen dioxide with mortality, which

is somewhat more supportive of a causal role for long-tern nitrogen dioxide in increasing all non-accidental and, especially, respiratory mortality (PHE, 2018). A 2018 review by the German Environment Agency (in German, with a summary in English) also supports a role for long-term nitrogen dioxide in causing cardiovascular mortality (Schneider et al., 2018). None of the more recent reviews were able to include the rather large number of new studies listed in Table 3.19 and Table 3.20, which provided further support for associations between long-term nitrogen dioxide concentrations and all-cause and respiratory mortality.

The GDG noted that one review specifically investigated how sensitive the associations between long-term nitrogen dioxide concentrations and mortality were to adjustment for different PM metrics (Faustini, Rapp & Forastiere, 2014). Associations with nitrogen dioxide were found to be generally robust.

The 5th percentile (where available) and mean or median of exposure distributions in studies included in the nitrogen dioxide and mortality meta-analysis are indicated in Table 3.17 and Table 3.18 based on data from the Huangfu & Atkinson (2020) systematic review and in Table 3.19 and Table 3.20 for the newly identified studies.

3.5.2.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

Interim targets were not specified for nitrogen dioxide in *Global update 2005*. As evident from Table 3.17, Table 3.18, Table 3.19 and Table 3.20, the mean or median concentrations of nitrogen dioxide were well below 40 µg/m³ in most studies.

The GDG recommends using the long-term air quality guideline from *Global update 2005* of 40 µg/m³ as interim target 1, as this is a level already shown to be achievable in many parts of the world.

As interim target 2, a level of 30 µg/m³ is proposed and, as interim target 3, a level of 20 µg/m³ is proposed. Proposing two additional interim targets provides reasonable guidance to policy-makers on how to bridge the gap between the 2005 air quality guideline and the new, much lower, AQG level.

The recommendation is an annual nitrogen dioxide AQG level of 10 µg/m³.

An interim target 1 of 40 µg/m³, an interim target 2 of 30 µg/m³ and an interim target 3 of 20 µg/m³ are proposed, as shown in Table 3.16.

Table 3.16. Recommended AQG level and interim targets for nitrogen dioxide

Recommendation	NO_2 (μg/m³)
Interim target 1	40
Interim target 2	30
Interim target 3	20
AQG level	**10**

If all-cause mortality in a population exposed to nitrogen dioxide at the AQG level is arbitrarily set at 100, then it will be 106, 104 and 102, respectively, in populations exposed to nitrogen dioxide at the interim target 1, 2 and 3 levels. For respiratory mortality, the numbers would be 109, 106 and 103, respectively, at the interim target 1, 2 and 3 levels. These projections are based on the linear HRs of 1.02 and 1.03 per 10-μg/m³ increase in nitrogen dioxide for all non-accidental and respiratory mortality, respectively, as reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Table 3.17. Studies on long-term nitrogen dioxide exposure and all non-accidental mortality included in the systematic review by Huangfu & Atkinson (2020), ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Tonne & Wilkinson (2013)	18.5	6.8	7.3[b]	–	1.01 (0.98–1.04)
Weichenthal, Pinault & Burnett (2017)[c]	21.6	–	6.3[d]	12.1	1.04 (1.03–1.04)
Crouse et al. (2015)	21.8	–	–	11.3	1.03 (1.03–1.04)
Turner et al. (2016)	21.8	9.6	9.6[d]	–	1.02 (1.01–1.03)
Yorifuji et al. (2013)	22.0	15.0	-2.7[b]	–	1.12 (1.07–1.18)
Carey et al. (2013)	22.5	7.4	10.3[b]	–	1.02 (1.00–1.05)
Beelen et al. (2014)	22.2	–	15.3[d]	19.9	1.01 (0.99–1.03)

Table 3.17 contd

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Hart et al. (2013)	26.1	–	8.3[d]	19.0	1.01 (1.00–1.03)
Hart et al. (2011)	26.7	13.3	8.3[d]	–	1.05 (1.02–1.08)
Bentayeb et al. (2015)	28.0	14.6	4.0[b]	–	1.07 (1.00–1.15)
Krewski et al. (2003)	30.3	–	–	–	1.08 (1.02–1.14)
Fischer et al. (2015)	31.0	–	19.0[d]	26.0	1.03 (1.02–1.04)
Hartiala et al. (2016)	35.9	3.4	30.3[b]	–	1.00 (0.75–1.34)
Filleul et al. (2005)	36.5	–	–	–	1.14 (1.03–1.26)
Lipfert et al. (2006)	37.2	–	16.5[d]	–	1.03 (0.99–1.07)
Brunekreef et al. (2009)[b]	38.0	–	22.0[d]	–	1.03 (1.00–1.05)
Jerrett et al. (2009)	39.1	–	32.0[d]	–	1.23 (1.00–1.51)
Chen et al. (2016)	40.7	1.6	38.1[b]	27.1	0.92 (0.90–0.95)
Cesaroni et al. (2013)[b]	43.6	8.4	29.8[b]	38.5	1.03 (1.02–1.04)
Desikan et al. (2016)[b]	44.6	4.3	37.5[b]	41.8	0.94 (0.76–1.17)
Rosenlund et al. (2008)[b]	48.5	–	–	–	0.95 (0.89–1.02)
Lipsett et al. (2011)	63.1	18.0	33.5[b]	–	0.98 (0.95–1.02)
Abbey et al. (1999)	69.2	24.4	29.1[a]	–	1.00 (0.99–1.01)
Yang et al. (2018)	104.0	–	–	91.0	1.00 (0.99–1.01)

–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Calculated from the mean and SD using the following formula: Me(di)an – 1.645 * SD.
[c] Considered to be at high RoB.
[d] Reported in paper or by authors on request.

Table 3.18. Studies on long-term nitrogen dioxide exposure and respiratory mortality included in the systematic review by Huangfu & Atkinson (2020), ordered by me(di)an concentration

Study	Me(di)an (μg/m³)	SD	P5	P25	HR (95% CI)[a]
Weichenthal, Pinault & Burnett (2017)[b]	21.6	–	6.3[c]	12.1	1.06 (1.04–1.08)
Crouse et al. (2015)	21.8	–	–	11.3	1.02 (1.01–1.04)
Turner et al. (2016)	21.8	9.6	9.6[d]	–	1.02 (1.00–1.04)
Yorifuji et al. (2013)	22.0	15.0	-2.7[d]	–	1.19 (1.06–1.34)
Dimakopoulou et al. (2014)	22.2	–	15.3[c]	19.9	0.97 (0.89–1.04)
Carey et al. (2013)	22.5	7.4	10.3[d]	–	1.08 (1.04–1.13)
Hart et al. (2011)	26.7	13.3	8.3[c]	–	1.04 (0.95–1.14)
Fischer et al. (2015)	31.0	–	19.0[c]	26.0	1.02 (1.01–1.03)
Katanoda et al. (2011)	32.0	–	–	–	1.07 (1.03–1.12)
Brunekreef et al. (2009)[a]	38.0	–	22.0[c]	–	1.11 (1.00–1.23)
Jerrett et al. (2009)	39.1	–	32.0[c]	–	1.08 (0.64–1.84)
Cesaroni et al. (2013)[a]	43.6	8.4	29.8[d]	38.5	1.03 (1.00–1.06)
Lipsett et al. (2011)	63.1	18.0	33.5[d]		0.96 (0.86–1.08)
Abbey et al. (1999)	69.2	24.4	29.1[d]		0.99 (0.98–1.01)
Yang et al. (2018)	104.0	–	–	91.0	1.00 (0.97–1.02)

–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Considered to be at high RoB.
[c] Reported in paper or by authors on request.
[d] Calculated from mean and standard deviation using the following formula: Me(di)an – 1.645 × SD.

Table 3.19. New studies on long-term nitrogen dioxide exposure and all non-accidental mortality published since autumn 2018, ordered by me(di)an concentration

Study	Me(di)an (µg/m³)	SD	P5	P25	HR (95% CI)[a]
Dirgawati et al. (2019)	13.4	4.1	6.7[b]	–	1.060 (1.000–1.120)
Brauer et al. (2019) – CCHS subjects	16.2	11.1	7.2[c]	–	1.024 (1.016–1.040)
Brauer et al. (2019); Pappin et al. (2019) – CanCHEC subjects	16.2	–	5.9[c]	–	1.004 (1.002–1.007)
Hanigan et al. (2019)	17.8	4.8	9.9[b]	14.3	1.060 (0.960–1.140)
Lefler et al. (2019)	20.1	10.7	2.5[b]	–	1.010 (1.002–1.017)
Klompmaker et al. (2020)	23.1	–	–	19.3	0.990 (0.960–1.010)
Hvidtfeldt et al. (2019)	25.0	–	17.9[c]	–	1.070 (1.040–1.100)
Eum et al. (2019)	26.7	–	–	18.2	1.027 (1.027–1.029)

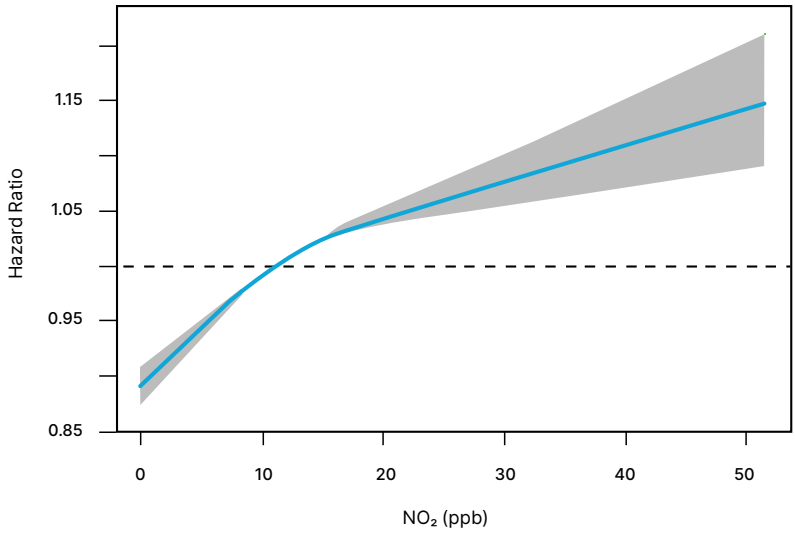
–, data unavailable; CCHS: Canadian Community Health Survey; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Calculated from the mean and SD using the following formula: Me(di)an – 1.645 * SD.
[c] Reported in paper or by authors on request.

Table 3.20. New studies on long-term nitrogen dioxide exposure and respiratory mortality published since autumn 2018, ordered by me(di)an concentration

Study	Me(di)an (µg/m³)	SD	P5	P25	HR (95% CI)[a]
Klompmaker et al. (2020)	23.1	–	–	19.3	0.980 (0.890–1.070)
Hvidtfeldt et al. (2019)	25.0	–	17.9[b]	–	1.030 (0.970–1.100)
Eum et al. (2019)	26.7	–	–	18.2	1.027 (1.023–1.030)

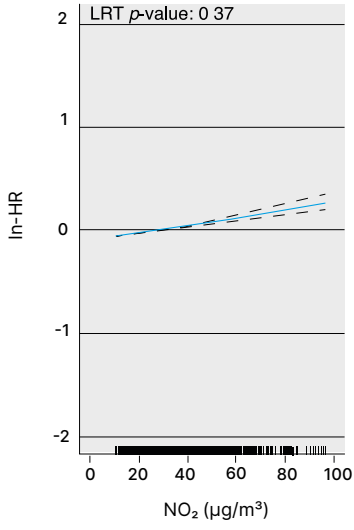
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Reported in paper or by authors on request.

Fig. 3.12. CRFs for long-term nitrogen dioxide exposure (ppb) and all non-accidental mortality in Canada[a]



[a] HRs are relative to the mean concentration of 11.6 ppb (= 22.9 μg/m³).
Source: reproduced from Crouse et al. (2015) with permission of the lead author.

Fig. 3.13. CRFs for long-term nitrogen dioxide exposure (μg/m³) and all non-accidental mortality in the Netherlands[a]



ln: natural logarithm; LRT: likelihood ratio test.
[a] ln-HR = log HR, relative to the mean nitrogen dioxide concentration. The likelihood-ratio test P value indicates that there was no significant deviation from linearity.
Source: reproduced from Fischer et al. (2015) with permission of the lead author.

3.5.3 Recommended AQG level for short-term exposure to nitrogen dioxide

Based on the methods for deriving an AQG level outlined in the guideline development protocol, this section provides an AQG level for short-term, daily average nitrogen dioxide that is based on all-cause non-accidental mortality and asthma hospital admissions and emergency room visits (Table 3.21).

The epidemiological evidence underpinning the AQG level is discussed in two systematic reviews commissioned by WHO, as explained in more detail in section 2.4. The reviews, conducted by Orellano et al. (2020) and Zheng et al. (2021), were published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating nitrogen dioxide to human health. However, comprehensive evaluations by authoritative bodies such COMEAP, Health Canada and US EPA were taken into account in the development of the AQG levels. This was especially relevant when assessing causality of the associations examined in the systematic reviews (see step 8).

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Orellano et al. (2020) on 24-hour average nitrogen dioxide and all-cause non-accidental mortality reported a meta-analytic effect estimate of RR = 1.0072 (95% CI: 1.0059–1.0085) per 10 μg/m^3 nitrogen dioxide, assuming a linear relationship. The certainty of the evidence was considered high according to GRADE. CRFs were provided by several studies. An example from a study in Austria shows an association between nitrogen dioxide and all-cause mortality at very low levels of exposure (Fig. 3.14) (Moshammer et al., 2020).

Step 2. Determine the lowest level of exposure measured

As discussed in the protocol for deriving AQG levels, the lowest concentrations in time-series studies of effects of daily variations in air pollution concentrations are often very low. Therefore, the 5th percentiles of these daily distributions cannot be used as starting points for AQG level development. In such cases, the protocol suggests identifying the 99th percentile of common distributions of daily air pollution concentrations corresponding to an average long-term concentration equivalent to the proposed annual AQG level. This is 10 μg/m^3 for nitrogen dioxide.

Common distributions observed in large numbers of cities around the world (data from Liu et al. (2019)) suggest a ratio of about 2.5 for 99th percentiles of daily concentrations to the annual mean nitrogen dioxide. Therefore, a short-term AQG level of 25 μg/m³ is suggested.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant. For short-term exposures, the CRFs from the systematic review by Orellano et al. (2020) were used to calculate the increase in mortality expected on a day with a 24-hour nitrogen dioxide concentration of 25 μg/m³ compared with a day with a 24-hour nitrogen dioxide concentration of 10 μg/m³. With an RR for all-cause mortality of 1.0072 per 10 μg/m³, the estimated excess mortality on such a day would be 1.1%. However, under compliance with the long-term AQG level, days with concentrations close to 25 μg/m³ will correspond to the far upper tail of the distribution of daily exposures. Most days will have much lower values, with close to half having concentrations below or far below the annual AQG level. The health burden related to a few days with higher concentrations corresponds to a very small fraction of the total air pollution-related burden.

Step 4. Determine the starting point for AQG level determination as the 99th percentile, as mentioned in step 3

The data obtained support a short-term AQG level of no more than 25 μg/m³, based on the association between short-term nitrogen dioxide and all-cause non-accidental mortality.

Step 5. Compare the AQG level across critical health outcomes: cause-specific mortality and asthma hospital admissions and emergency room visits

Studies on short-term associations and cause-specific mortality were not reviewed. However, another systematic review commissioned by WHO assessed the evidence for associations between nitrogen dioxide and daily hospital admissions for asthma (Zheng et al., 2021). This review found an effect estimate of RR = 1.014 (95% CI: 1.009–1.019) per 10 μg/m³, which would produce an excess morbidity 2.1% on a day at the proposed short-term AQG level of 25 μg/m³ compared with a day at the proposed long-term AQG level of 10 μg/m³. As is the case when considering mortality in step 3, under compliance with the long-term AQG level, days with concentrations close to 25 μg/m³ will correspond to the far upper tail of the distribution of daily exposures. Most days will have much lower values, with close to half having concentrations below or far below the annual AQG level. The health burden related to a few days with higher concentrations corresponds to a very small fraction of the total air pollution-related burden.

Step 6. Assess certainty of the evidence

As mentioned in step 1, the certainty level is high for the evidence linking short-term nitrogen dioxide concentration variations to short-term mortality variations. In addition, as shown in Fig. 3.14, there is evidence that this association persists to very low levels of exposure.

Step 7. Consider new evidence

Several new studies have been published since autumn 2018. The GDG did not made an inventory of all new time-series studies. The MCC Collaborative Research Network has reported new findings from a very large database on short-term mortality effects of $PM_{2.5}$ and ozone (Liu et al., 2019; Vicedo-Cabrera et al., 2020); an analysis from the same database on short-term effects of nitrogen dioxide was also published (Meng at al., 2021). The effect estimates from this new analysis are in agreement with those from the WHO-commissioned systematic review.

Step 8. Reconsider causality

The association between short-term nitrogen dioxide concentrations and all-cause mortality was judged to be suggestive of a causal relationship in the 2016 outcome prioritization framework (see section 2.3.3), following authoritative evaluations by Health Canada, US EPA and other bodies. However, the association between short-term nitrogen dioxide concentrations and respiratory effects was judged to be causal. This judgement provides strong support for a short-term AQG level for nitrogen dioxide in view of the reported association with asthma hospital admissions and emergency room visits.

The GDG noted that one review specifically investigated how sensitive the associations between short-term nitrogen dioxide and mortality were to adjustment for different PM metrics (Mills et al., 2016). Associations with nitrogen dioxide were found to be generally robust.

3.5.3.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

An interim target 1 of 120 $\mu g/m^3$ is proposed – which is roughly comparable to the existing 1-hour 2005 air quality guideline of 200 $\mu g/m^3$. An interim target 2 of 50 $\mu g/m^3$ is also proposed. Both interim targets use the same definition of 99th percentiles of the distribution of 24-hour concentrations over a one-year period.

The recommendation is a short-term (24-hour) nitrogen dioxide AQG level of 25 µg/m³, defined as the 99th percentile (equivalent to three to four exceedance days per year) of the annual distribution of 24-hour average concentrations.

An interim target 1 of 120 µg/m³ and an interim target 2 of 50 µg/m³ are proposed, as shown in Table 3.21.

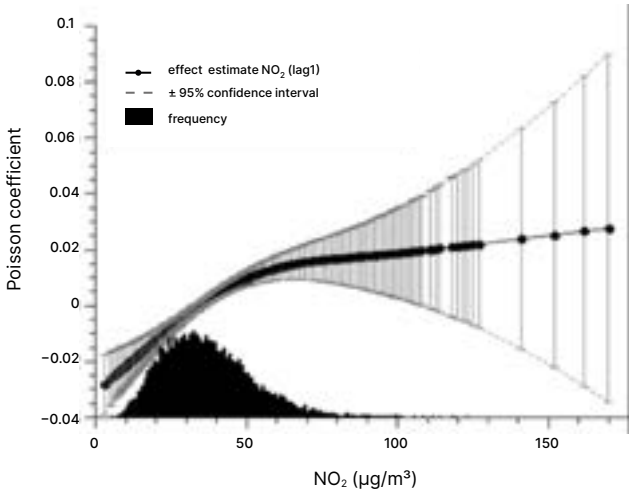
Table 3.21. Recommended short-term (24-hour) AQG level and interim targets for nitrogen dioxide[a]

Recommendation	NO_2 (µg/m³)
Interim target 1	120
Interim target 2	50
AQG level	**25**

[a] Defined as the 99th percentile of the annual distribution of 24-hour average concentrations (equivalent to 3–4 exceedance days per year).

If mortality in a population exposed to nitrogen dioxide for a day at the AQG level of 25 µg/m³ is arbitrarily set at 100, then it will be 107 and 102, respectively, in populations exposed to nitrogen dioxide at the interim target 1 and 2 levels. These projections are based on the linear HR of 1.0072 HR per 10-µg/m³ increase in nitrogen dioxide of all non-accidental mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Fig. 3.14. Association between 24-hour average nitrogen dioxide concentrations (μg/m³) and mortality in Vienna, Austria[a]



[a] The corresponding linear effect estimate is a 0.21% increase in total mortality per previous-day NO_2 increase of 10 μg/m³.
Source: Moshammer et al. (2020).

3.6 Sulfur dioxide

3.6.1 General description

The general description comes from *Global update 2005*.

> Historically, sulfur dioxide and PM derived from the combustion of fossil fuels have been the main components of air pollution in many parts of the world. The most serious problems have been experienced in large urban areas where coal has been used for domestic heating or for poorly controlled combustion in industrial installations. In such situations, the complex of pollutants has generally been considered collectively, drawing on findings from epidemiological studies carried out decades ago in areas formerly heavily polluted. Guidelines developed in this way had been related to averaging times of 24 hours in respect of acute effects and one year in respect of chronic effects.
>
> Separate attention has been paid to sulfur dioxide alone, based largely on findings from controlled human exposure studies. These allow guidelines to be developed in terms of shorter averaging periods of the order of one hour. These are relevant to exposures to peak concentrations that may arise from sources burning coal or heavy oil, whether or not accompanied by substantial concentrations of PM.

> Epidemiological studies published in the last decade [i.e. 1995–2004] provide suggestive evidence on the health effects of sulfur dioxide. Thus, a section has been introduced in this revision focusing on epidemiological results in locations where the sources of sulfur dioxide are mainly motor vehicles and various industries.
>
> Sulfur dioxide is derived from the combustion of sulfur-containing fossil fuels and is a major air pollutant in many parts of the world. Oxidation of sulfur dioxide, especially at the surface of particles in the presence of metallic catalysts, leads to the formation of sulfurous and sulfuric acids. Neutralization, by ammonia, leads to the production of bisulfates and sulfates.
>
> Sulfur dioxide is a colourless gas that is readily soluble in water. Sulfuric acid is a strong acid formed from the reaction of sulfur trioxide (SO_3) with water. Sulfuric acid is strongly hygroscopic. As a pure material it is a colourless liquid with a boiling point of 330 °C. Ammonium bisulfate (NH_4HSO_4), which is also a strong acid but is less acidic than sulfuric acid as a pure material, is a crystalline solid with a melting point of 147 °C. The formation of very small droplets of sulfuric acid occurs by nucleation. Many vapours are able to condense on the surface of existing very fine nuclei and lead to the growth of composite particles. (WHO Regional Office for Europe, 2006).

Conversion factors: at 20 °C and 1013 hPa, 1 ppm = 2660 µg/m^3 and 1 mg/m^3 = 0.3759 ppm.

3.6.2. Recommended AQG level for 24-hour exposure to sulfur dioxide

Based on the methods for deriving an AQG level outlined in the guideline development protocol, the GDG recommends an AQG level for short-term, 24-hour mean sulfur dioxide concentration based on its relationship with asthma hospital admissions and emergency room visits, daily non-accidental mortality and respiratory mortality (Table 3.22). As discussed in Chapter 2, the association between sulfur dioxide and mortality was added to the list of pollutant–outcome pairs at a later stage to improve continuity with *Global update 2005*.

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO on asthma hospital admissions and emergency room visits (Zheng et al., 2021) and another on daily sulfur dioxide mortality (Orellano, Reynoso & Quaranta, 2021). These reviews were published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating sulfur dioxide to human health.

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Zheng et al. (2021) on sulfur dioxide and asthma hospital admissions and emergency room visits reported a meta-analytic effect estimate of RR = 1.010 (95% CI: 1.001–1.020) per 10 μg/m³ sulfur dioxide, assuming a linear relationship. The certainty of the evidence was considered low according to GRADE. More elaborate analyses of the CRF shape were not provided by any of the studies on asthma included in the systematic review. The systematic review by Orellano, Reynoso & Quaranta (2021) on sulfur dioxide and daily mortality reported a meta-analytic effect estimate of RR = 1.0059 (95% CI: 1.0046–1.0071) per 10 μg/m³ sulfur dioxide, assuming a linear relationship. For respiratory mortality, the meta-analytic effect estimate was RR = 1.0067 (95% CI: 1.0025–1.0109) per 10 μg/m³ sulfur dioxide, assuming a linear relationship. The certainty of the evidence was considered high according to GRADE for all non-accidental mortality and moderate for respiratory mortality.

Step 2. Determine the lowest level of exposure measured

As discussed in the protocol for deriving AQG levels, the lowest concentrations in time-series studies of effects of daily variations in air pollution concentrations are often very low. The minimum concentration reported by most of the studies included in the systematic reviews by Zheng et al. (2021) and Orellano, Reynoso & Quaranta (2021) was below 1 μg/m³. The protocol suggests identifying as the daily AQG level the 99th percentile of a distribution of daily air pollution concentrations corresponding to an average long-term concentration equivalent to the annual AQG level. However, in the case of sulfur dioxide, there is no annual AQG level that can be used as a point of departure, so this approach cannot be applied.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant. For short-term exposures, the assumption of a linear CRF and a risk coefficient from the systematic reviews by Zheng et al. (2021) and Orellano, Reynoso & Quaranta (2021) were used to calculate the increase in asthma hospital admissions and emergency room

visits and daily non-accidental mortality and respiratory mortality relative to a daily mean sulfur dioxide concentration of 0 μg/m³. With an RR of 1.010 per 10 μg/m³, any 10-μg/m³ increase would produce a 1% increase in asthma hospital admissions and emergency room visits. The increases in non-accidental mortality and respiratory mortality would be 0.6% and 0.7%, respectively, per 10 μg/m³.

Step 4. Determine the starting point for AQG level determination as the 99th percentile, as mentioned in step 3

In the proposed short-term AQG levels for $PM_{2.5}$, PM_{10}, ozone and nitrogen dioxide, a comparison was made between the expected excess deaths or asthma hospital admissions and emergency room visits at the 99th percentiles of daily distributions corresponding to a distribution that is in compliance with the proposed long-term AQG levels for these pollutants. For non-accidental mortality, these excess estimates were up to 1.72% for deaths related to ozone and 4.8% for asthma hospital admissions and emergency room visits related to ozone. Similar percentage increases related to sulfur dioxide, relative to a 0 μg/m³ concentration, would be expected at a daily mean of about 30 μg/m³ (3% increase in asthma hospital admissions and emergency room visits, 1.8% increase in daily non-accidental mortality). The MCC Collaborative Research Network database (A. Gasparrini, London School of Hygiene and Tropical Medicine, unpublished data, 23 June 2020; Liu et al., 2019) documented a ratio of 3.9 between the 99th percentile of daily concentrations and the annual mean sulfur dioxide concentration across hundreds of cities from all over the world. Following the same logic used for pollutants for which there is a proposed long-term AQG level, the starting point for a short-term sulfur dioxide AQG level would be 40 μg/m³. The rationale is that with a ratio of about 4 between the 99th percentile and annual mean, 40 μg/m³ would correspond to an increase of 30 μg/m³ over an annual mean of 10 μg/m³, which is about the same as the overall mean concentration observed across almost 400 locations worldwide in the MCC Collaborative Research Network database (A. Gasparrini, London School of Hygiene and Tropical Medicine, unpublished data, 23 June 2020; Liu et al., 2019). The GDG recognizes that the choice for a background of 10 μg/m³ is, to some extent, arbitrary but notes that the estimated excess mortality at days with concentrations at the recommended AQG level is small and is roughly comparable across all pollutants considered in this report.

Step 5. Compare the AQG level across critical health outcomes

No other health outcomes were evaluated in the systematic reviews.

Step 6. Assess certainty of the evidence

As mentioned in step 1, the evidence base supporting an association between 24-hour average sulfur dioxide and asthma hospital admissions and emergency

room visits was considered to be of low certainty. For all non-accidental mortality, it was considered to be of high certainty.

Step 7. Consider new evidence

No new studies on the relation between sulfur dioxide exposure and asthma hospital admissions and emergency room visits and non-accidental or respiratory mortality were considered.

Step 8. Reconsider causality

The association between short-term sulfur dioxide concentrations and asthma hospital admissions and emergency room visits was judged to be causal for respiratory effects in the 2016 outcome prioritization framework (see section 2.3.3), based on assessments by Health Canada and the US EPA. The US EPA published a new ISA on sulfur oxides in 2017 (US EPA, 2017) that did not change that assessment, and which classifies the short-term association with mortality as suggestive of a causal relationship.

3.6.2.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

Recommended interim targets are the same as in *Global update 2005*. There are still some places in the world where such high sulfur dioxide concentrations occur, and these areas would benefit from maintaining the existing interim targets.

The recommendation is a short-term (24-hour) sulfur dioxide AQG level of 40 μg/m³, defined as the 99th percentile (equivalent to three to four exceedance days per year) of the annual distribution of 24-hour average concentrations.

An interim target 1 of 125 μg/m³ and an interim target 2 of 50 μg/m³ are proposed, as shown in Table 3.22.

If mortality in a population exposed to sulfur dioxide for a day at the AQG level of 40 μg/m³ is arbitrarily set at 100, then it will be 105 and 101, respectively, in populations exposed to sulfur dioxide at the interim target 1 and 2 levels. These projections are based on the linear HR of 1.0059 per 10-μg/m³ increase in sulfur dioxide of all non-accidental mortality reported in the systematic review. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

Table 3.22. Recommended short-term (24-hour) AQG level and interim targets for sulfur dioxide[a]

Recommendation	SO_2 (μg/m³)
Interim target 1	125
Interim target 2	50
AQG level	**40**

[a] Defined as the 99th percentile (equivalent to 3–4 exceedance days per year) of the annual distribution of 24-hour average concentrations.

3.7 Carbon monoxide

3.7.1 General description

The general description comes from the *WHO guidelines for indoor air quality: selected pollutants*.

> Carbon monoxide (CO) is a colourless, non-irritant, odourless and tasteless toxic gas. It is produced by the incomplete combustion of carbonaceous fuels such as wood, petrol, coal, natural gas and kerosene. ...
>
> The molecular weight of carbon monoxide is similar to that of air (28.01 vs approximately 29). It mixes freely with air in any proportion and moves with air via bulk transport. It is combustible, may serve as a fuel source and can form explosive mixtures with air. It reacts vigorously with oxygen, acetylene, chlorine, fluorine and nitrous oxide. Carbon monoxide is not detectible by humans either by sight, taste or smell. It is only slightly soluble in water, blood serum and plasma; in the human body, it reacts with haemoglobin to form carboxyhaemoglobin (COHb) (WHO Regional Office for Europe, 2010).

Conversion factors: at 20 °C and 1013 hPa, 1 ppm = 1.165 mg/m³ and 1 mg/m³ = 0.858 ppm.

3.7.2 Recommended AQG level for 24-hour exposure to carbon monoxide

Based on the methods for deriving an AQG level outlined in the guideline development protocol, this section provides an AQG level for short-term, 24-hour mean carbon monoxide concentration based on its association with hospital admissions and mortality from myocardial infarction (Table 3.23).

The epidemiological evidence underpinning the AQG level is discussed in a systematic review commissioned by WHO, as explained in more detail in section 2.4. The review, conducted by Lee et al. (2020), was published in *Environment International* (Whaley et al., 2021) as open access.

As discussed in section 2.3, there has been no separate, independent assessment of the mechanistic, toxicological and human clinical studies relating carbon monoxide to human health.

This section follows the eight steps outlined in the protocol for AQG level development. Tables and figures mentioned during the eight steps are listed at the end of the discussion of each recommendation.

Step 1. Assess RR estimates and, when available, CRFs

The systematic review by Lee et al. (2020) on carbon monoxide and hospital admissions and mortality from myocardial infarction reported a meta-analytic effect estimate of RR = 1.052 (95% CI: 1.017–1.089) per 1 mg/m^3 carbon monoxide, assuming a linear relationship. The certainty of the evidence was considered moderate according to GRADE. More elaborate analyses of the CRF shape were not provided by any of the myocardial infarction studies included in the systematic review. However, the effects were seen mostly in studies with higher carbon monoxide levels, with the effect estimate being RR = 1.019 (95% CI: 1.011–1.027) in studies with a median carbon monoxide level exceeding 1.15 mg/m^3 compared with RR = 1.00 (95% CI: 0.998–1.003) in the rest of the studies.

Step 2. Determine the lowest level of exposure measured

As discussed in the protocol for deriving AQG levels, the lowest concentrations in time-series studies of effects of daily variations in air pollution concentrations are often very low. The minimum concentration reported by most of the studies included in the systematic review by Lee et al. (2020) was below 0.5 mg/m^3 and the mean carbon monoxide level ranged from 0.35 mg/m^3 to 4.56 mg/m^3; in half of the studies, the median carbon monoxide level was below 1.15 mg/m^3. The protocol suggests identifying as the daily AQG level the 99th percentile of a distribution of daily air pollution concentrations corresponding to an average long-term concentration equivalent to the annual AQG level. However, in the case of carbon monoxide, there is no annual AQG level that can be used as a point of departure, so this approach cannot be applied.

Step 3. Determine the minimal relevant increase in health outcomes

The GDG decided to consider as relevant any increase in risk for an adverse health outcome related to long-term exposure to a pollutant. For short-term exposures,

the assumption of a linear CRF and a risk coefficient from the systematic review by Lee et al. (2020) were used to calculate the increase in myocardial infarction hospital and emergency room admissions and mortality relative to a daily mean carbon monoxide concentration of 0 mg/m³. With an RR of 1.052 per 1 mg/m³, any 1 mg/m³-increase would produce a 5.2% increase in events. However, the Lee et al. (2020) review showed that the magnitude of the RR estimate was highly dependent on inclusion of three partly overlapping studies from East Asia conducted in low carbon monoxide, high nitrogen dioxide and high PM atmospheres (Hsieh et al., 2010; Cheng, Tsai & Yang, 2009; Tsai et al., 2012). Excluding these studies produced an RR of 1.016 (95% CI: 1.009–1.023). In addition, the review showed that there were only three effect estimates for myocardial infarction mortality, none of which suggested an effect from carbon monoxide. The additional exclusion of these estimates produced an RR for myocardial infarction admissions of 1.015 (95% CI: 1.007–1.024). As previously mentioned, the effects were mostly seen in studies with higher carbon monoxide levels, with an effect estimate of RR = 1.019 (95% CI: 1.011–1.027) in studies with a median carbon monoxide level exceeding 1.15 mg/m³ compared with RR = 1.00 (95% CI: 0.998–1.003) in the rest of the studies. For guideline development, the GDG considered the RR of 1.019 that was observed in studies with a median carbon monoxide of more than 1.15 mg/m³ to be more relevant because it excludes obvious outliers, is focused on one outcome (myocardial infarction admissions) rather than two (admissions plus mortality) and is restricted to the concentration range over which effects were actually demonstrated. Using this RR, the expected excess myocardial infarctions would be 5.4% on a 4-mg/m³ day compared with a day with a carbon monoxide concentration of 1.15 mg/m³. The excess would be 11.1% at the 2010 WHO indoor 24-hour guideline for carbon monoxide of 7 mg/m³ (WHO Regional Office for Europe, 2010).

Step 4. Determine the starting point for AQG level determination as the 99th percentile, as mentioned in step 3

A 99th percentile of 4 mg/m³ corresponds to an estimated annual mean of 1.33 mg/m³, based on a 3 : 1 ratio between the 99th percentile and annual mean observed in the large MCC Collaborative Research Network database (A. Gasparrini, London School of Hygiene and Tropical Medicine, unpublished data, 23 June 2020; Liu et al., 2019; Chen et al., 2021). Such a mean would roughly correspond to the median of 1.15 mg/m³, above which the studies included in Lee et al. (2020) showed an elevated risk of exposure. In the development of the short-term AQG levels for $PM_{2.5}$, PM_{10}, ozone and nitrogen dioxide, a calculation was always made of the differences in events between the mean and the 99th percentile. In the case of carbon monoxide, that difference would be 5.1%. The GDG recommends a short-term AQG level, defined as 99th percentile of daily

mean concentrations in a year, of no more than 4 mg/m³, based on the association between short-term carbon monoxide and hospital admissions and emergency room visits for myocardial infarctions. Although the risk of myocardial infarction hospital admissions and emergency room visits is expected to be elevated by about 5% on such days, the overall health burden related to a few days with higher concentrations corresponds to a very small fraction of the total air pollution-related burden.

Step 5. Compare the AQG level across critical health outcomes
No other health outcomes were evaluated in the systematic review.

Step 6. Assess certainty of the evidence
As mentioned in step 1, the evidence base supporting an association between 24-hour average carbon monoxide and hospital admissions and emergency room visits due to myocardial infarction was considered to be of moderate certainty.

Step 7. Consider new evidence
No new studies were found on the relation between myocardial infarction admissions/deaths and carbon monoxide exposure.

Step 8. Reconsider causality
The association between short-term carbon monoxide concentrations and myocardial infarctions was judged to be likely causal in the 2016 outcome prioritization framework (see section 2.3.3), based on assessments by Health Canada and US EPA, both of which date back to 2010 and have not been revised since. Of note, US EPA did not develop a standard for 24-hour carbon monoxide at the time, despite evidence of associations persisting at levels below 1 mg/m³ or 2 mg/m³ (Bell et al., 2009).

3.7.2.1 Interim targets

Interim targets are proposed as incremental steps in a progressive reduction of air pollution and are intended for use in areas where pollution is high. For a more detailed rationale for establishing and using interim targets, see section 2.5.3.

The recommendation is a short-term (24-hour) carbon monoxide AQG level of 4 mg/m³, defined as the 99th percentile (equivalent to three to four exceedance days per year) of the annual distribution of 24-hour average concentrations.

An interim target 1 of 7 mg/m³ is proposed, as a point of reference to the existing 24-hour indoor WHO air quality guideline.

Table 3.23. Recommended short-term (24-hour) AQG level and interim targets for carbon monoxide[a]

Recommendation	CO (mg/m³)
Interim target 1	7
AQG level	4

[a] Defined as the 99th percentile (equivalent to 3–4 exceedance days per year) of the annual distribution of 24-hour average concentrations.

If the number of myocardial infarctions in a population exposed to carbon monoxide for a day at the AQG level of 4 mg/m³ is arbitrarily set at 100, the number will be 106 in populations exposed to carbon monoxide at the interim target 1 level. This projection is based on the linear HR of 1.019 per 1-mg/m³ increase in carbon monoxide for hospital admissions due to myocardial infarction. At higher concentrations, the CRF may no longer be linear, which would change the numbers in this example.

3.8 Summary of recommended air quality guideline levels and interim targets

Table 3.24 summarizes the recommended AQG levels and interim targets for all pollutants. The evidence underlying all of the recommended AQG levels was rated as of high or moderate certainty and all recommendations are classified as strong according to the adapted GRADE approach (discussed in Chapter 2).

Table 3.25 shows the air quality guidelines for nitrogen dioxide, sulfur dioxide and carbon monoxide for short averaging times that were not re-evaluated and, therefore, remain valid.

Table 3.24. Summary of recommended long- and short-term AQG levels and interim targets

Pollutant	Averaging time	Interim target				AQG level
		1	2	3	4	
$PM_{2.5}$, µg/m³	Annual	35	25	15	10	5
	24-hour[a]	75	50	37.5	25	15
PM_{10}, µg/m³	Annual	70	50	30	20	15
	24-hour[a]	150	100	75	50	45
O_3, µg/m³	Peak season[b]	100	70	–	–	60
	8-hour[a]	160	120	–	–	100
NO_2, µg/m³	Annual	40	30	20	–	10
	24-hour[a]	120	50	–	–	25
SO_2, µg/m³	24-hour[a]	125	50	–	–	40
CO, mg/m³	24-hour[a]	7	–	–	–	4

[a] 99th percentile (i.e. 3–4 exceedance days per year).
[b] Average of daily maximum 8-hour mean O_3 concentration in the six consecutive months with the highest six-month running-average O_3 concentration.

Table 3.25. Air quality guidelines for nitrogen dioxide, sulfur dioxide and carbon monoxide (for short averaging times) that remain valid

Pollutant	Averaging time	Air quality guideline that remain valid
NO_2, µg/m³	1-hour	200
SO_2, µg/m³	10-minute	500
CO, mg/m³	8-hour	10
	1-hour	35
	15-minute	100

Table 3.26 shows a side-by-side comparison of the 2005 air quality guidelines and the 2021 AQG levels.

Table 3.26. Recommended 2021 AQG levels and 2005 air quality guidelines

Pollutant	Averaging time	2005 air quality guideline	2021 AQG level
$PM_{2.5}$, µg/m³	Annual	10	5
	24-hour[a]	25	15
PM_{10}, µg/m³	Annual	20	15
	24-hour[a]	50	45
O_3, µg/m³	Peak season[b]	–	60
	8-hour[a]	100	100
NO_2, µg/m³	Annual	40	10
	24-hour[a]	–	25
SO_2, µg/m³	24-hour[a]	20	40
CO, mg/m³	24-hour[a]	–	4

[a] 99th percentile (i.e. 3–4 exceedance days per year).
[b] Average of daily maximum 8-hour mean O_3 concentration in the six consecutive months with the highest six-month running-average O_3 concentration.

3.8.1 Important AQG level updates to *Global update 2005*

The most important updates in these guidelines are listed below.

1. The $PM_{2.5}$ annual AQG level has been lowered from 10 µg/m³ to 5 µg/m³. This reflects the new evidence of effects on mortality occurring at concentrations below 10 µg/m³. In this update of the air quality guidelines, an analysis was introduced to identify the most appropriate level of the long-term air quality guidelines that is more formalized than what was used in 2005. However, the change from 10 µg/m³ to 5 µg/m³ primarily reflects the new evidence about effects occurring at low levels of exposure.
2. The 24-hour AQG level for $PM_{2.5}$ changed from 25 µg/m³ to 15 µg/m³. In 2005 a ratio of 2.5 was assumed between the 99th percentile of 24-hour average concentrations and annual averages. This ratio was changed to 3 based on empirical data from the very large MCC Collaborative Research Network (A. Gasparrini, London School of Hygiene and Tropical Medicine, unpublished data, 23 June 2020; Liu et al., 2019).

3. The PM_{10} annual AQG level has been reduced from 20 μg/m³ to 15 μg/m³. This reflects the new evidence of effects on mortality occurring at concentrations below 20 μg/m³. In this update of the air quality guidelines, an analysis was introduced to identify the most appropriate level of the long-term air quality guidelines that is more formalized than what was used in 2005. However, the change from 20 μg/m³ to 15 μg/m³ primarily reflects the new evidence about effects occurring at low levels. It is important to note that the assessment of PM_{10} was based on studies that had actually measured PM_{10}, without taking into consideration the ratios between PM_{10} and $PM_{2.5}$. In 2005 based on empirical data, a PM_{10} : $PM_{2.5}$ ratio of 2 was used to establish the PM_{10} AQG levels. The GDG notes that the empirical PM_{10} : $PM_{2.5}$ ratios have not changed, but the method used to derive the AQG levels has changed. The resulting PM_{10} annual AQG level is less protective than the $PM_{2.5}$ annual AQG level in most practical circumstances.

4. The 24-hour AQG for PM_{10} changed from 50 μg/m³ to 45 μg/m³. In 2005 a ratio of 2.5 was assumed between the 99th percentile of 24-hour average concentrations and annual averages. This ratio was changed to 3 based on empirical data from the very large MCC Collaborative Research Network (A. Gasparrini, London School of Hygiene and Tropical Medicine, unpublished data, 23 June 2020; Liu et al., 2019). As a result of the combined effects of the new derivation procedure and the changed ratio, the 24-hour AQG level for PM_{10} is not much lower in 2021 than in 2005. The resulting PM_{10} 24-hour AQG level is less protective than the $PM_{2.5}$ 24-hour AQG level in most practical circumstances.

5. A new long-term peak-season average ozone AQG level has been established. This is based on new evidence on the long-term effects of ozone on total mortality and respiratory mortality. The short-term AQG level was re-calculated using the protocols outlined in section 2.5. The resulting short-term AQG level of 100 μg/m³ is the same as the 2005 short-term air quality guideline, which was based on morbidity and lung function effects. Therefore, in practical terms, the guidance for ozone has not changed.

6. The annual AQG level for nitrogen dioxide changed from 40 μg/m³ to 10 μg/m³. This was primarily because this update of the air quality guidelines is based on the effects of long-term nitrogen dioxide on all-cause mortality and respiratory mortality. The 2005 air quality guideline was based on morbidity effects observed in children exposed indoors to nitrogen dioxide from gas cooking. The chosen level was originally proposed in a document prepared by the International Labour Organization, UNEP and WHO (International Programme on Chemical Safety, 1997). It was justified as follows:

> On the basis of a background level of 15 μg/m³ (0.008 ppm) and the fact that significant adverse health effects occur with an additional level of 28.2 μg/m³ (0.015 ppm) or more, an annual guideline value of 40 μg/m³ (0.023 ppm) is proposed. This value will avoid the most severe exposures (International Programme on Chemical Safety, 1997).

As is evident from this quotation, the annual AQG of 40 μg/m³ was in fact expected to be associated with "significant adverse health effects". A background of 15 μg/m³ is not all that different from the AQG level of 10 μg/m³ that is recommended in this report.

7. Following the protocol established in section 2.5, a new 24-hour AQG level of 25 μg/m³ for nitrogen dioxide was recommended. The 2005 1-hour AQG level of 200 μg/m³ was not re-evaluated. The GDG points out that in most practical circumstances, the 24-hour AQG level in this update is more stringent than the 2005 1-hour AQG level.

8. Following the protocol established in section 2.5, a 24-hour AQG level for sulfur dioxide of 40 μg/m³ was recommended. This is based on a new evaluation of the effects of short-term sulfur dioxide concentrations on all-cause mortality and respiratory mortality. This AQG level is higher than the 2005 24-hour air quality guideline of 20 μg/m³. The 2005 air quality guideline was also primarily based on an evaluation of the short-term effects of sulfur dioxide on mortality. No formal method was applied to derive a guideline value in 2005. The considerations at the time were:

> In consideration of (a) the uncertainty of sulfur dioxide in causality, (b) the practical difficulty of reaching levels that are certain to be associated with no effects and (c) the need to provide greater degrees of protection than those provided by the guidelines published in 2000, and assuming that reduction in exposure to a causal and correlated substance is achieved by reducing sulfur dioxide concentrations, there is a basis for revising the 24-hour guideline for sulfur dioxide downwards, adopting a prudent precautionary approach (WHO Regional Office for Europe, 2006).

The GDG argues that in comparison the recommended 24-hour AQG level of 40 μg/m³ is better justified, and coherent with the approaches followed in the recommendations for short-term AQG levels for the other pollutants covered in this report.

9. Following the protocol established in section 2.5, a 24-hour AQG level for carbon monoxide of 4 mg/m³ was recommended. This is based on a new evaluation of the effects of short-term carbon monoxide concentrations on hospital admissions for myocardial infarction.

3.9 Supporting burden of disease calculations

To support discussions on the updating of AQG levels, WHO performed a rapid scenario analysis to explore the reductions in disease burden attributable to annual ambient $PM_{2.5}$ globally (WHO, 2018) that would occur if the 2016 levels were reduced to the current interim target 1 (35 µg/m³), interim target 2 (25 µg/m³), interim target 3 (15 µg/m³), interim target 4 (10 µg/m³) and AQG levels.

The methods and results are described in more detail in Evangelopoulos et al. (2020). The methodology of this calculation was the same as in the GBD 2016 study, which used a set of non-linear, cause-specific exposure–response functions. These are not directly comparable to the linear CRFs reported in the systematic reviews produced for the purpose of AQG level derivation in this document. In addition, Evangelopoulos et al. (2020) did not perform a scenario analysis for the current AQG level, which was decided after their publication. However, the analysis was conducted for this document. For further methodological details, see GBD 2016 Risk Factors Collaborators (2017).

Table 3.27 illustrates the total estimated number of deaths attributable to ambient $PM_{2.5}$ in 2016 by WHO region and worldwide. In all these scenarios, the indicated levels are assumed to reflect the population-weighted mean exposure. The population-weighted mean is the average concentration in a sub-area (region or country) weighted by the distribution of the population within that sub-area, relative to its total population. This accounts for spatial relationships between locations of populations and concentrations, in contrast to area-weighting, which is simply the average concentration within a sub-area, irrespective of where the population may reside.

As an illustration, results show that if interim target 4 (equivalent to the 2005 air quality guideline) had been achieved in 2016, then in terms of population-weighted average, the estimated burden of disease would have been reduced substantially: achievement of interim target 4 would have resulted in a 47.8% decrease in total deaths attributed to $PM_{2.5}$ exposure compared with the number calculated using the 2016 levels of exposure worldwide. The highest impact would have been observed in the WHO South-East Asia and African regions (reductions of 57% and 60%, respectively).

Meeting the interim targets would also have had a notable benefit on health, especially in those regions where exposures far exceed interim targets. Even if interim target 1 had been met, reductions of 20% and 14%, respectively, in burden of disease attributable to ambient $PM_{2.5}$ would have been observed in the South-East Asia and Eastern Mediterranean regions.

Table 3.27. Region-specific and global deaths attributable to ambient $PM_{2.5}$ under 2016 air pollution levels and percentage reduction through achievement of the recommended interim targets or AQG level[a]

WHO region	Global/regional deaths & % reduction through achievement of interim target or AQG level[a]					
	Air pollution level, 2016	Interim target 1	Interim target 2	Interim target 3	Interim target 4	AQG level
African Region						
n (UI), in 000s	474 (411–547)	403 (329–481)	349 (270–429)	255 (182–351)	188 (126–284)	60 (30–142)
% reduction (UI)	–	14.5 (9.5–21.9)	26.2 (17.4–37.0)	45.9 (32.0–59.1)	60.4 (44.0–72.0)	87.3 (71.6–93.6)
Region of the Americas						
n (UI), in 000s	249 (204–306)	249 (204–306)	247 (202–304)	230 (185–286)	203 (159–258)	89 (49–144)
% reduction (UI)	–	0.0 (0.0–0.0)	0.6 (0.4–0.9)	7.4 (5.6–9.5)	18.2 (14.4–22.5)	64.1 (50.6–79.4)
South-East Asian Region						
n (UI), in 000s	1 351 (1 193–1 515)	1 078 (940–1 244)	948 (804–1 110)	742 (610–906)	580 (460–732)	223 (128–353)
% reduction (UI)	–	19.7 (16.3–25.1)	29.5 (24.7–36.55)	44.6 (38.0–52.8)	56.8 (49.3–64.5)	83.3 (74.8–90.3)
European Region						
n (UI), in 000s	464 (383–552)	463 (382–551)	457 (376–545)	436 (356–523)	385 (308–471)	157 (85–253)
% reduction (UI)	–	0.2 (0.1–0.2)	1.5 (1.2–1.9)	6.2 (5.1–7.7)	17.1 (14.2–20.4)	65.9 (52.0–81.5)

Table 3.27 contd

WHO region	Global/regional deaths & % reduction through achievement of interim target or AQG level[a]					
		Interim target 1	Interim target 2	Interim target 3	Interim target 4	AQG level
Eastern Mediterranean Region						
n (UI), in 000s	336 (301–369)	289 (255–322)	253 (220–287)	199 (169–236)	158 (130–194)	64 (37–96)
% reduction (UI)	–	13.8 (11.5–16.9)	24.3 (20.4–28.9)	40.4 (34.4–46.4)	52.6 (45.7–58.9)	80.7 (72.2–88.4)
Western Pacific Region						
n (UI), in 000s	1 278 (1 119–1 449)	1 160 (1 009–1 324)	1 024 (876–1 191)	818 (673–978)	643 (512–796)	248 (138–386)
% reduction (UI)	–	9.2 (7.9–11.2)	19.8 (17.2–23.9)	36.1 (31.7–42.5)	49.7 (44.2–56.5)	80.6 (71.8–88.8)
Global						
n (UI), in 000s	4 155 (3 685–4 662)[b]	3 646 (3 179–4 188)	3 276 (2 818–3 840)	2 677 (2 237–3 222)	2 155 (1 736–2 674)	848 (484–1 310)
% reduction (UI)	–	12.0 (9.7–15.5)	20.8 (17.0–26.1)	35.2 (29.4–42.3)	47.8 (40.8–55.2)	79.5 (70.1–87.9)

UI: uncertainty interval.
[a] Based on 2016 figures and assuming all other relevant health factors remain unchanged.
[b] These values are slightly different than the ones reported in the WHO Burden of Disease 2016 report (WHO, 2018) due to rounding.
Note: for the definition of uncertainty interval, see WHO (2018).

The scenario analysis showed that if the interim targets were achieved, the greatest benefit in terms of reduced health impact would be observed in countries with high $PM_{2.5}$ concentrations and large populations. If population-weighted concentrations were to comply with the AQG level, then premature mortality could be reduced by as much as 45–50 deaths per 100 000 people.

On the other hand, much smaller changes in premature mortality would occur in high-income countries because in most cases the ambient $PM_{2.5}$ concentrations are already below the interim targets.

The derived reductions in the health burden relate to national or WHO regional level, population-weighted mean concentrations. However, policy-makers may require compliance with the AQG level not just at the level of the population average but in all areas where people live. Therefore, Table 3.27 underestimates the health benefits of full compliance with the AQG level for all locations.

Estimates of the ultimate population-weighted mean concentrations once interim targets or AQG levels have been achieved everywhere are not yet available; thus, the related benefits have not been described here. However, an impact assessment study provided estimates for a scenario in which the new $PM_{2.5}$ interim target 4 (10 μg/m³) had been achieved throughout Switzerland, including at hot spots (Castro et al., 2020). Under this scenario, the population-weighted mean concentration of $PM_{2.5}$ is expected to be only 83% of the interim target 4 value.

4

Good practice statements about other PM types

4.1 Introduction

The GDG decided not to formulate air quality guideline (AQG) levels for the specific types of PM (i.e. BC/EC, SDS and UFP) that were prioritized during the preliminary phase. This decision was made because the GDG considered that the quantitative evidence on independent adverse health effects from these pollutants was still insufficient at the time of deriving the AQG levels. The GDG decided that the best manner for addressing these pollutants in the guideline document was to formulate good practice statements (discussed in section 2.5.3), as outlined in the *WHO handbook for guideline development*, *2nd edition* (WHO, 2014a). That is, when a GDG is confident that a large body of diverse evidence that is hard to synthesize indicates that the desirable effects of a particular course of action far outweigh its undesirable effects (WHO, 2014c).

Section 4.4 (on SDS) is substantially more detailed than sections 4.2 (on BC/EC) and 4.3 (on UFP), and includes several statements on the mitigation measures for population exposure to pollution from SDS. This is intentional, since the mitigation of exposure to pollution from SDS requires different, less standard, approaches than those related to anthropogenic pollution (black carbon and UFP), that focus on source emission reduction.

4.2 Black carbon/elemental carbon

There is concern over the potential impacts on health of black carbon, and a review of the literature by WHO (WHO Regional Office for Europe, 2013a) concluded that evidence links black carbon particles with cardiovascular health effects and premature mortality, for both short- (24-hour) and long-term (annual) exposures. In studies that take black carbon and $PM_{2.5}$ into account simultaneously, associations remained robust for black carbon (WHO Regional Office for Europe, 2013a). Even when black carbon may not be the causal agent, black carbon particles are a valuable additional air quality metric for evaluating the health risks of primary combustion particles from traffic, including organic particles, that are not fully taken into account with $PM_{2.5}$ mass levels. An assessment by US EPA also summarized the evidence of associations between a series of health effects and black carbon concentrations, with conclusions similar to those of the earlier WHO review (US EPA, 2019a).

Black carbon is a measure of airborne soot-like carbon that is determined with optical methods. It is closely related to the mass concentration of elemental carbon (i.e. carbon in various crystalline forms) that is ascertained chemically. BC/EC is typically formed through the incomplete combustion of fossil fuels, biofuel and biomass, and is emitted from both anthropogenic and natural sources.

It consists of pure carbon in several forms, and the relevant particle size fraction can include known carcinogens and other toxic species. Black carbon is a powerful climate-warming agent that acts by absorbing heat in the atmosphere and by reducing albedo (the ability to reflect sunlight) when deposited on snow and ice (Bond et al., 2013).

To address concerns about the health and environmental effects of BC/EC, three good practice statements (Box 4.1) have been formulated. The following sections provide a rationale for each of the statements.

Box 4.1. Good practice statement – BC/EC

Based on insufficient evidence to propose an AQG level, the GDG decided to formulate the following three good practice statements on BC/EC directed to countries and regional authorities.

1. Make systematic measurements of black carbon and/or elemental carbon. Such measurements should not replace or reduce the existing monitoring of pollutants for which guidelines currently exist.
2. Undertake the production of emission inventories, exposure assessments and source apportionment for BC/EC.
3. Take measures to reduce BC/EC emissions from within the relevant jurisdiction and, where considered appropriate, develop standards (or targets) for ambient BC/EC concentrations.

4.2.1 Rationale for statement 1 – measurement of black carbon and/or elemental carbon

Black carbon is a measure of airborne soot-like carbon that is defined operationally by the method used for its measurement, that is, the optical absorption of specific wavelengths by particles collected on a filter. The extent of optical absorption is then converted to black carbon concentrations expressed in units of $\mu g/m^3$ via a calibration based on a mass measurement of elemental carbon. Continuous measurements of black carbon are often made with aethalometers, which use

an optical approach and a standard conversion to mass concentration. Black carbon is a metric similar to elemental carbon, with the latter being a chemical measurement; both are measures of soot-like (graphitic) carbon. Elemental carbon is also defined operationally; it is usually determined by thermo-optical (chemical) techniques, in which the carbonaceous material is driven off the filter at high temperatures in an oxygen-rich environment. There is a close relationship between black carbon and elemental carbon mass measurements, which (to a very good approximation) is linear, but the slope may vary by the specific PM mixture and should be verified locally to reflect local conditions.

There are several measurement methods for black carbon. Hansen (2005) provides a detailed description of a common measurement method. EU Directive 2008/50/EC (European Parliament & Council of the European Union, 2008) requires measurements of elemental carbon, but filter measurements of black carbon or related optical parameters such as absorbance are much simpler and cheaper to make than elemental carbon measurements and, therefore, are much more applicable globally. For example, Jeronimo et al. (2020) describe a low-cost method of measurement(). It should be noted further that black carbon and its optical properties are more relevant to the climate than elemental carbon.

Elemental carbon is required to be measured by EU Directive 2008/50/EC, and the European Committee for Standardization (CEN) has developed a measurement method (CEN, 2017; Brown et al., 2017). As yet, no similar standard exists for black carbon but descriptions of methods of reporting have been given in the EU-funded Aerosol, Clouds and Trace Gases Research Infrastructure (ACTRIS, 2020) and described by the World Meteorological Organization (WMO) (Petzold et al., 2013). Although recommending a standard method for BC/EC monitoring is outside of the scope of WHO air quality guidelines, defining a standard and easy-to-apply method by relevant organizations would facilitate the recommended monitoring.

4.2.2 Rationale for statement 2 – production of emission inventories, exposure assessments and source apportionment for BC/EC

BC/EC emissions arise from incomplete or inefficient combustion and, hence, tend to come from local sources in urban areas and from specific combustion sources such as solid fuel or fuel-oil-fired power plants. Sources include passenger cars, buses, and trucks and other heavy goods vehicles, particularly diesel engines (both on-road and off-road); residential solid fuel use such as wood and coal, as well as liquid fuel such as kerosene; and power plants using heavy fuel oil and coal. Shipping, agricultural waste burning and wildfires are also sources of black BC/EC.

Emission factors for BC/EC are often uncertain, but guidance is available via several guidebooks (EEA, 2019; US EPA, 2019b).

The nature of these local sources means that, in general, exposures to BC/EC are more spatially variable than the total $PM_{2.5}$, so exposure assessments could be more challenging but more informative about the true spatial contrasts in exposures. Assessments could be based on models with fine spatial resolution as well as on measurements. Modelling approaches might involve small-scale urban dispersion models based on Gaussian plume methods, boundary-layer scaling plume models, urban and large-scale 3D chemical transport models, and land-use regression models. Use of well-formulated emission inventories coupled with dispersion air quality models will yield the source apportionment necessary to formulate abatement policies to reduce air pollutants.

4.2.3 Rationale for statement 3 – implementation of measures to reduce BC/EC, including the development of standards where appropriate

Epidemiological studies have already been carried out using black carbon and elemental carbon as exposure metrics (Janssen et al., 2012; US EPA, 2019a). Most studies have been in Europe and North America, and further work in other areas of the world – as well as in Europe and North America – would be valuable, particularly since there now exists recommendations for reporting black carbon measurements, as described above.

There has been considerable discussion in the past over the differential toxicity of the various components of $PM_{2.5}$, but with no clear consensus so far. However, the earlier review of the literature in the WHO REVIHAAP project did state that PM components deriving from combustion were particularly toxic (WHO Regional Office for Europe, 2013a). In addition, much of the consideration of this issue has focused on the question of whether or not there is a better metric than total $PM_{2.5}$ mass to account for the associations demonstrated in the epidemiological studies. It seems unlikely that a clear answer to this question will be forthcoming in the near future and, indeed, in terms of actions to improve public health this may not be the right question to ask.

A more appropriate question to ask may be whether there is an additional metric or component that countries might target for emission reductions next to the total $PM_{2.5}$ mass. For many countries or regions – where the incomplete or inefficient combustion of carbon-containing material is common and where a substantial part of population exposure to PM is due to BC/EC – actions to reduce BC/EC would seem to be an appropriate complementary strategy and a good practice to strengthen clean air policies. BC/EC particles contain known toxic constituents such as carcinogens and are co-emitted with other toxic pollutants that are also products of incomplete combustion, that is, carbon monoxide, polycyclic aromatic

hydrocarbons and VOCs. Using total $PM_{2.5}$ as a control metric could mean that targets could be met with no specific pressure to reduce the primary combustion particles and known toxic constituents of BC/EC. Moreover, control of BC/EC requires paying stronger attention to spatial hot spots of primary PM pollution, which are less well captured or identified with $PM_{2.5}$ mass concentrations; thus, compliance with $PM_{2.5}$ standards may not necessarily guarantee low enough levels of elemental carbon for compliance.

In addition, given the carcinogenicity of elemental carbon, the strategy to keep its concentrations as low as possible is in line with the prevailing risk reduction strategy generally pursued for carcinogens. On the other hand, the control of total $PM_{2.5}$ mass in many areas is not totally under the control of a single country or jurisdiction – in many areas long-range transport of secondary PM is a significant contributor of $PM_{2.5}$ mass. Including BC/EC as an indicator of local emission reductions might compensate for the limited ability to influence total $PM_{2.5}$ concentration. Finally, there are sound climatic reasons for reducing black carbon concentrations: along with methane and ozone, black carbon is one of the most important short-lived climate pollutants, the reduction of which could produce rapid improvements in actions to stop climate warming (Bice et al., 2009; Bond et al., 2013; Miller & Jin, 2019).

To illustrate typical ambient levels of black carbon, the results from the United Kingdom Black Carbon Network can be used (Butterfield et al., 2016). Annual mean concentrations of black carbon measured in 2015 were 0.2–0.4 μg/m³ in rural sites, 1.0–2.0 μg/m³ in urban background stations and 1.4–5.1 μg/m³ in roadside locations. Black carbon made up a significant proportion of PM mass concentration at roadside sites, contributing to 12–21% of PM_{10} and 18–32% of $PM_{2.5}$. In an urban background location, these proportions were 5% and 9%, respectively, and in rural background locations were 2–3% of each of the PM fractions.

Black carbon mean concentrations observed in epidemiological studies ranged from 0.65 μg/m³ to 3.9 μg/m³, while for elemental carbon the means generally ranged from 0.47 μg/m³ to 3.5 μg/m³ and reached 7.5–8.8 μg/m³ in individual studies from Asia (Khreis et al., 2017; Luben et al., 2017).

Illustrative annual mean concentrations where statistically significant associations with health outcomes have been found were 1.08–1.15 μg/m³ for black carbon and 0.5–0.8 μg/m³ for elemental carbon (Luben et al., 2017).

Although the evidence base is insufficient to set a certain AQG level to provide a basis for legally binding limit values, adoption of an air quality standard or

target (e.g. in the form of a concentration reduction obligation) might be a good instrument to force local actions on BC/EC reduction.

Strategies to control BC/EC emissions should consider local conditions. They may address emissions from biomass and other polluting fuels used for cooking and heating, emissions from diesel vehicles and off-road machinery (World Bank, 2014), and emissions from agricultural (and communal) waste burning and from wildfires.

4.3 Ultrafine particles

UFP are generally considered as particulates with a diameter less than or equal to 0.1 µm, that is, 100 nm (typically based on physical size, thermal diffusivity or electrical mobility). There was already considerable evidence on the toxicological effects of UFP at the time that *Global update 2005* was being prepared, which was acknowledged in the document (WHO Regional Office for Europe, 2006). However, it was stated that the evidence from epidemiology was insufficient to recommend guidelines for UFP. Since then, the body of epidemiological evidence has grown, and two systematic reviews have assessed scientific research papers published from 1997 to 2017 (HEI, 2013; Ohlwein et al., 2019), documenting the rising number of studies being conducted. The studies demonstrated short-term effects of exposure to UFP, including mortality, emergency department visits, hospital admissions, respiratory symptoms, and effects on pulmonary/systemic inflammation, heart rate variability and blood pressure; and long-term effects on mortality (all-cause, cardiovascular, IHD and pulmonary) and several types of morbidity. However, various UFP size ranges and exposure metrics were used, preventing a thorough comparison of results across studies (US EPA, 2019a). Therefore, there was a consensus in the GDG that the body of epidemiological evidence was not yet sufficient to formulate an AQG level.

At the same time, however, there is a large body of evidence from exposure science that is sufficient to formulate good practice advice. The most significant process generating UFP is combustion and, therefore, the main sources of the UFP include vehicles and other forms of transportation (aviation and shipping), industrial and power plants, and residential heating. All of these utilize fossil and biofuels, as well as biomass. Since everyone is exposed to the emissions from these sources, exposure to UFP is of concern.

To address concerns about the health and environmental effects of UFP, four good practice statements (Box 4.2) have been formulated. The following sections provide a rationale for each of the statements.

Box 4.2. Good practice statement – UFP

The GDG decided to formulate the following four good practice statements on UFP to guide national and regional authorities and research towards measures to reduce ambient ultrafine particle concentrations.

1. Quantify ambient UFP in terms of particle number concentration (PNC) for a size range with a lower limit of ≤ 10 nm and no restriction on the upper limit.
2. Expand the common air quality monitoring strategy by integration of UFP monitoring into existing air quality monitoring. Include size-segregated real-time PNC measurements at selected air monitoring stations in addition to, and simultaneously with, other airborne pollutants and characteristics of PM.
3. Distinguish between low and high PNC to guide decisions on the priorities of UFP source emission control. Low PNC can be considered < 1000 particles/cm3 (24-hour mean). High PNC can be considered > 10 000 particles/cm3 (24-hour mean) or 20 000 particles/cm3 (1-hour).
4. Utilize emerging science and technology to advance approaches to the assessment of exposure to UFP for application in epidemiological studies and UFP management.

4.3.1 Rationale for statement 1 – quantification of ambient UFP

PNC is the most common measure used to characterize UFP, and the measurement technologies for this are well established; however, there is no agreed international (or national) standard method on this as yet. The existing instrumental methods for PNC measurement do not provide information on particles in the UFP-specific size range (< 100 nm), and both their lower and upper detection limits vary; the lower limit typically ranges from 2 nm to 20 nm. Therefore, the term quasi-ultrafine refers to particles substantially smaller than 1 μm but larger than 100 nm. In this document, PNC refers to the number concentration of quasi-UFP. The choice of the lower cut-off of measurement is usually critical, since the majority of UFP are often within a smaller size range, particularly in environments affected by fresh combustion emissions; the upper range is less critical. The error (underestimation) for lower size limits up to 10 nm can be calculated and

corrected for. The uncertainty in the calibration of instruments measuring PNC is based on a standardized methodology (ISO 27891:2015 (ISO, 2015)) and varies between 30% for lower concentrations (< 1000 particles/cm³) to 10% for typical urban background concentrations (about 10 000 particles/cm³) (Morawska et al., 2008; Thinking Outside the Box team, 2019).

4.3.2 Rationale for statement 2 – expanding UFP monitoring

Whereas the theories underpinning UFP emission and formation processes are generally well developed, local understanding of the origin of UFP (primary/secondary, specific sources) and their chemical composition (solid/liquid, organic carbon/elemental carbon, metals and toxicity) is generally very limited in most parts of the world; UFP and precursor emission inventories and PNC source apportionments hardly exist. Generally, there is very little or no relationship between PNC and mass concentration of larger particles ($PM_{2.5}$), and the existence and degree of relationship between PNC and traffic-emitted gaseous pollutants (carbon monoxide and NO_x) or black carbon varies, depending on location. Therefore, no other pollutant is a good proxy for UFP. However, quantitative knowledge of UFP is needed, since focusing only on $PM_{2.5}$ may result in overlooking the impact of UFP and there is no evidence that mitigating particle mass only (PM_{10}, $PM_{2.5}$), as the existing air quality measures do, will necessarily lead to a reduction in UFP (ANSES, 2019; Thinking Outside the Box team, 2019).

UFP monitoring would provide a good base for evaluation of effects of pollution mitigation and could be used for future epidemiological studies on the health effects of UFP and for distinguishing these effects from the effects of other pollutants. Note that the UFP measurements should not hinder the existing measurements of pollutants for which guidelines currently exist.

4.3.3. Rationale for statement 3 – distinction between low and high PNC

In urban areas, road traffic and other forms of transportation (aviation and shipping) are usually the main sources of UFP. These particles are emitted directly by the sources or formed in the air from gaseous precursors that are usually also emitted by the same sources. In addition, emissions from industrial sources, power plants, residential heating and biomass burning are sources of UFP, contributing to various extents to the UFP concentrations in urban air. Due to the nature of source emissions and particle formation, the spatiotemporal variation of the absolute level of PNC across a single city area is substantially larger than the spatiotemporal variation of larger particles (measured as particle mass concentration), for example $PM_{2.5}$. Based on literature review and expert opinion, there is general agreement that concentrations below 1000 particles/cm³ (24-hour mean), typically observed in environments not affected by anthropogenic emissions,

can be considered as low (de Jesus et al., 2019; Thinking Outside the Box team, 2019). It is proposed that 24-hour mean concentrations exceeding the typical levels observed in urban background areas (10 000 particles/cm³) or 1-hour mean concentrations exceeding levels found usually in all urban microenvironments (20 000 particles/cm³) can be considered high.

4.3.4 Rationale for statement 4 – utilization of emerging science and technology to advance population exposure assessment

Estimation of the population exposure to UFP in short- and long-term epidemiological studies (including repeated peak exposures) is significantly more complex than assessment of the exposure to $PM_{2.5}$ and PM_{10}. It would be highly beneficial to develop and utilize standardized measurement procedures that enable meaningful comparison between the results from different studies, which is of particular significance for human exposure and epidemiological studies. Considering the complexity of the measurements, variety of instruments available and difference in the aims of the measurement/monitoring, it is not likely that standard methods to measure UFP will be accepted/established in the foreseeable future. However, scientific progress on many fronts makes personal exposure assessment possible by providing estimates of variation among the different results based on differences in the instruments being used or their settings. Furthermore, there are modelling tools that can allow obtaining the source contributions to UFP concentrations and can increase the robustness of meta-analysis of multicity data for epidemiological studies. Therefore, future long-term studies might consider modelling, increasing the number of monitors or utilizing mobile platforms to collect data across larger urban areas in order to cover the spatial variability in cities (ANSES, 2019; Thinking Outside the Box team, 2019).

4.4 Sand and dust storms

At their first meeting in 2016, the GDG members agreed that SDS needed to be addressed in this update of the WHO air quality guidelines. Dealing with SDS has become a growing priority within the global community, as reflected by the adoption of several resolutions by the UN General Assembly (UN, 2016, 2017, 2018b, 2019b). Improving the implementation of sustainable land management practices, taking measures to prevent and control the main factors of SDS, and improving the development of early warning systems as tools to combat SDS feature among the key priorities for action (UNEP, 2016b).

The discussion and arguments reported here have to take into account the fact that there are countries that are located in desert regions and countries that do not include desert land but are affected by desert dust. SDS events that originated

in specific regions can impact various countries owing to the proven long-range transport of dust over countries and, even, continents (Tanaka & Chiba, 2006; UNEP, WMO & UNCCD, 2016; Middleton, 2017). Indeed, a relevant issue to take into consideration is the difference between geographical regions such as the Middle East, the Sahel and northeast Asia, which have considerable SDS events, and others such as eastern Asia, southern Europe, parts of North America, and western Africa, that have experienced various episodes of transported desert dust. Desert dust is usually composed of mineral particles that originate from arid and semi-arid land surfaces, but "sometimes, after having travelled great distances, they may be observed over areas where no dust or sand covers the ground" (WMO, 2020b). SDS are usually prompted by intense winds that elevate large amounts of sand and dust from bare, dry soils into the air (WMO, 2020a). It has to be considered that there is no precise distinction between sand storms and dust storms, since there is a continuum of particle sizes in any storm. Importantly, desert dust events have coincided with substantial increases in measured concentrations of both the PM_{10} and $PM_{2.5}$ size fractions. Furthermore, research from southern Europe suggests an increased accumulation of anthropogenic pollutant concentration during events of transported dust, likely owing to a number of related meteorological phenomena (Querol et al., 2019a).

The WHO-commissioned toxicological review of 67 experimental studies concluded that SDS may be a significant risk factor for inflammatory and allergic lung diseases such as child and adult asthma. Studies, mainly using doses that reflect or at least approach real-world exposures during a dust event, have demonstrated that sand dust particles collected from surface soils (i.e. at the source) and dust-storm particles sampled at remote locations away from the source (and as such, mixed with industrial pollutants and microorganisms) induce inflammatory lung injury and aggravate allergen-induced tissue eosinophilia. No studies were identified that included specific cardiovascular end-points. In vitro findings suggest desert dust surface reactions may enhance the toxicity of aerosols in urban environments (Fussell & Kelly, 2021).

The WHO-commissioned systematic review of adverse health effects from SDS summarized the evidence from 93 studies conducted worldwide. The studies indicate an overall effect of desert dust on cardiovascular mortality and respiratory morbidity, but the evidence is still inconsistent when accounting for sources of PM in different geographical areas (Tobias et al., 2019a, 2019b). In addition, previously published reviews, systematic or not, reported inconsistent results across studies and geographical regions (de Longueville et al., 2013; Hashizume et al., 2010; Karanasiou et al., 2012; Zhang et al., 2016). An existing limitation in the scientific literature is the lack of studies on the long-term health effects of SDS. The health

outcomes studied more frequently include (i) daily mortality, natural-cause and cause-specific; (ii) cardiovascular and respiratory morbidity; and (iii) morbidity as documented in hospital admissions and emergency room visits, mainly for cardiovascular and respiratory diseases, including asthma and COPD. Overall, the four reviews (de Longueville et al., 2013; Hashizume et al., 2010; Karanasiou et al., 2012; Zhang et al., 2016) had similar conclusions, suggesting that potential health effects linked to SDS may include increased cardiovascular mortality and respiratory hospital admissions. A range of other health impacts, such as injuries and death from transport accidents due to reduced visibility or the potential implications for disease incidence of meningitis and coccidioidomycosis, have also been reported (Ashley et al., 2015; Baddock et al., 2013; Goudie, 2014). The published studies differed in terms of settings, assessment methods for SDS exposure, lagged exposures examined and epidemiological study designs applied. Moreover, none of the previous reviews attempted to assess the quality of the evidence across the published studies.

The available evidence comes from studies that assessed the health effects of dust events as a binary risk exposure (mainly conducted in eastern Asia), comparing the occurrence of health events during dust and non-dust days, and from studies that considered dust events as an effect modifier for the health effects of any given PM fraction (mainly in southern Europe). Studies considering the effects of desert dust and anthropogenic PM (APM) concentrations independently revealed different effects in eastern Asia (higher association with specific cardiovascular mortality outcomes and ambulance calls related to Asian dust than to suspended PM) and southern Europe (similar health effects for Saharan dust and APM). When the role of APM during dust events was considered, the health effects of APM appeared to be stronger during dust days than during non-dust days. It should be noted that only studies considering short-term exposure have been conducted; there has been no study on the health effects of long-term exposure to sand and desert dust. The populations most susceptible to suffering the short-term effects of suspended particulates are considered to be older persons, individuals with chronic cardiopulmonary disorders, and children (Goudie, 2014).

Based on the available studies, the GDG agreed that formulating an AQG level for SDS was not possible due to insufficient evidence on quantitative and qualitative health risk-related characteristics of SDS. The GDG decided that the best manner for addressing SDS in the guideline document was to formulate qualitative practical recommendations focused on the likely consequences of desert dust and on options for mitigating it. Potential interventions can be part of short- or long-term strategies. Examples of possible short-term options outlined by the GDG in different meetings included: (i) strengthening and/or establishing

air quality management programmes; (ii) measuring PM components for the purpose of source apportionment; (iii) conducting research on health impacts and epidemiological studies; and (iv) cleaning up road dust on streets. During the discussions other options were also mentioned: (i) alerting public health authorities and vulnerable populations of increased levels of SDS; (ii) reducing local emissions from anthropogenic sources of dust and other pollutants during dust episodes; (iii) informing the public about personal interventions to reduce outdoor and indoor air pollution sources; and (iv) demonstrating the impact of policies towards lowering anthropogenic pollution (Argyropoulos et al., 2020; Katra & Krasnov, 2020; Querol et al., 2019b).

Long-term mitigation interventions are more complex. A review by Middleton & Kang (2017) classified interventions to mitigate SDS hazards into measures to prevent wind erosion occurring at source and measures to address the atmospheric transport of the particles and their deposition. If wind erosion is reduced, land degradation can be halted and eventually reversed and, in turn, SDS impacts can be mitigated. In agriculture, for example, a number of techniques are available for wind erosion control, including those that minimize the actual risk (e.g. cultivation practices such as minimum tillage) and those that minimize the potential risk (e.g. planting windbreaks) (Middleton & Kang, 2017). In general terms, long-term strategies such as reforestation plans have been implemented at various scales and for many years in different places; these were also meant as climate change mitigation measures (Jindal, Swallow & Kerr, 2008; UNEP, WMO & UNCCD, 2016).

All of the actions that address the impacts of SDS associated with particle transport and deposition include a range of monitoring, early warning, forecasting and communication activities. It is worth emphasizing that there is always a need to understand the context when discussing or implementing the good practices recommended in Box 4.3. Rationales for each of the good practice statements follow Box 4.3.

At the local, national and regional levels, the potential success of the implementation of these good practices is conditioned by actions that address the impacts of SDS with a range of monitoring, early warning, forecasting and communication activities. Other planned short-term actions – in general, relevant and desirable for reducing the overall impact of air pollution – can, if implemented, also decrease the exposure to SDS. These include (i) alerting public health authorities and vulnerable populations of increased levels of air pollution, in particular of SDS; (ii) reducing local emissions from anthropogenic sources of dust and other pollutants, in particular during dust episodes; (iii) informing the public

about personal interventions to reduce outdoor and indoor air pollution sources, in particular during SDS episodes, as sheltering during SDS episodes is sometimes the only feasible intervention (indoor air quality should be better than outdoor); and (iv) demonstrating the impact of policies towards lowering anthropogenic pollution. These actions are the mandate of national or local authorities, and international organizations can support policies by providing data, expertise and support.

Box 4.3. Good practice statement – SDS

Considering the available evidence, the GDG decided to formulate the following five good practice statements on SDS for frequently affected areas.

1. Maintain suitable air quality management and dust forecasting programmes. These should include early warning systems and short-term air pollution action plans to alert the population to stay indoors and take personal measures to minimize exposure, and subsequent short-term health effects, during SDS incidents with high levels of PM.
2. Maintain suitable air quality monitoring programmes and reporting procedures, including source apportionment activities to quantify and characterize the PM composition and the percentage contribution of SDS to the overall ambient concentration of PM. This will enable local authorities to target local emissions of PM from anthropogenic and natural sources for reduction.
3. Conduct epidemiological studies, including those addressing long-term effects of SDS, and research activities aimed at better understanding the toxicity of the different types of PM. Such studies are especially recommended for areas where there is a lack of sufficient knowledge and information about the health risk due to frequent exposure to SDS.
4. Implement wind erosion control through the carefully planned expansion of green spaces that considers and is adjusted to the contextual ecosystem conditions. This calls for regional collaboration among countries in the regions affected by SDS to combat desertification and carefully manage green areas.

Box 4.3 contd

5. Clean the streets in those urban areas characterized by a relatively high population density and low rainfall to prevent resuspension by road traffic as a short-term measure after intense SDS episodes with high dust deposition rates. Cleaning can be done by washing and/or sweeping. For the former, non-drinking, underground water from the subway drainage system or treated urban waters should be used (Querol et al., 2019a). This intervention is not feasible in many countries where water is scarce. In such cases, minimizing some of the local urban sources of dust such as construction and demolition activities can be a better alternative intervention. Before planning street cleaning, local authorities should:
    - assess the magnitude of the problem;
    - evaluate rainfall statistics;
    - select the streets that are most critically affected by the dust load situation;
    - ascertain the accumulation rate of sediments; and
    - determine the most effective cleaning method (e.g. frequency, timing and cleaning machine characteristics).

In partnership with other UN agencies, in particular, WMO, research institutes and academic institutions, WHO can ensure expertise and support in relation to dust measurements and their impacts. For example, the WHO Global Ambient Air Quality Database on air pollution, which is updated on a voluntary basis, can strengthen the adoption of good practices by providing a global framework of analysis. This can occur if countries affected by SDS send the WHO Global Database on Air Quality, for a given year, lists of affected zones, cities and agglomerations; information on concentrations and sources; and evidence demonstrating that observed PM concentrations are attributable, at least in part, to SDS episodes. This may provide the basis for different health impact (mortality and morbidity) calculations of air pollution that take into account the SDS contribution. The influence of SDS on air quality management is potentially very significant in orienting decisions, for example on setting national or local standards. Although this process should be based on this update of the WHO air quality guidelines and its AQG levels as the benchmark for setting standards, the rules concerning compliance assessment could be adjusted to accommodate local SDS risks.

4.4.1 Rationale for statement 1 – strengthening and/or establishing air quality management programmes

Preparedness and emergency response procedures in depositional areas need to cover diverse sectors such as public health surveillance, hospital services, air and ground transportation services, and public awareness and resilience. Since emergency response services are generally applied at local level, further subnational-level reviews and planning are needed.

A review by Querol et al. (2019b) suggested that setting up early warning systems for SDS by relevant authorities is an appropriate action to (i) inform exposed and vulnerable populations about behavioural measures that minimize the risks of high dust exposure levels; and (ii) implement special policy and regulatory measures at the local and regional levels to decrease anthropogenic air pollution emissions during dust episodes.

WMO established the Sand and Dust Storm Warning Advisory and Assessment System (SDS-WAS) (WMO, 2020c) to improve capabilities for more reliable SDS forecasting, intended for 40 of its Member States, with the Northern Africa-Middle East-Europe Node hosted by Spain, the Asian Node hosted by China, and the Pan-American Node with its Regional Center hosted by the United States and Barbados, respectively. The SDS-WAS mission is to achieve comprehensive, coordinated and sustained observations and modelling capabilities for SDS in order to improve SDS monitoring to increase the understanding of the dust processes and enhance dust prediction capabilities (WMO, 2020c).

Akhlaq, Sheltami & Mouftah (2012) provided an overview of the tools available for SDS prediction and detection, including data requirements and modelling approaches. Technologies include lookout towers, video-surveillance, sensory information, satellite imagery and unmanned aerial vehicles. The authors note that the best approach to use depends on the type of SDS, but that a hybrid approach consisting of wireless sensor networks and satellite imagery is appropriate for detecting and predicting all types of SDS.

The authorities in charge of the warning system should assess the most appropriate means to disseminate alerts to the population. Several means may be considered, such as media coverage, dedicated websites, messaging through social media and dedicated smartphone apps. It is also important to define the target population and identify vulnerable populations that can be particularly affected by SDS, as well as the facilities and other infrastructure that may be needed for such events. The involvement of health professionals and, in particular, of the medical profession should be considered, for example, general

practitioners who, knowing the population, can rapidly identify susceptible individuals based on their age, comorbidities, socioeconomic status or social isolation. Although the evidence on adverse health effects from SDS remains preliminary, there is some literature suggesting the effectiveness of public health alerts in promoting behavioural change. Messages that are generally issued by authorities include the following: staying indoors (appropriate in many settings), avoiding exposure, refraining from exercise, following asthma plans (for asthmatic patients), driving with care (for cases of SDS affecting visibility such as dry thunderstorms or haboob), and visiting the doctor if respiratory or cardiovascular symptoms occur (Middleton & Kang, 2017; WHO, 2020a).

Although there is evidence of the cost–effectiveness of early warning systems, especially for those related to weather services, there is no direct evidence for SDS. To be cost–effective, four elements must be present in any early warning system: knowledge of risks, monitoring and alert services, communication, and response capability. Systems are typically cost–effective when the monitored event is relatively frequent, significant harms can occur and there are affordable preventive measures (Rogers & Tsirkunov, 2010; World Bank, 2019). Specifically, it is not just the frequency of events but their intensity that should be considered. However, there is no cut-off, that is, no specific number of episodes per year, to orient decisions. This issue is similar to considering alert systems for wildfires that can affect an area; tools are available to assess the air quality impacts of such events, including their frequency and intensity. If these events are only rare and mild, usually a conventional weather forecast is sufficient to warn the public. These systems and their structure should take into account existing time series of events and evaluate the potential health impacts using epidemiological methods and tools.

Querol et al. (2019b) provided an example of the system established in Portugal and Spain as good practice. The system consists of three modules that allow SDS predicting, detecting SDS when they occur, and quantifying the daily contributions of desert dust to ambient $PM_{2.5}$ and PM_{10} concentrations.

4.4.2 Rationale for statement 2 – strengthening air quality monitoring programmes through identification of dust sources

SDS are usually prompted by intense winds that elevate large amounts of sand and dust from bare, dry soils into the air and transport them for long distances. As a result of this phenomenon, approximately 40% of aerosols in the troposphere are dust particles derived from wind erosion. The main areas from which mineral dust originates are the arid regions of northern Africa, the Arabian Peninsula, and central and eastern Asia (WMO, 2020a). Saharan dust may contribute more than

60% of the total PM_{10} concentration in Mediterranean countries and the Middle East during a strong dust pollution event (Pey et al., 2013; Querol et al., 2009). This may lead to exceedances of the daily average interim target 4 value for PM_{10} of 50 μg/m³. Causes of SDS are affected by direct and indirect drivers in natural ecosystems, direct and indirect drivers in human-dominated ecosystems, and land degradation feedback processes (UNEP, WMO & UNCCD, 2016). In recent centuries, human activities and climate change have aggravated the problem of desert storm generation. The natural composition of desert dust can be affected by several human sources (Mori et al., 2003; Rodríguez et al., 2011). This makes the distinction between natural PM and APM sources and assessment of the health effects of desert dust difficult (Perez & Künzli, 2011; Querol et al., 2019b).

A review commissioned by WHO (Querol et al., 2019b) suggested that acquiring reliable exposure data for source apportionment is a first critical step for epidemiological and health impact assessment studies of SDS. For desert dust, Querol et al. (2019b), based on earlier work by Escudero et al. (2007), recommended the following procedure for source apportionment as a method to quantify desert dust contributions to PM levels for air quality reporting purposes.

- Collect daily $PM_{2.5}$ and PM_{10} data, measured at remote or regional background air quality monitoring stations close to the urban area under evaluation.
- Calculate the 30-day moving 40th percentile PM concentration without taking into account PM levels on the SDS days. The 40th percentile equates to the $RBPM_{10}$ and $RBPM_{2.5}$ levels without the dust contribution.
- Determine the net dust PM (NDPM) levels in PM_{10} and $PM_{2.5}$ ($NDPM_{10}$ and $NDPM_{2.5}$) for the regional background by subtracting $RBPM_{10}$ and $RBPM_{2.5}$ from the bulk PM_{10} and $PM_{2.5}$ levels at the reference regional background-monitoring site.
- At the nearby urban area, $NDPM_{10}$ and $NDPM_{2.5}$ can be considered the net desert dust contribution for the specific area during the specific SDS day. The result of the subtraction of the $NDPM_{10}$ and $NDPM_{2.5}$ values from the urban PM_{10} and $PM_{2.5}$ levels, are the APM loads during the dust days (APM_{10} and $APM_{2.5}$).
- Once the series of NDPM and APM are obtained, the health effects could be evaluated for PM, NDPM and APM.

Source apportionment with receptor modelling, based on sampling and chemical analysis of PM, is also suggested. However, when there are other important sources of non-desert dust (e.g. local soil or urban dust), this approach may be unable to differentiate sources.

A potential solution is implementing the study at a reference rural/remote site. As the review by Querol et al. (2019a) showed, local pollution in areas far away from dust sources can be enhanced under intense SDS (by thinning of the boundary layer and the interaction of mineral dust and gaseous pollutants) and dust can be co-transported with pollutants and microorganisms such as fungi and spores.

Better monitoring systems can support decision-makers to establish to what extent disease outbreaks are the result of transported sand and dust and to assess the contribution that human activities have made to that process. That is, they can help better comprehend the impact of human activities on SDS and how these ultimately impact the environment and social systems.

4.4.3 Rationale for statement 3 – conducting health impacts research and epidemiological studies in areas affected by SDS

WHO has followed a systematic process to review the effects of desert SDS on human health. This has allowed for summarizing quantitatively, using meta-analysis, the effects of dust on several mortality and morbidity outcomes (Tobias et al., 2019b).

Various epidemiological studies on the health effects of dust events have formulated hypotheses in different ways. They have compared health outcomes between days without and with desert dust events, assessed differences in association between total PM and health on days without and with desert dust events, or looked for independent effects of dust-derived PM and APM on health.

The summary of the evidence of the systematic review on desert dust indicated inconsistent results, depending on the way of assessing the effect of dust on health and the geographical region where the studies were conducted. The comparability of short-term estimates of desert dust health effects obtained in different studies could be improved by standardizing the modelling of desert dust exposure, as proposed by Tobías & Stafoggia (2020). Furthermore, studies on long-term effects of SDS are needed.

4.4.4 Rationale for statement 4 – desertification and wind erosion reduction interventions

There is a recognized pathway that links the presence of green spaces and health benefits (Markevych et al., 2017; Rojas-Rueda et al., 2019). Green spaces play an important role that is under intense scrutiny, from both empirical studies and models, in terms of ecosystem services and co-benefits to improve (mental and physical) health, mitigate climate change and provide spaces for physical activities (Egorov et al., 2016).

Various techniques, mainly reforestation plans, have been implemented in different ways in many countries to reduce exposure to desert dust (FAO, 2009, 2021). Most of these techniques were developed to protect cultivated fields from soil loss (Nordstrom & Hotta, 2004), for carbon sequestration projects and to address desertification. Health impacts have rarely been taken into account in most of the projects (Donovan, 2017). Nevertheless, tree and shrub planting should be taken into account to reduce PM in areas heavily affected by desert dusts following careful studies of the environmental conditions of the land and areas where such plans are going to be implemented.

On an international level, there is well-established agreement that

> [t]here is need for an integrated multi-scale approach for effective SDS control. Control measures at the field scale to protect soil and reduce wind speed locally, need to be combined with landscape measures over large areas to reduce wind speed, reduce sand and dust mobilization and increase deposition of sand and dust out of the atmosphere. Measures must simultaneously tackle different components of the landscape, including cropland, rangeland and deserts, as well as other sources, such as building sites, mines, etc. Integrated, landscape level measures are especially critical given the transboundary impacts of SDS.
>
> Control of anthropogenic sources of SDS is synonymous with sustainable land management [...] and integrated landscape management [...] and requires a long-term vision (UNEP, WMO & UNCCD, 2016).

Such initiatives are successful in the long-term only if they carefully consider existing water resources and utilize well-adapted plant species.

It is worth considering that most of the published studies supporting greening interventions have been carried out in North American (e.g. Nowak & Heisler, 2010), European (Selmi et al., 2016) and some Asian cities (e.g. Yang et al., 2005); some research results are available from areas in desert regions (e.g. Cohen, Potchter & Schnell (2014)). Overall, however, there is a lack of systematic studies in cities and in rural areas heavily affected by desert dust. Most of the studies are mainly urban, although the impacts of desert dust are not negligible for populations living in rural areas. It is worth noting that water resource management can represent a more crucial issue than greening in various countries.

4.4.5 Rationale for statement 5 – urban street cleaning

A review of street cleaning as a measure to mitigate the impact of road dust offers indirect evidence of the benefits of this type of intervention (IDAEA, 2013). The authors found that sweeping alone did not decrease PM levels in the short term, although a reduction could not be excluded in the long term. In contrast, washing – alone or in combination with sweeping – yielded more promising findings, with PM_{10} reductions observed in most reviewed studies. PM_{10} reductions varied within 7–30% of the daily mean PM_{10} concentration depending on the local situation, and were observed in a variety of settings, including Asia, Europe and North America.

In addition, street washing and sweeping can be cost–effective in reducing the health impacts of pollution from road traffic, as indicated in an analysis from the United Kingdom (Ballinger et al., 2016).

The practice of street cleaning should be carefully discussed before adoption due to the use of resources and energy that may not produce the expected overall public health benefits. Additionally, there are no studies that provide direct evidence of the effectiveness of street cleaning for reducing desert dust exposure and/or its adverse health effects after intense episodes with high dust deposition rates.

5

Dissemination of the guidelines

These guidelines will be distributed through multiple communication platforms to reach a wide range of audiences. This includes formal communication lines through WHO offices to relevant national authorities, professional organizations and agencies and nongovernmental organizations; more informal local-scale, on-the-ground platforms; and social media using tools to raise awareness and campaigns to foster engagement. In addition, collaboration platforms with other UN agencies, regional bodies and national partners will be used to facilitate dissemination.

It is important to widely distribute and disseminate the information provided in these updated guidelines, and using effective communication to do so will be key to successful uptake. Although these guidelines are universally applicable, additional and/or different approaches and strategies may be required to disseminate and communicate information about them in low- and middle-income countries, particularly where poverty and inequity could add to the complexity of the distribution and communication process.

The communication strategy for the guidelines aims to address all different types of audiences by modifying the language used to present the guidelines and diversifying the tools and channels used to maximize reach and impact to all relevant users. Communication is based on the provision of strong and clear messages and the establishment of relationships with all relevant stakeholders across sectors to ensure the usefulness, acceptability, understanding and uptake of the final product.

5.1 Tools and approaches to raise awareness of the guidelines

Several tools and approaches will be used, including dedicated WHO webpages, communication materials, awareness-raising campaigns, and specific information dissemination and communication approaches.

The WHO website is the major channel for disseminating information on the air quality guidelines to a range of users and for targeting policy-makers, health-care professionals, governmental agencies, the media, academia and the public. The website provides general information on the project and links to relevant documents and resources.

Lay versions, graphical materials, and materials developed in different official languages for promotion and awareness-raising purposes are available on social media platforms. Other means to communicate the guidelines include answers

to frequently asked questions, factsheets and key messages on air pollution and health addressed to policy-makers or health practitioners.

Advocacy and outreach activities in key high-level forums are planned as part of the road map for implementation of this update of the WHO air quality guidelines. A prime example is the joint BreatheLife campaign (led by WHO, the Climate and Clean Air Coalition (CCAC) and UNEP), which aims to mobilize individuals and cities to protect human health and the planet from the adverse effects of air pollution (WHO, CCAC & UNEP, 2018). Another example is the WHO Urban Health Initiative, which promotes the consideration of human health in city development (WHO, 2020c). A specific package to train health-care professionals in air pollution and health will also be launched.

Dissemination of the WHO air quality guidelines is a whole-of-society effort. This means that, while WHO will be targeting several strategic small- and large-scale communication forums, the availability and accessibility of the air quality guidelines will enable their wide distribution among interested parties. This includes civil society organizations, which can further share them through their related initiatives.

In addition, WHO aims to participate in relevant conferences, workshops and stakeholder meetings to introduce the guidelines to audiences globally. These include:

- large, high-profile events with a predominant policy focus;
- smaller workshops or meetings of end-users of the guidelines;
- meetings of professional medical societies;
- events and conferences of the scientific community working on air pollution and health;
- articles, opinions and/or editorials in leading scientific journals;
- meetings, conferences and personal engagements at the local and grass-roots levels, for example at relevant national association events or targeted consultation in affected communities;
- press releases to civil society by local organizations;
- engagement by governments and by WHO regional and country offices; and
- national-level patient groups and networks.

5.2 Risk communication

Effective risk communication enables and empowers people who are facing health risks to make informed decisions that can improve their personal well-being. These people, in turn, can educate others, which can

ultimately empower communities to take actions to reduce risks and increase healthy behaviours. The air quality guidelines provide the evidence base from which successful risk communication about air pollution effects on human health can take place. The provision of air quality guideline (AQG) levels, for instance, aims to prompt action to reduce health risks from exposure to air pollutants. By outlining who is most affected by exposure to air pollution, these guidelines are also able to provide direction in terms of to whom risk communication should be targeted in order to be most successful.

It should be noted that risk communication around air pollution is difficult and many factors need to be considered, including understanding how people perceive risk and ensuring that the risks of poor air quality are communicated in a way that empowers rather than disempowers people. In order to do this effectively, using the WHO air quality guidelines as a base, different stakeholders will need to play a role, including governments and civil society. This highlights the importance of dissemination of the guidelines in forms fit for different audiences, particularly for those who are most impacted by poor air quality. Specific information on the principles of risk communication is available in different WHO publications (WHO Regional Office for Europe, 2013b; WHO, 2017, 2020a).

5.3 Advocacy and engagement of stakeholders

The air quality guidelines advocate for services and regulatory frameworks that promote the management and reduction of air pollution to protect the health and well-being of individuals and communities. The successful dissemination and communication of the air quality guidelines aim to ensure the adoption of the guidelines into relevant institutional, community, national and international policies in order to transform existing systems and processes and, ultimately, improve human health.

Any successful advocacy strategy requires collaborative approaches and the effective engagement of relevant stakeholders across sectors. Participatory approaches are deemed valuable, particularly in lower-income contexts. This is because a consultative dialogue is often more successful at tangibly bringing across abstract concepts to communities, for instance, rather than one-way information sessions.

WHO will use its convening power to facilitate effective cooperation and ensure that key stakeholders (not only from different sectors but also from various perspectives, including local and national governments, civil society and academia) can share and benefit from their respective expertise, experience and resources.

6

Implementation of the guidelines

The WHO air quality guidelines set goals for protecting public health on a worldwide scale. They were established through a rigorous process of revision and evaluation of scientific evidence on the health effects of air pollutants and, like other WHO guidelines, are not legally binding recommendations. National standards are developed through a policy-making process by each country, have legal status and are based on the specific conditions of the country itself. Supranational (e.g. EU) and regional standards may also be developed, depending on the political structure of the area. The establishment of adequate legislation for protection of the population from the health effects of air pollutants is an essential step for all countries. The transfer of guidelines into practicable standards is an integral part of public health and environmental protection policy and is a challenge for most countries. The continuous improvement of air quality requires a formidable effort by those countries dedicated to addressing this major environmental health problem in order to progressively reduce the potential health effects, irrespective of the air pollution level at which they start. Abatement measures and air quality improvement should aim to achieve the interim targets and, finally, the air quality guideline (AQG) levels as expeditiously as possible (additional guidance on interim targets can be found in section 2.5.3). Up-to-date knowledge and information on levels of air pollution and guidance on interim targets can increase awareness and provide an incentive for the adoption of measures to reduce the level of pollutants, monitor progress and evaluate results.

This chapter examines that process and provides an overview of the general usefulness of the WHO air quality guidelines, with an emphasis on the careful assessment of national needs, capacity-building and the additional elements that are necessary in the development of national standards. Once standards have been established, there is a need for a proper implementation strategy and management of air quality with monitoring, training and enforcement. Health risk assessment is an essential tool to inform public policy decisions by providing an understanding of pollution-related disease burden and the potential for burden reduction. Collaborations of the health-care sector and many different stakeholders are essential to maintain public health protection.

6.1 Significance of the guidelines: an evidence-informed decision support tool

AQG levels are widely seen as a practical instrument for advancing emission reductions and the design of effective measures and policies. WHO guidelines equip policy-makers and other end-users across a range of different needs with the necessary evidence base to inform their decisions. They serve as a reference for assessing whether, and how much, the exposure of a population

(including particular vulnerable and/or susceptible subgroups) is associated with health concerns. For various target audiences and for each stakeholder group, they can function as a critical tool to be used in multiple ways and integrated into their work for years to come.

6.1.1 Use by authorities

Health risk assessments are an important tool for authorities (at international to local levels) when deciding on necessary emission reduction measures because they provide estimates of the health burden/impacts on the population and, therefore, allow a comparison of the consequences among different policy options. These options can include measures to reduce emissions from various sources, measures aimed at reducing concentrations of pollutants in ambient air, measures aimed at reducing exposure of individuals and the population, and/or measures related to urban planning. In principle, the priority should be to prevent emissions of pollutants and reduce them at source.

6.1.2 Use by technical experts and decision-makers

For technical experts and decision-makers, the guidelines are vital in providing information on concentration–response relationships that give insight into the consequences of certain regulations or standards on the associated health effects. They are essential quantitative inputs to quantify the impact of air pollution on health and can be useful at the national and international levels when developing air quality limits or standards as they provide the scientific basis to identify the levels at which air pollution can cause a significant and unacceptable health impact. They provide valuable information used in cost–effectiveness and cost–benefit analyses of various policies and, based on these recommendations, national governments and international organizations can be better informed when introducing air quality standards to ensure the protection of people's health.

6.1.3 Use by civil society, patient and other advocacy groups

They can also be used by civil society, patient and other advocacy groups to raise awareness and encourage actions to protect the population, including susceptible groups such as children, from exposure to air pollution. They can be used to help inform these groups to advocate to policy-makers to improve air quality levels. They are of great value for communicating the health risks and potential cost–effective solutions to reducing air pollution. Organizations responsible for risk communication and general awareness-raising can use these guidelines for promotion campaigns and appropriate risk communication. The guidelines provide scientific evidence on a range of health effects associated with air pollutants and facilitate appropriate risk communication to specific vulnerable and susceptible groups.

Therefore, they need to be promoted broadly to citizens, national and local authorities, and nongovernmental organizations responsible for risk communication.

6.1.4 Use by health/environmental impact assessment practitioners

For health/environmental impact assessment practitioners, these guidelines provide concentration–response relationships that give insight into the expected health effects at observed or expected air pollution levels under various future scenarios. They provide vital input to assist in deriving the health burden or impact of air pollution; in that sense, they can be used when conducting studies to obtain an evaluation of the magnitude of the health problem for a particular situation. The systematic reviews developed in support of these guidelines will support practitioners in raising awareness of the credibility of the issue of air pollution as a public health problem and in applying the recommended concentration–response relationships uniformly so as to justify their use in different countries.

6.1.5 Use by researchers and academics

Researchers and academics will also benefit from the guidelines as they clearly identify critical data gaps that need to be filled in the future through a structured research agenda in order to better protect the population from the harmful effects of air pollution. In addition, the importance of the burden of disease related to air pollution provides an opportunity to justify the inclusion of content related to the guidelines in university curricula for a variety of medical professionals and scientists.

6.2 Assessment of national needs and capacity-building

National needs, including the need for capacity-building, differ greatly among countries. They depend in great part on the existence and level of implementation of national, regional and international policies. In many countries, air pollution is now perceived as a major and growing environmental and public health problem. Nevertheless, significant differences are still evident in multiple areas:

- the existence and operation of air pollution monitoring systems;
- the availability of and public access to data;
- air quality management policies, regulations and standards;
- the availability of trained human resources to understand, assess and monitor health impacts; and
- implementation of universal health coverage and cross-sectoral collaboration.

The existence and operation of air pollution monitoring systems differs by country and city.

Conditions at the country and city levels, specifically for the annual mean $PM_{2.5}$, have been documented as interactive maps as part of the WHO Global Health Observatory (WHO, 2021a). Progress in combining satellite remote sensing, global chemical transport models, land-use regression models, high-resolution dispersion models and surface measurements (including those made using low-cost sensors) has made information on exposure increasingly available, including in some of the most highly polluted and data-poor regions. However, these estimates need to be grounded and evaluated with existing or new ground-based monitoring; further development of these methods depends to a large extent on the availability of surface measurements in all regions of the world.

The availability of and public access to data to assess population exposure to ambient air pollution and quantify the health impacts or burden related to air pollution for past and current scenarios or future projections also differs by country.

Differences also exist between countries in the development and implementation of air quality management policies, regulations and standards that take into consideration the latest research evidence on the health impacts of ambient air pollutants. Policies to reduce emissions of air pollutants, which are clearly preferable and should be the main focus of any air quality management plan, are highly context dependent: what might be effective and contribute to improving public health in one setting might not work in another. Therefore, understanding the particular situation, including the main emissions, sources and nature of the populations exposed, is critical to the development of effective risk management policies and strategies and is important for decision-making. Most critical is to understand the current level of air pollution in relation to the guidelines.

Lastly, there are differences in the implementation and strengthening of universal health coverage and in the level of cooperation of the health sector in decision-making with other sectors. These include the environment, transport, land planning, housing and energy, agriculture, industrial, and building sectors at the national, regional and, in some cases, international levels.

6.3 Moving from guidelines to air quality standards

The primary aims of these guidelines are to provide a uniform basis for the protection of public health from adverse effects of air pollution and to eliminate or reduce exposure to those pollutants known or likely to be hazardous. Based on the extensive scientific evidence available, the guidelines aim to identify the optimal level of air quality to protect public health in different contexts; they

provide a pathway to countries to transform the recommended AQG levels into legally enforceable standards. This section discusses ways in which this may be done, drawing from and expanding upon previous documents (WHO Regional Office for Europe, 1987, 1998, 2000b), each of which is a useful resource on this topic. The discussion here is limited to pollutants measured in ambient air and does not include the setting of emission standards.

6.3.1 Air quality standards

Air quality standards are the cornerstone of air quality management. Such standards are adopted and enforced by regulatory authorities to define the acceptable level of air pollution for a country or region. They define the level of an air pollutant, such as a concentration measured in ambient air for a specific averaging time. Unlike the case for a guideline value, several additional elements are usually specified in the definition of a standard. These include the averaging time, the measurement technique and strategy, data handling procedures (including quality assurance/quality control), and the statistics (for example, choice of a particular percentile) and form used to derive the value to be compared with the standard. The definition of a standard may also include a permitted number of exceedances of a certain numerical value in a given period.

Air quality standards may be based solely on scientific evidence and public health considerations. However, other features such as legal aspects, cost–benefit or cost–effectiveness may also be examined. In practice, there are generally several opportunities within a legal framework to address economic issues, as well as issues related to technological feasibility, infrastructural measures and sociopolitical considerations. These can be considered during the standard-setting process or when designing appropriate measures to control emissions. This process may result in the establishment of multiple standards, such as an adverse effect-oriented standard as a long-term goal and less stringent interim standards to be achieved within shorter periods of time.

Standards also depend on political choices about which health and environmental effects should be prevented and the extent to which populations should be protected. They also depend on the country's economic development level, capability in air quality management and other factors. Given that the benefits of clean air policies largely outweigh the cost of managing air pollution (Amann et al., 2017), the political choice for the adoption of rigorous standards may find broad societal support for economic reasons. Some countries have separate standards for the protection of public health and for the environment. Moreover, the stringency of a standard can be influenced by provisions designed to account for individuals or populations who might be more susceptible to the effects of

air pollution, such as children, older adults, and individuals with asthma or other pre-existing diseases. Consideration of environmental justice or other equity issues that affect disadvantaged segments of the population may be accounted for when deriving standards. It also might be important to specify whether effects are considered for individual pollutants or for a combined exposure to several pollutants. Air quality standards should be regularly reviewed and revised as new scientific evidence emerges on adverse effects on public health and the environment.

6.3.2 Legal aspects

Within established legal frameworks, and using the WHO air quality guidelines as a starting point, the development of standards involves a consideration of several aspects. These are in part determined by the emission sources, characteristics of populations and physical properties of the environment, and include the following determinations: (i) which pollutants should be regulated; (ii) the adverse health effects against which the population needs to be protected; (iii) which individuals or subpopulations are most at risk for the effects of air pollution; (iv) what level of risk and related costs for society are acceptable to the populations; (v) what uncertainties remain in the evidence base and how they will affect the decision-making process; and (vi) the feasibility of complying with the proposed standards (which includes assessing the costs and benefits of compliance).

Legislation on, as well as the format of, air quality standards varies from country to country but, in general, the following aspects should be considered:

- identification and selection of the pollutants to which the legislative instrument will apply;
- the numerical value of the standards for the various pollutants or the process for making decisions about the appropriate standards, applicable detection methods and monitoring methodology;
- actions to be taken to implement the standard, such as the definition of the time frame needed/allowed for achievement of compliance with the standard, considering emission control measures and necessary abatement strategies; and
- identification of the responsible enforcement authorities.

Depending on their position within a legislative framework, standards may or may not be legally binding. In some countries, the constitution contains provisions regarding the protection of public health and the environment. The development of a legal framework based on constitutional provisions generally comprises two regulatory actions.

The first is the enactment of a formal legal instrument, such as an act, law, ordinance or decree. The second is the development of regulations, by laws, rules and orders.

6.3.3 Factors to be considered in setting standards

The recommendations (Chapter 3) of these WHO air quality guidelines are based on serious health effects (mortality or hospital admissions/emergency room visits) in a general population and are not designed to focus on the protection of sensitive groups. It is notable that epidemiological studies of the general population include sensitive groups, and these sensitive groups contribute, in part, to the reported risk estimates. Furthermore, such studies often do not provide separate CRFs for various subgroups of the population. However, in setting a standard for the control of an environmental pollutant, consideration may be given to additional aspects, including the adverse effects that the standard will address. A hierarchy of effects on health can be identified, ranging from minor and temporary illnesses to acute, severe illness, chronic disease and death. Distinguishing between adverse and non-adverse effects can pose considerable difficulties (Thurston et al., 2017). Of course, more serious effects are generally accepted as adverse. In considering effects that are either temporary and reversible or involve biochemical or functional changes with uncertain clinical significance, judgements must be made as to which of these less serious effects should be considered adverse. With any definition of adversity, a significant degree of subjectivity and uncertainty remains. Judgements as to adversity may differ between countries because of factors including different cultural backgrounds and different levels of health status.

Susceptible populations or groups are defined here as those who are more sensitive because of impairment by concurrent disease or other physiological limitations and specific characteristics that make the health consequences of exposure more significant (e.g. the developmental phase in children and reduction in the physiological reserve capacity of older people). Other vulnerable groups may also be judged to be at special risk owing to their exposure patterns or to having an increased effective dose for a given exposure (e.g. outdoor workers, athletes). These populations may vary across countries owing to differences in the number of people with inadequate medical care; existence of endemic disease; prevailing genetic factors; or prevalence of debilitating diseases, nutritional deficiencies and lifestyle factors. The setting of air quality standards generally takes into account other considerations beyond public health impacts such as economic and technological aspects and, as such, is considered a political decision.

Another factor to be considered in developing standards is information about the concentration–response relationship for the pollutant of concern. Where adequate evidence is available, concentration–response relationships for a number of pollutants are presented in this update of the WHO air quality guidelines.

In developing standards, regulators should consider the degree of uncertainty about concentration–response relationships. Differences in the population structure (age, health status), climate (temperature and humidity) and geography (altitude, different ecosystems) can have an impact on the prevalence, frequency and severity of effects and may modify the concentration–response relationships provided in these guidelines in their application to a particular population.

Important factors to be considered in developing standards are the number of people who are exposed to concentrations of concern and the distribution of exposure among various population groups at current pollution concentrations and at the different concentrations at which standards might be set. As well as monitoring data, the results of exposure modelling can be used at this stage of a risk assessment. The origin of background air pollution, including long-range pollution transport and its contribution to ambient levels, should also be evaluated when considering standards. It is important that guidelines are health based and, therefore, do not consider background values, whereas standards may include considerations of background levels (e.g. in the case of ozone, background increases with a warming climate).

The extent to which ambient air quality estimates from monitoring networks or models correspond to personal exposure in the population should also be considered in standard setting. This will depend on the pollutant in question (e.g. personal exposure to carbon monoxide is poorly characterized by fixed-site monitors) and other local characteristics, including lifestyle, climatic conditions, spatial distribution of pollution sources and local determinants of pollution dispersion.

Other important exposure-related concerns include how much total human exposure is due to ambient, outdoor sources as opposed to indoor sources, and how to apportion the regulatory burden among the different routes of exposure (e.g. PM from outdoor sources versus PM from household cooking with fossil fuels) for pollutants where multiple routes of exposure are important. These may vary substantially between countries. For example, indoor air pollution levels are normally quite substantial in households in countries where fossil and/or biomass fuels in unvented stoves are used for cooking and heating in homes. However, further discussion of the evolving methods of exposure assessment is beyond the scope of these guidelines.

6.3.4 Risk assessment

Generally, the central question in developing air quality standards to protect public health is the degree of protection associated with the different pollution levels at which standards might be established. In the framework of quantitative risk assessment, various proposals for standards can be considered in health or ecological risk models. These models represent a tool that is increasingly used to inform decision-makers about some of the possible consequences of pollution associated with various options for standards (or, alternatively, the reduction in adverse effects associated with moving from current conditions to a particular standard). Regulatory risk assessments are likely to result in different risk estimates across countries owing to differences in exposure patterns and in the size and characteristics of susceptible and vulnerable populations at special risk.

It is important to recognize that there are many uncertainties at each stage of a regulatory risk assessment. The results of sensitivity and uncertainty analyses should be presented to characterize the impact of major uncertainties on the risk estimates. In addition, the methods used to conduct the risk assessments should be clearly described and the limitations and caveats associated with the analysis should be discussed. In addition, the degree of acceptability of risk may vary between countries because of differences in social norms and the degree of adversity and risk perception among the general population and various stakeholders. How the risks associated with air pollution compare with risks from other pollution sources or human activities may also influence risk acceptability (GBD 2019 Risk Factors Collaborators, 2020).

6.4 Air quality management

Risk to health from inhaled pollutants varies with the concentrations of pollutants inhaled and the mechanisms by which they cause adverse effects, which may be acute or chronic. The sources of exposure to airborne contaminants are myriad, even for the pollutants covered by the WHO air quality guidelines, and pollutants are encountered as people move through multiple environments throughout the day. The microenvironmental model is a comprehensive construct for exposures to inhaled agents and for considering risk reduction through air quality management (National Research Council, 2012). A microenvironment is a place where time is spent and that has a particular pollutant concentration profile during the time spent there; for example, a motor vehicle represents a microenvironment during the time spent commuting. A microenvironment with a high concentration of pollution, such as an urban street canyon, could make a substantial contribution to total exposure, even if only a brief period of time were

spent there. This model is useful for considering how air quality guidelines and standards can reduce personal exposures and for linking air quality management to benefit public health.

This model is also advantageous for considering the numerous microenvironments relevant to air pollution and associated risks to health, and how characteristics of the environment determine exposures. Table 6.1 lists some key microenvironments in urban environments, the pollution sources within these environments and some of the main pollutants present in them. The residence is particularly important because most people spend the majority of their time at home. In urban areas, the air contaminants in the home include those generated by indoor sources, such as cooking and tobacco smoking, and the indoor penetration of outdoor air pollutants, including PM and carbon monoxide generated by local traffic. Streets, which may have hot spots of air pollution generated by traffic or industrial sources, are another key and distinct microenvironment, and one that can be directly benefited by air quality management. The relative significance of different microenvironments across the world varies by where time is spent, the nature of buildings and housing, the distribution of sources and the stringency of measures taken to manage air quality (Samet, 2010).

Table 6.1. Sources of air pollution in urban microenvironments

Microenvironment	Sources	Pollutants
Home	Cooking, space heating, parked vehicles, hobbies, smoking, household products, pets, rodents, insects	PM, CO, NO_x, VOCs, allergens
Transportation environments	Vehicle and industrial emissions, road dust, background pollution, smoking	PM, including ultrafine PM, CO, NO_x, O_3, VOCs, aeroallergens, carcinogens
Streets	Vehicle emissions, road dust, background pollution	PM, including ultrafine PM, CO, NO_x, O_3, VOCs, carcinogens, lead
Work environments	Industrial processes, smoking, background pollution	PM, CO, VOCs, NO_x, carcinogens
Entertainment environments	Cooking and space heating, background pollution, smoking	PM, VOCs, carcinogens

CO: carbon monoxide; NO_x: nitrogen oxides; O_3: ozone.
Source: reproduced from Samet (2010) with permission from publisher.

The WHO air quality guidelines address air pollution and, hence, cover the many microenvironments where people spend time. At times, the increased breathing rate that results from certain activities may increase the dose of inhaled pollutants at a given concentration. In outdoor environments, there may be high-level exposures, sometimes transient, that may reflect particular industrial sources, traffic hot spots or more general sources, for example wildfires or agricultural burning. Risks for some adverse health effects, such as lung cancer or all-cause mortality, are driven by longer-term and cumulative exposures. Hence, the WHO air quality guidelines include both 24-hour (or even shorter time periods, such as 1 hour for nitrogen dioxide or 10 minutes for sulfur dioxide) and annual averaging times.

In many countries around the world, most time is spent indoors, making indoor microenvironments critical in determining the total exposure to air pollution. Ambient air pollution penetrates indoors, so exposures to pollutants that are covered by the guidelines also occur in homes and other indoor places. Conversely, indoor sources do contribute to outdoor air pollution. An example is the burning of biomass fuels for heating and cooking. The extent of penetration of ambient pollutants into indoor environments varies across pollutants. For PM, the degree of penetration depends on the size distribution of the ambient PM, whereas for gases the reactivity of the pollutant is key (e.g. ozone is highly reactive, which causes concentrations to quickly decay indoors). Also critical are the characteristics of the building, that is, how airtight it is and whether it has an air handling system (and, if so, its characteristics) or an air cleaning system for particles and gases. In higher-income countries, a central air handling system (i.e. a heating, ventilation and air-conditioning system) may be equipped to remove particles.

Modification of time–activity patterns is a widely used governmental and personal strategy to reduce pollution exposure. Air quality indices inform the public when concentrations have reached a level at which health is threatened. Typically, recommendations are tailored to the level reached and the susceptibility of those exposed, for example, people with asthma; avoiding outdoor environments and outdoor exercise is an anchoring strategy. In some locations, particularly those where air pollution is known to reach very high levels, people may use personal protection and air purifiers. These approaches vary in their effectiveness, but neither is a satisfactory alternative to governmental actions to reduce outdoor pollution concentrations.

The development of low-cost monitors for airborne PM allows people to measure one key air pollutant in their specific microenvironments (Lewis, von

Schneidemesser & Peltier, 2018). Although the accuracy of these monitors does not reach the level required for reference monitors used by regulatory agencies, they can provide a useful complement to reports from governmental agencies and can be a valuable resource when central site monitoring of known accuracy is not available. The results can be complementary if aggregated for so-called citizen science purposes, particularly by improving the spatial resolution over that provided by regulatory monitoring networks. People also use the personal monitoring results for guiding their time–activity patterns, particularly those related to time spent outdoors.

Air quality regulation and management include various policy measures to protect population health. Such policy measures need to be informed by previous evidence regarding their efficacy. A specific type of applied research activity, accountability research, assesses whether a certain policy has had an effect on reducing emissions and decreasing concentrations. Such research may also contribute to estimating the burden of disease that might be avoided if certain actions are taken (van Erp et al., 2008).

A proper evaluation of the evidence for effective air quality interventions is under development and a systematic review of the available evidence is accessible from the Cochrane Library (Burns et al., 2019). This document articulates the challenges and limitations of this kind of research. Few existing studies directly examine the effects of these interventions on environmental concentrations of pollutants or the resulting health outcomes. Therefore, the health benefits of interventions must be inferred from the reductions in emissions. In the future, as new policies are introduced, decision-makers should consider a built-in evaluation component, which could facilitate more systematic and comprehensive evaluations.

Specific evidence-informed suggestions for air quality management, according to a hierarchy of interventions, have been proposed (PHE, 2020). In this case, the first priority is preventing, reducing or replacing polluting activities to reduce emissions. The second priority is taking actions to reduce the concentration of air pollution once the polluting activity has occurred and the third is individual avoidance of exposure. The hierarchy for the most effective approaches starts with reducing emissions, followed by reducing concentrations and then reducing exposure. Five areas for potential action have been suggested:

- vehicles and fuels, including for heating
- spatial planning
- industry
- agriculture
- behavioural change.

In addition, high-level interventions have been identified with the potential to benefit health by reducing emissions, concentrations and exposures to the pollutants that cause harm. A report from a WHO consultation in 2019 (WHO, 2020a) provides an overview of the issues related to interventions that are critical for managing air pollution exposure at individual level (e.g. physical activity, use of face masks and air purifiers). A Cochrane review on the topic is also in press; the review protocol has been published (Janjua et al., 2019).

6.5 Methodological guidance for health risk assessment of air pollution

An air pollution health risk assessment estimates the health impact to be expected from measures that affect air quality in different socioeconomic, environmental and policy circumstances. As such, it is an important tool for informing public policy decisions. This section describes in broad terms how the health risks of outdoor air pollution and its sources are estimated and provides an overview of the general principles for the proper conduct of health risk assessment for various scenarios and purposes. This section draws from a previous document (WHO Regional Office for Europe, 2016b) to provide a general understanding of the concepts, scope and principles of health risk assessments.

Health risk assessments aim to estimate the risks of past, current or future exposure to air pollution and of the changes in exposure that may result from planned policies or other modifications of air quality. An air pollution health risk assessment may be quantitative or qualitative; it generally assesses (i) the amount of air pollution present (i.e. pollutant concentrations); (ii) the amount of contact (exposure) of the targeted population; and (iii) how harmful the concentration is to human health (i.e. the resulting health risks to the exposed population). The estimates provided by a health risk assessment are intended to inform the decisions of policy-makers and/or other stakeholders.

As an analytical tool, health risk assessments include a comprehensive assessment of the health impacts of policies, programmes and projects that affect environmental conditions – known as a health impact assessment. Health risk assessments and health impact assessments are different concepts, although the two terms are sometimes used interchangeably. A health impact assessment, which is an extension of the overall risk assessment, is often characterized by a combination of procedures, methods and tools used to judge the effects that a policy, programme or project may have on the health of a population and on the distribution of those effects within the population; it may also identify appropriate actions to manage those effects.

The main purpose of a health risk assessment is to answer policy questions about the likely health impacts of planned policies or modifications of those policies.

Air pollution health risk assessments are often used to answer the following policy questions.

- What is the public health burden associated with current levels of air pollution?
- What are the human health benefits associated with changing an air quality policy or applying a more stringent air quality standard?
- What are the human health impacts of emissions from specific sources or selected economic sectors, and what are the benefits of policies related to these?
- What are the human health impacts of current policy or implemented actions?
- What are the policy implications of the uncertainties of the assessment?

The first step in a health risk assessment is planning. This includes the definition of the policy question to be evaluated, determination of the availability of data and resources, and selection of appropriate methods and tools. Sources of data required for the health risk assessment include, but are not limited to, the level of air pollution, the exposed population and the health effect, and the relationship of risk to exposure (e.g. CRF). During the planning process, selection of the methods to be implemented may depend on data availability or may determine the data requirements. In addition, the identification of different tools that will be useful in the health risk assessment occurs in the planning step.

Estimating population exposure to air pollutants is the next step in the health risk assessment. Data on population exposure to air pollutants generally come from monitoring by local or national institutions. Estimates of population exposure based on measured air pollution data are often limited by the restricted geographical and time coverage of the data. Recently, predicted estimates of pollutant concentrations from statistical models have become more common and can be used to estimate exposure in locations that do not have air quality monitors. Progress in combining satellite remote sensing, global chemical transport modelling, land-use regression models and high-resolution local dispersion models in combination with existing ground-based monitoring has made information on key air pollutant indicators increasingly available, including in some of the most highly polluted and data-poor regions. It may be difficult to harmonize data from different locations, since measurements and model predictions are often made using different procedures and techniques.

When estimating the change in population exposure caused by a hypothetical change in emissions or pollutant concentrations, monitoring data may be used as a baseline level. However, air quality modelling is needed to estimate future concentration changes resulting from policies and technological innovations.

The next step in the health risk assessment is estimating the health risk. To provide useful advice aimed at answering a specific question, a specific health end-point or set of health end-points in a specific population must be identified. The health risk assessment is unlikely to cover the full range of possible adverse health effects in all possible groups of the population but may focus on those health effects that affect the most people or the most susceptible populations. The quantitative risk of air pollution to health in a population is usually represented by a CRF, which is typically based on a risk estimate from epidemiological studies.

Quantifying the health impact is the next step in the health risk assessment. Health risk assessments often report results in terms of the number of attributable deaths or cases of disease, years of life lost or disability adjusted life-years, or to the change in life expectancy attributable to the total exposure to air pollution or to a change in exposure. These metrics aggregate different types of health impact and can be used to highlight different aspects of the health status of a population. It is important to note that these metrics provide expected values for a whole population and cannot be applied to individuals in that population. Tools for health risk assessment calculation are widely available from WHO (AirQ+) or other sources (such as the US EPA BenMAP-CE) (Sacks et al., 2020).

In summary, an air pollution health risk assessment can quantify the health impact of air pollution or of changes in air pollution resulting from different socioeconomic, environmental or policy circumstances. In many countries, health risk assessments are formally required as part of the decision-making process for new programmes, projects, regulations and policies that may affect air quality. Those conducting a health risk assessment need to understand how to do it; know what data are available and needed, and where to find them; and know how to communicate the results. It is a challenging, yet important, task to find a balance between the complexity of information and tools used and the need to produce understandable results for policy-makers and others who do not necessarily have a technical background or expertise in the field.

6.6 Role of the health sector

Health-care professionals are now regularly faced with questions and concerns from patients about the impact that air pollution can have on their health. This holds particularly true for individuals who suffer from chronic conditions, such as asthma, COPD, diabetes, heart failure and IHD. Parents with young children also often have concerns. However, many health-care professionals working in different disease areas and settings are unable or unprepared to advise.

Engagement of the health community as trusted, connected and committed advocates is crucial. The health sector has a role in:

- raising awareness of the impact of air quality on health using evidence provided by the WHO air quality guidelines;
- advising the public and patients about how the impact of air pollutants above WHO air quality guidelines can be mitigated at an individual level; and
- joining advocacy efforts at the national and international levels to ensure that the health arguments for the WHO air quality guidelines are heard in national policy discussions.

Scientific evidence on the impact of air pollution on health is developing rapidly, and these new guidelines provide AQG levels for different pollutants based on a review of the latest evidence. However, the practical implications for patients and the public, specifically in relation to acute air pollution episodes and the impact on chronic conditions, are unclear to many in the health sector. For this reason, in addition to publishing the guidelines, further efforts are needed to promote the understanding, support and engagement of those in the health sector.

For the WHO air quality guidelines to have a significant impact on the lives of people most vulnerable and susceptible to the effects of air pollution, cooperation with professional societies is crucial to raise awareness of and strengthen the messages related to air pollution, as well as to ensure appropriate education and training for health-care workers. Examples include presenting the AQG levels and what they mean for health in a practical and easy-to-understand format, and providing guidance on what actions individuals can take to reduce exposure when the AQG levels are exceeded. Explaining the risk from air pollution to an individual in relation to other risk factors, such as smoking, is also important. There is a clear role for organizations such as medical societies and patient organizations to work with WHO to communicate the WHO air quality guidelines in the most accessible manner and tailored to the needs of different target groups.

6.7 Intersectoral and multistakeholder cooperation

In addition to the increased role that the health sector should play, intersectoral and multistakeholder action is crucial for the successful development and implementation of air quality policies, including achievement of the goals and targets of the 2030 Agenda for Sustainable Development (PHAC & WHO, 2008; WHO Regional Office for Europe, 2018). In many countries, responsibilities for air quality are shared among government institutions, but collaboration is not always optimal. Since air quality is influenced by policies formulated in diverse sectors, whole-system approaches are needed for protecting the public's health.

Key to effective air quality policy is the adoption of a whole-of-government approach. This approach involves downstream and upstream coordination among governance domains and levels, as well as horizontal cooperation across sectors, supported by the appropriate selection of interventions, financing mechanisms and legal instruments (WHO Regional Office for Europe, 2018). Specific models have been available at national level since the 1990s, such as the national environment health action plans (WHO Regional Office for Europe, 1999). An example of this model is the National Air Quality Cooperation Programme in the Netherlands, which fosters cooperation among different levels of government through consensus, legislation and public participation (Joint Task Force on the Health Aspects of Air Pollution, 2018).

In a similar vein, the Health in All Policies approach can help ensure that the health impacts of air pollution are considered in formulating policy outside the health sector (WHO, 2014d). For example, the California Health in All Policies Task Force convened a multisectoral working group to deal with the issues of transit-oriented development, including its impact on air pollution, active transportation and social cohesion (Government of South Australia & WHO, 2017). Among low- and middle-income countries, Thailand provides an example of promoting the Health in All Policies approach. In 2012 Thailand's National Health Assembly brought together all parties and sectors to exchange knowledge and formulate policy proposals on biomass burning from power plants and from forest fires related to agriculture (Government of South Australia & WHO, 2017; Rajan et al., 2017; NHCO, 2019).

Of particular importance is the exchange of knowledge and experiences, not only between government and the scientific community but also through engaging the private sector, civil society, communities and citizens. An inclusive, multistakeholder approach also contributes to building trust and legitimacy in the policy process, and results in more equitable and context-specific policies (WHO Regional Office for Europe, 2018). Moreover, civil society is a key player in raising awareness and promoting action to tackle air pollution challenges in many

parts of the world. The private sector, in turn, has an important role in delivering context-relevant technological solutions and services. Therefore, government authorities can nurture a favourable environment by building capacity, promoting partnerships and aligning incentives (Joint Task Force on the Health Aspects of Air Pollution, 2018; Chatterton et al., 2017; CCAC & UNEP, 2019).

To control air pollution regionally, policy instruments are in place to facilitate dialogue, cooperation, and exchange of information and experiences among countries. These include, for example, the United Nations Economic Commission for Europe (UNECE) Convention on Long-Range Transboundary Air Pollution, the Malé Declaration on Control and Prevention of Air Pollution and Its Likely Transboundary Effects for South Asia, the Acid Deposition Monitoring Network in East Asia, the Association of Southeast Asian Nations' Agreement on Transboundary Haze Pollution, and the Eastern Africa Regional Framework Agreement on Air Pollution (CCAC & UNEP, 2019; UNECE, 2011). In particular, the Joint Task Force on the Health Aspects of Air Pollution, established within the UNECE Convention on Long-range Transboundary Air Pollution, is a well-established intersectoral platform for working on air pollution and health and for helping define priorities for action (WHO Regional Office for Europe, 2021b).

On the other hand, the 2030 Agenda for Sustainable Development offers a framework to combat air pollution at global level. Within the framework, connections can be identified between approximately 10 of the SDGs and air pollution, including implicit links at target level. SDG 17 (Partnerships for the Goals) offers targets for intersectoral, multilevel and multistakeholder collaboration to address air pollution that are aligned with the Paris Agreement on climate change (Longhurst et al., 2018).

7

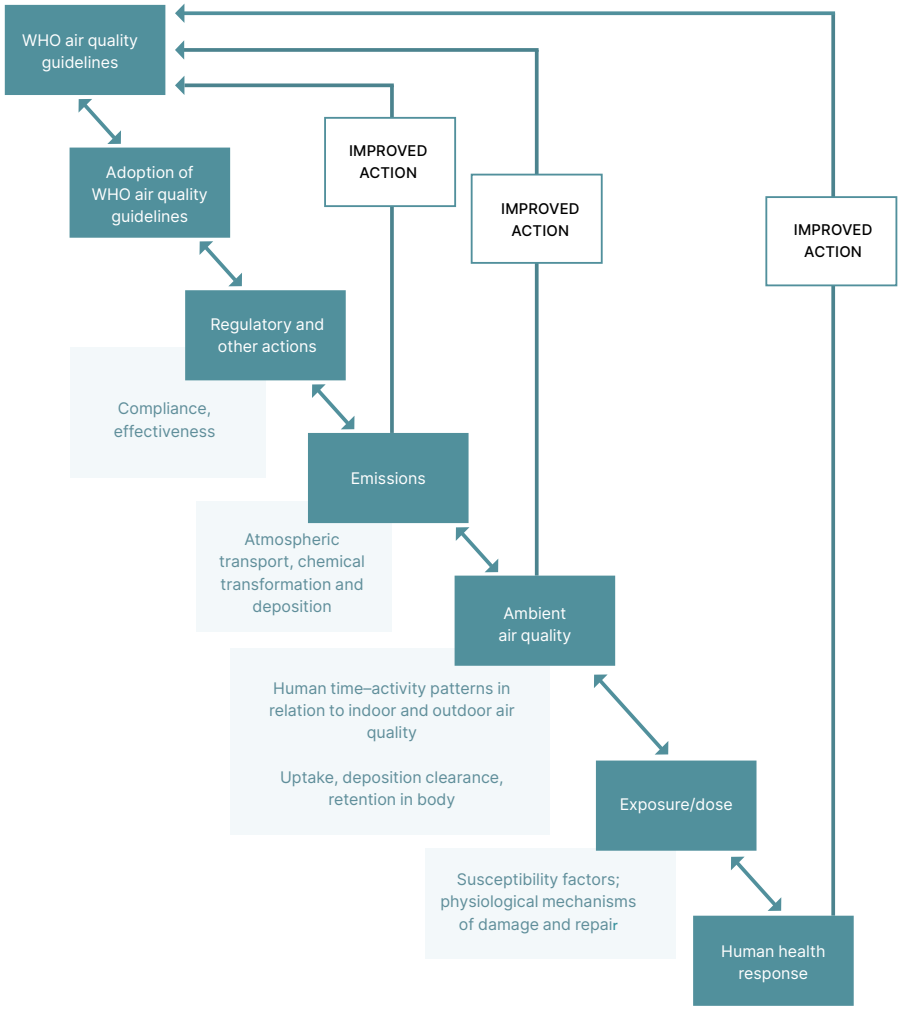
Monitoring and evaluation of the guidelines

The WHO air quality guidelines have the overall purpose of reducing the burden of disease attributable to air pollution globally, aligned with the targets set in the SDGs (UN, 2015) that offer a useful framework for considering gains made in terms of burden reduction. Targets for the SDGs have been set to ensure healthy lives and promote well-being at all ages and to make cities and human settlements inclusive, safe, resilient and sustainable. The WHO air quality guidelines are expected to effectively guide countries towards improving air quality, resulting in a beneficial impact on health risks, and moving closer to meeting several of the SDGs. Monitoring and evaluation of the consequences of implementing the updated guidelines will be key to ensuring their impacts on the reduction of disease burden from air pollution, specifically by:

- evaluating the transfer of the recommendations into local, national, regional and/or international legislation, action plans and other management actions;
- monitoring the achievement of SDG indicators that are directly affected by the recommendations;
- evaluating newly developed or revised air quality standards and other air quality management policies related to ambient air quality that are implemented in countries following publication of the guidelines, in order to determine whether WHO recommendations were used as the basis for their development; and
- surveying different stakeholders to evaluate the quality and usefulness of the guidelines.

An implicit sequence of steps to achieve health targets (such as SDG targets), summarized in Fig. 7.1, follows from promulgation of a guideline or standard. Taking the actual use of the guidelines by national or other regulatory authorities as a starting point, there is a sequence of steps to achieve health benefits, some of which can be tracked (HEI Accountability Working Group, 2003). In considering monitoring and evaluation, the length of time from any action to its health benefits also needs to be acknowledged. This could be a multiyear sequence, particularly for those countries lacking air quality standards and guidelines from the start.

Fig. 7.1. Chain of events within the air pollution accountability framework[a]



[a] HEI defines the air pollution accountability framework as a chain of events that includes the regulation of interest, air quality, exposure/dose and health outcomes, and suggests that accountability research should address the impacts of each of these linkages. Each box represents a link between regulatory action and the human health response to air pollution. Arrows connecting the links indicate possible directions of influence. Text below the arrows identifies general indices of accountability at that stage. At several stages, the knowledge gained from accountability assessments can provide valuable feedback for improving regulatory or other action.

Source: reproduced from the HEI Accountability Working Group (2003), with the permission of the publisher.

7.1 Tracking the implementation of the guidelines

As indicated in Fig. 7.1, the starting point is the actual adoption of the air quality guideline (AQG) levels or interim targets. At this stage of the process, there are steps that can be monitored in a systematic manner. For example, Kutlar Joss et al. (2017) developed a potentially replicable methodology for determining what standards are in place throughout the world. This approach can be followed in maintaining the ongoing tracking of utilization of the WHO air quality guidelines in practice. With the introduction of these updated guidelines, ways to track their dissemination and implementation in countries should be put in place. As a next step, governmental actions need to be taken to incorporate the updated AQG levels or interim targets into regulations or other actions that impact air pollution sources. Such actions can also be tracked by establishing a database (that is periodically updated), as one potential model, which is illustrated in the *WHO report on the global tobacco epidemic 2019* (WHO, 2019b). Based on data compiled by Swiss TPH (Kutlar Joss et al., 2017), WHO developed an interactive tool that provides a snapshot of national air quality standards for classical pollutants for various averaging times. Presented as a map, the tool uses the WHO air quality guidelines and interim targets as references and will be updated regularly (WHO, 2021b).

7.2 Assessing population exposure to ambient pollution

The availability of appropriate population exposure monitoring is critical, as illustrated in Fig. 7.1. Measurement of air pollutant concentrations at fixed-location monitoring sites is the long-standing approach used for air quality management, trend assessment and exposure estimation for epidemiological analyses. However, there is still a lack of air pollution monitoring and inadequate numbers of monitors in rural areas and locations other than major cities in many countries. Thus, monitoring metrics could be the extent of monitoring and the implementation of monitoring to cover gaps. New modelling approaches incorporating satellite and other data may also be useful. In recent decades, in addition to existing air pollution monitoring networks, advanced methods of exposure assessment have become available with the use of satellite observations and various modelling tools to support epidemiological studies, as well as health impact and risk assessment.

Global air pollution concentrations and trends and related estimates of population exposure on priority air pollutant indicators have been compiled in the WHO Global Ambient Air Quality Database, as described in section 1.3.1. Additionally, this update of the WHO air quality guidelines has identified a number of advances in the global development of air pollution monitoring protocols and exposure assessment methods that can be adopted to increase result comparability across studies.

7.3 Health benefits from implementation of the guidelines

The WHO air quality guidelines have the overall purpose of benefiting the health of populations worldwide. The health benefits of the updated WHO air quality guidelines will be realized through reducing population exposures to ambient air pollution via several steps (see Fig. 7.1). Disease burden reflects both the underlying health of populations and the exposures received. Scientific evidence evaluated during the development of this update shows that health risks attributable to air pollution are large and increasing, particularly due to the increases in air pollution exposure in low- and middle-income countries and to ageing of the world population. Major health benefits are expected to be achieved when ambient air pollution levels are reduced widely, following implementation of the guidelines at a global scale. The databases described in section 1.3.1 can be used to inform global estimates of disease and economic burden, and the ongoing estimates of disease burden made by WHO and sister UN agencies within the framework of the SDGs and by the research community will also be useful for tracking progress.

Furthermore, as summarized in Chapter 3, the updated AQG levels and interim targets are derived with improved global CRFs and provide a set of health and exposure indicators for evidence-informed benchmarking of the health impacts of air pollution. These indicators are consistent with SDG targets and can be monitored and evaluated throughout the implementation of the WHO air quality guidelines within and across countries. By adopting the updated guidelines, progress towards achieving the SDG targets can be explicitly monitored and assessed. In particular, this is the case for indicator 3.9.1 on the mortality rate attributed to ambient air pollution and indicator 11.6.2 on the annual mean levels of fine PM, for which WHO is a custodian agency (discussed in section 1.3.7). Such measurements will assist stakeholders to assess their progress in the reduction of disease burden caused by implementation of the WHO air quality guidelines, which will likely result, in parallel, in a further reduction of air pollution.

Countries will need to incorporate the multistep process of air quality management at national level, and stakeholders could be directly and periodically surveyed to evaluate the quality and usefulness of the guidelines towards the goal of reducing disease burden and meeting the applicable SDG targets. Sustained progress in improving air quality is the goal of implementation of the guidelines; monitoring of the guidelines impact on reducing disease burden can provide a strong rationale for potential future updates of the guidelines.

8

Future research needs

There is extensive evidence, which was reviewed to support this update of the WHO air quality guidelines, demonstrating the health effects of exposure to major air pollutants. Evidence from toxicology and epidemiology is sufficient to justify actions to reduce population exposure. Nevertheless, uncertainties and knowledge gaps remain, and future research is needed to reduce these. Suggestions for future research that may help in this regard are listed below. These include further strengthening the policy-relevant scientific base and evidence to support decision-making worldwide, especially in low- and middle-income countries.

- **Set priorities for policy-relevant scientific questions: how, why and for whom do the health effects of air pollution exist?**
  - Assess the shape of the exposure–response relationships at both low and high air pollution concentration levels – the former are now being observed in parts of Europe, North America and Oceania, and the latter are now being observed in parts of Asia and the Eastern Mediterranean Region.
  - Study the toxicity of different sources of air pollution (e.g. tailpipe and non-tailpipe emissions, aviation and shipping emissions, specific industrial sources, wood smoke and desert dust). This includes research into the health effects of technology-driven changes in areas such as primary energy production, where mixtures of coal and biomass replace coal in places.
  - Study the health effects of particle size fractions for which there are limited data.
  - Define sensitive subgroups of the population that need to be protected (e.g. related to socioeconomic status, nutrition, pregnancy, critical windows of development, and young older age) due to the risk of immediate, delayed or lifetime effects.
  - Study multipollutant exposures to determine the relative importance of specific air pollutants (such as nitrogen dioxide, carbon monoxide) and components of PM, with an examination of additive, synergistic or antagonistic effects, including in the presence of pollens or other airborne allergens. This is an area where mechanistic research will likely play an important role.
  - Study the interaction with other environmental and behavioural factors such as traffic noise, green space and allergen exposure; physical activity and diet; and high and low temperatures and other climatic conditions.

- Undertake research into a broader range of health end-points, as the list of organ systems and conditions possibly affected by air pollution is steadily increasing.
  - Study the neurological effects, including the effects on brain morphology in young children and older people, on child development, and on cognitive decline and reduced ability to perform activities of daily life in older people.
  - Study the cardiometabolic effects – emerging evidence links diabetes to air pollution exposure (Yang B-Y et al., 2020), an association in clear need of further corroboration and characterization.
  - Study the effects on various cancer forms (excluding lung cancer, for which a relationship with air pollution has been established).
  - Study the short-term effects of exposure leading to worsening of symptoms for diseases such as allergic, cardiovascular and respiratory conditions and indicated by a wider set of (also subclinical) health status indicators, such as lung function tests or biomarkers.
- Improve the methodology in exposure assessment, study design and evidence synthesis and evaluation.
  - Study exposure assessment – inform this by integrating data form multiple sources (e.g. from large numbers of low-cost sensors) and data fusion (satellite observations, emission sources, dispersion models and ground-based monitoring).
  - Assess multiple sources of exposure in different locations (including home indoor, work indoor and transportation) and time–activity patterns.
  - Assess multiple sources of exposure in populations from different regions, living in different climates, of different socioeconomic status, etc.
  - Improve statistical methods for use in epidemiological studies, such as methods to correct for exposure measurement error in health analyses, multipollutant modelling approaches and methods to correct for confounding.
  - Expand the framework of causal inference by incorporating different study and analysis designs, including novel approaches in epidemiology such as the use of propensity scores, instrumental variables, difference-in-difference analyses and regression discontinuity.
  - Improve methodological aspects related to the evaluation of the quality of individual studies and the synthesis and overall evaluation of the scientific evidence, including determination of the certainty of the body of evidence (e.g. GRADE or other approaches).
- Undertake research into mechanisms of health effects.
  - Study the biological mechanisms explaining epidemiological associations

with all-cause and respiratory mortality of (mixtures represented by) nitrogen dioxide and ozone, especially at low concentration levels.

- Study the mechanisms of effects of (mixtures represented by) nitrogen dioxide and ozone on the cardiovascular system.
- Study the effects of mixtures containing particles of different sizes as wells as gaseous pollutants to understand the underlying pathophysiology due to surface interactions between pollutants and molecular or cellular structures (e.g. proteins, lipids, DNA and RNA).

- Continue to develop burden and health impact assessment.
  - Improve methods and input data for health risk assessments, which play a key role in identifying the overall and relative importance of air pollution and its sources for population health. They provide the foundation for identifying priorities and tracking the effectiveness of solutions.
  - Improve the apportionment of population exposure to specific sources or source categories to enable source-specific health risk assessment at the local, national and regional levels.
  - Establish solid mechanisms for the regular review of evidence related to the quantification of CRFs and health burden assessments, including the integrated assessment of burdens from complex mixtures.
  - Integrate air-pollution-related health risk assessment into a comprehensive health impact assessment of actions focused on other determinants of health (such as physical activity, diet and climate).

- Improve assessment of the effectiveness of interventions (accountability research).
  - Evaluate key long-term interventions in all parts of the world, for example local traffic interventions, interventions to reduce emissions from industrial sources, changes in energy use (gas vs electricity), efforts to reduce exposure for at-risk communities and reductions in biomass burning.
  - Evaluate key short-term community (e.g. school closures) and individual (e.g. face masks) interventions during acute episodes, including studies of population exposure, health effects, and societal and economic implications. Evaluation should include conditions critical for successful intervention, for example, sensitivity to socioeconomic conditions; methods of communication; use of adequate exposure indicators; and target group knowledge, attitude and engagement.
  - Develop study methods to assess the effectiveness of interventions and which can provide direct evidence for the attribution of changes in air quality and health to an air quality improvement intervention, as well as to integrate (climate) related co-benefits and dis-benefits.

9

Updating the guidelines

The number of studies of air quality and health has significantly increased since *Global update 2005*, including new studies published after the completion of the systematic reviews conducted for this update. Taken together, the guidelines were informed by a wealth of epidemiological studies that shed light on the risks of exposure to air pollution at both the lower and upper bounds of the concentration–response relationships for the classical air pollutants, including the shapes of such relationships.

WHO will continue monitoring scientific progress in the field to assess the need for future updates. This activity will be facilitated by the Global Air Pollution and Health – Technical Advisory Group, which was established in 2021 (WHO, 2020d), and by annual meetings of the Joint Task Force on the Health Aspects of Air Pollution, established in 1998, within the UNECE Convention on Long-range Transboundary Air Pollution (WHO Regional Office for Europe, 2021b).

Moreover, participation in scientific meetings, follow-up on emerging issues, and close interaction with thematic/technical experts and stakeholders will continue so as to keep abreast of the scientific progress and gauge the need for updating the guidelines. In general, however, the recommendations made in these guidelines are expected to remain valid for a period of up to 10 years.

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Annex 1. Groups engaged during the development of the guidelines

Tables A1.1–A1.7 give details of the various teams involved in the development of the guidelines at various stages.

Table A1.1. WHO steering group

Name (membership period)	Position	Department
Heather Adair-Rohani (2016–2021)	Technical Officer	WHO headquarters, Geneva, Switzerland
Magaran Monzon Bagayoko (2016–2019)	Scientist, Protection of the Human Environment	WHO Regional Office for Africa, Brazzaville, Congo
Carlos Dora (2016–2017)	Coordinator, Interventions for Healthy Environments	WHO headquarters, Geneva, Switzerland
Sophie Gumy (2016–2021)	Technical Officer	WHO headquarters, Geneva, Switzerland
Mohd Nasir Hassan (2016–2017)	Team Leader, Environmental Health	WHO Regional Office for the Western Pacific, Manila, Philippines
Marie-Eve Héroux (2016–2017)	Technical Officer, Air Quality And Noise	WHO Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany
Dorota Jarosińska (2016–2021)	Programme Manager, Living and Working Environments	WHO Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany
Rok Ho Kim (2017–2020)	Coordinator, Health and the Environment	WHO Regional Office for the Western Pacific, Manila, Philippines
Dana Loomis (2016–2017)	Head, Monographs Group	International Agency for Research on Cancer, Lyon, France

Table A1.1 contd

Name (membership period)	Position	Department
Mazen Malkawi (2016–2021)	Regional Adviser, Environmental Health Exposures	WHO Regional Office for the Eastern Mediterranean, Regional Centre for Environmental Health Action, Amman, Jordan
Guy Mbayo (2020–2021)	Technical Officer, Climate Change, Health and Environment	WHO Regional Office for Africa, Brazzaville, Congo
Pierpaolo Mudu (2016–2021)	Technical Officer	WHO Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany
Lesley Jayne Onyon (2016–2021)	Regional Adviser, Occupational and Environmental Epidemiology	WHO Regional Office for South-East Asia, New Delhi, India
Elizabet Paunović (2016–2018)	Head of Office	WHO Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany
Román Pérez Velasco (2017–2021)	Technical Officer, Environment and Health	WHO Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany
Genandrialine Peralta (2020–2021)	Coordinator, Health and the Environment	WHO Regional Office for the Western Pacific, Manila, Philippines
Nathalie Röbbel (2019–2021)	Unit Head, Air Quality and Health	WHO headquarters, Geneva, Switzerland
Agnes Soares da Silva (2016–2021)	Adviser, Environmental Epidemiology	WHO Regional Office for the Americas, Washington, DC, the United States
Nadia Vilahur Chiaraviglio (2016; 2018)	Consultant; Scientist	WHO Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany (2016); International Agency for Research on Cancer, Lyon, France (2018)
Hanna Yang (2017–2020)	Technical Officer, Air Quality	WHO Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany

Table A1.2. Guideline development group

Name (membership period)	Position and affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Marwan Al-Dimashki (2016–2021)	Chief Environmental Consultant, Kuwait Environment Public Authority, Safat, Kuwait	M	3, 6
Emmanuel K.-E. Appoh (2016–2021)	Head, Environmental Quality Department, Environmental Protection Agency, Accra, Ghana	M	5, 6
Kalpana Balakrishnan (2016–2021)	Associate Dean (Research) and Director, WHO Collaborating Centre for Occupational and Environmental Health, Sri Ramachandra University, Chennai, India	F	5, 6
Michael Brauer (2016–2021)	Professor, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada	M	1, 3
Bert Brunekreef (2016–2021)	Professor Emeritus, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands	M	1, 7
Aaron J. Cohen (2016–2021)	Consulting Principal Scientist, Health Effects Institute, Boston, MA, the United States	M	1, 7
Francesco Forastiere (2016–2021)	Senior Researcher, Institute for Biomedical Research and Innovation, National Research Council (CNR–IRIB), Palermo, Italy	M	1, 2
Lu Fu (2017–2021)	China Director, Clean Air Asia, Beijing, China	F	4–6
Sarath K. Guttikunda (2016–2021)	Director, Urban Emissions, Goa, India	M	1, 3
Mohammad Sadegh Hassanvand (2016–2021)	Associate Professor, Institute for Environment Research, Tehran University of Medical Sciences, Tehran, Iran	M	1, 3
Marie-Eve Héroux (2017–2021)	Head, Air Quality Assessment Section, Health Canada, Ottawa, ON, Canada	F	1, 6, 7
Wei Huang (2016–2021)	Professor, School of Public Health, Peking University, Beijing, China	F	2, 6

Table A1.2 contd

Name (membership period)	Position and affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Haidong Kan (2016–2021)	Professor and Director, School of Public Health, Fudan University, Shanghai, China	M	1, 5
Nguyen Thi Kim Oanh (2016–2021)	Professor, Environmental Engineering and Management, Asian Institute of Technology, Pathumthani, Thailand	F	3
Michał Krzyżanowski (2016–2021)	Visiting Professor, School of Public Health, Imperial College London, London, England, the United Kingdom	M	1, 6, 7
Nino Künzli (2016–2021)	Professor and Unit Head, Education and Training, Swiss Tropical and Public Health Institute (Swiss TPH) and University of Basel, Basel, Switzerland	M	1
Thomas J. Luben (2016–2021)	Senior Epidemiologist, United States Environmental Protection Agency, Research Triangle Park, NC, the United States	M	1, 7
Lidia Morawska (2016–2021)	Distinguished Professor and Director, International Laboratory for Air Quality and Health, Queensland University of Technology, Brisbane, QLD, Australia	F	3, 7
Kaye Patdu (2016–2017)	Head of Programs, Clean Air Asia, Manila, Philippines	F	5, 6
Pippa Powell (2016–2021)	Director, European Lung Foundation, Sheffield, England, the United Kingdom	F	5
Horacio Riojas-Rodríguez (2016–2021)	Environmental Health Director, National Institute of Public Health (INSP), Cuernavaca, Mexico	M	1, 3–5
Jonathan Samet (2016–2021)	Dean and Professor, Colorado School of Public Health, Aurora, CO, the United States	M	1, 6
Martin Williams[b] (2016–2020)	Professor, School of Public Health, Imperial College London, London, England, the United Kingdom	M	3, 6
Caradee Y. Wright (2016–2021)	Senior Specialist Scientist, Environment and Health Research Unit, South African Medical Research Council (SAMRC), Pretoria, South Africa	F	3

Table A1.2 contd

Name (membership period)	Position and affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Xia Wan (2016–2021)	Professor, Peking Union Medical College, School of Basic Medicine, Beijing, China	F	1
André Zuber (2016–2017)	Policy Officer, Industrial Emissions, Air Quality & Noise Unit, Directorate-General for Environment, European Commission, Brussels, Belgium	M	6

[a] Area of expertise/interest: 1. Health effects of air pollution – epidemiological evidence and/or risk assessment; 2. Health effects of air pollution – toxicological and clinical evidence; 3. Air pollution emissions and atmospheric chemistry/exposure assessment; 4. Best practices, interventions and/or health economics; 5. Vulnerable groups, equity, human rights, gender and/or developing country perspective; 6. End-user perspective, policy implications, implementation of the guidelines; 7. Methodology and guideline development.
[b] Deceased 21 September 2020.

Table A1.3. Systematic review team[a]

Systematic review topic	Experts involved	Affiliation
Long-term exposure to $PM_{2.5}$ and PM_{10} All-cause and cause-specific mortality	Jie Chen	Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands
	Gerard Hoek	Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands
Long-term exposure to O_3 and NO_2 All-cause and respiratory mortality	Richard Atkinson	Population Health Research Institute, St George's, University of London, London, England, the United Kingdom
	Peijue Huangfu	Population Health Research Institute, St George's, University of London, London, England, the United Kingdom
Short-term exposure to $PM_{2.5}$, PM_{10}, O_3 and NO_2 All-cause and cause-specific mortality	Ariel Bardach	Institute for Clinical Effectiveness and Health Policy (IECS-CONICET), Buenos Aires, Argentina
	Agustín Ciapponi	Institute for Clinical Effectiveness and Health Policy (IECS-CONICET), Buenos Aires, Argentina
	Pablo Orellano	Centre for Research and Technology Transfer San Nicolás, National Technology University (UTN-CONICET), San Nicolás, Argentina
	Nancy Quaranta	San Nicolás Regional Faculty, National Technology University (UTN), San Nicolás, Argentina Scientific Research Commission of the Province of Buenos Aires, La Plata, Argentina
	Julieta Reynoso	San Felipe General Hospital, San Nicolás, Argentina
Short-term exposure to SO_2 All-cause and respiratory mortality	Pablo Orellano	Centre for Research and Technology Transfer San Nicolás, National Technology University (UTN-CONICET), San Nicolás, Argentina
	Nancy Quaranta	San Nicolás Regional Faculty, National Technology University (UTN), San Nicolás, Argentina Scientific Research Commission of the Province of Buenos Aires, La Plata, Argentina
	Julieta Reynoso	San Felipe General Hospital, San Nicolás, Argentina

Table A1.3 contd

Systematic review topic	Experts involved	**Affiliation**
Short-term exposure to O_3, NO_2 and SO_2 Emergency department visits and hospital admissions due to asthma	Wei-jie Guan	State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, China
	Mei Jiang	State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, China
	Hua-liang Lin	Sun Yat-sen University, Guangzhou, China
	Pablo Orellano	Centre for Research and Technology Transfer San Nicolás, National Technology University (UTN-CONICET), San Nicolás, Argentina
	Xue-yan Zheng	Institute of Non-communicable Disease Control and Prevention, Guangdong Provincial Center for Disease Control And Prevention, Guangdong, China
Short-term exposure to CO Myocardial infarction	Kuan Ken Lee	British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, Scotland, the United Kingdom
	Mark R. Miller	British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, Scotland, the United Kingdom
	Nicholas L. Mills	British Heart Foundation Centre for Cardiovascular Science and the Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, the United Kingdom
	Anoop S.V. Shah	British Heart Foundation Centre for Cardiovascular Science and Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, the United Kingdom
	Nicholas Spath	British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, Scotland, the United Kingdom

[a] Specific contributions are reported in the articles published in the special issue of *Environment International*: *Update of the WHO global air quality guidelines: systematic reviews* (Whaley et al., 2021; see main reference list).

Table A1.4. External methodologists

Methodological topic	Methodologist (period of service)	Affiliation
Systematic review and guideline development (guideline methodology)	**Jos Verbeek** (2016–2020)	Coordinating Editor, Cochrane Work Review Group, Kuopio, Finland
RoB assessment	**Rebecca Morgan** (2017–2019)	Assistant Professor, McMaster University, Hamilton, ON, Canada

Table A1.5. External review group – individual experts

Name	Affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Samir Afandiyev	Public Health and Reforms Centre, Baku, Azerbaijan	M	2, 3, 6
Mohammad Alolayan	College of Life Sciences, Kuwait University, Kuwait City, Kuwait	M	3, 6
Richard Ballaman	Federal Office of the Environment, Bern, Switzerland	M	6
Jill Baumgartner	Institute for Health and Social Policy, McGill University, Montreal, QC, Canada	F	1, 5
Hanna Boogaard	Health Effects Institute, Boston, MA, the United States	F	1, 3
David M. Broday	Faculty of Civil and Environmental Engineering, Technion – Israel Institute of Technology, Haifa, Israel	M	3
Richard T. Burnett	Population Studies Division, Health Canada, Ottawa, ON, Canada	M	1, 6
Jacob Burns	Institute for Medical Informatics, Biometry and Epidemiology, Pettenkofer School of Public Health, Ludwig-Maximilians-University, Munich, Germany	M	7
Flemming Cassee	National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands	M	2

Table A1.5 contd

Name	Affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Evan Coffman	United States Environmental Protection Agency, Research Triangle Park, NC, the United States	M	1, 7
Séverine Deguen	School of Public Health (EHESP), Rennes, France	F	1, 5
Sagnik Dey	Centre for Atmospheric Sciences, Indian Institute of Technology, New Delhi, India	M	3, 5, 6
Dimitris Evangelopoulos	School of Public Health, Imperial College London, London, England, the United Kingdom	M	1
Mamadou Fall	Faculty of Medicine, Pharmacy and Dentistry, Cheikh Anta Diop University (UCAD), Dakar, Senegal	M	1–3
Neal Fann	United States Environmental Protection Agency, Research Triangle Park, NC, the United States	M	1, 4
Daniela Fecht	School of Public Health, Imperial College London, London, England, the United Kingdom	F	3, 5
Julia Fussell	School of Public Health, Imperial College London, London, England, the United Kingdom	F	2
Davina Ghersi	National Health and Medical Research Council, Canberra, ACT, Australia	F	6, 7
Otto Hänninen	Finnish Institute for Health and Welfare (THL), Helsinki, Finland	M	1, 2, 6
Barbara Hoffmann	Institute for Occupational, Social and Environmental Medicine, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany	F	1, 2
Michael Holland	Ecometrics Research and Consulting, Reading, England, the United Kingdom	M	4, 6
Yun-Chul Hong	Institute of Environmental Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea	M	1, 2, 6
Bin Jalaludin	School of Public Health and Community Medicine, University of New South Wales, Kensington, NSW, Australia	M	1, 5

Table A1.5 contd

Name	Affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Meltem Kutlar Joss	Swiss TPH, University of Basel, Basel, Switzerland	F	1, 6
Juleen Lam	Department of Health Sciences, California State University, East Bay, Hayward, CA, the United States	F	1, 7
Kin Bong Hubert Lam	Nuffield Department of Population Health, University of Oxford, Oxford, England, the United Kingdom	M	1, 4
Puji Lestari	Institute of Technology Bandung, Bandung, Indonesia	F	3, 6
Morton Lippmann	NYU School of Medicine, New York University, New York, NY, the United States	M	1–3
Sylvia Medina	Public Health France, Saint-Maurice, France	F	1, 6
Rajen Naidoo	School of Nursing and Public Health, University of Kwazulu Natal, Durban, South Africa	M	1, 5, 6
Mark J. Nieuwenhuijsen	Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain	M	1, 3
Jeongim Park	Department of Environmental Health Science, Soonchunhyang University, Asan, Republic of Korea	F	1, 3
Rita Pavasini	Cardiology Centre, University of Ferrara, Ferrara, Italy	F	2
Annette Peters	Helmholtz Zentrum München – German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany	F	1, 2
Vincent-Henri Peuch	Copernicus Atmosphere Monitoring Service, European Centre for Medium-Range Weather Forecasts, Reading, England, the United Kingdom	M	3, 6
C. Arden Pope III	College of Family, Home, and Social Sciences, Brigham Young University, Provo, UT, the United States	M	1, 4
Reginald Quansah	School of Public Health, College of Health Sciences, University of Ghana, Legon, Ghana	M	5–7

Table A1.5 contd

Name	Affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Xavier Querol Carceller	Institute of Environmental Assessment and Water Research (IDAEA), Spanish National Research Council (CSIC), Barcelona, Spain	M	3, 4
Matteo Redaelli	Agency for Food, Environmental and Occupational Health & Safety (ANSES), Maisons-Alfort, France	M	1, 7
Eva Rehfuess	Institute for Medical Informatics, Biometry and Epidemiology, Pettenkofer School of Public Health, Ludwig-Maximilians-University Munich, Munich, Germany	F	6, 7
Alexander Romanov	Scientific Research Institute for Atmospheric Air Protection (SRI Atmosphere), Saint Petersburg, Russian Federation	M	3, 6
Anumita Roychowdhury	Centre for Science and Environment (CSE), New Delhi, India	F	4–6
Jason Sacks	United States Environmental Protection Agency, Research Triangle Park, NC, the United States	M	1, 7
Paulo Saldiva	Faculty of Medicine, University of São Paulo, São Paulo, Brazil	M	2
Najat Saliba	Faculty of Arts and Science, American University of Beirut, Beirut, Lebanon	F	3
Andreia C. Santos	London School of Hygiene and Tropical Medicine, University of London, London, England, the United Kingdom	F	4
Jeremy Sarnat	Rollins School of Public Health, Emory University, Atlanta, GA, the United States	M	1, 3
Paul T.J. Scheepers	Radboud Institute for Health Sciences, Nijmegen, the Netherlands	M	2, 7
Srijan Lal Shrestha	Central Department of Statistics, Tribhuvan University, Kirtipur, Kathmandu, Nepal	M	1, 3, 5

Table A1.5 contd

Name	Affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Mónica Silva González	Proklima International, Latin America and the Caribbean, German Corporation for International Cooperation (GIZ), Eschborn, Germany	F	5, 6
Kirk R. Smith[b]	School of Public Health, University of California Berkeley, Berkeley, CA, the United States	M	1, 4, 5
Massimo Stafoggia	Department of Epidemiology, Lazio Region Health Service, Rome, Italy	M	1, 4
David M. Stieb	Air Quality Health Effects Research Section, Health Canada, Vancouver BC, Canada	M	1, 2, 7
Jordi Sunyer	Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain	M	1
Duncan C. Thomas	Keck School of Medicine, University of Southern California, Los Angeles, CA, the United States	M	1, 7
George D. Thurston	NYU School of Medicine, New York University, New York, NY, the United States	M	1
Linwei Tian	School of Public Health, The University of Hong Kong, China, Hong Kong SAR	M	1, 2
Aurelio Tobías Garces	Institute of Environmental Assessment and Water Research (IDAEA), Spanish National Research Council (CSIC), Barcelona, Spain	M	1, 4, 7
Rita Van Dingenen	European Commission Joint Research Centre, Ispra, Italy	F	3
Sotiris Vardoulakis	National Centre for Epidemiology and Population Health, Australian National University, Canberra ACT, Australia	M	1, 4
Giovanni Viegi	Institute of Biomedicine and Molecular Immunology "Alberto Monroy", National Research Council (CNR-IBIM), Palermo, Italy	M	1, 2

Table A1.5 contd

Name	Affiliation	Sex	Area of expertise specifically sought for guidelines[a]
Kuku Voyi	School of Health Systems and Public Health, University of Pretoria, Hatfield, South Africa	F	1, 2, 5
Heather Walton	School of Public Health, Imperial College London, London, England, the United Kingdom	F	1, 6
Paul Whaley	Lancaster Environment Centre, Lancaster University, Lancaster, England, the United Kingdom	M	7
Takashi Yorifuji	Graduate School of Environmental and Life Science, Okayama University, Okayama, Japan	M	1, 2

[a] Area of expertise/interest: 1. Health effects of air pollution – epidemiological evidence and/or risk assessment; 2. Health effects of air pollution – toxicological and clinical evidence; 3. Air pollution emissions and atmospheric chemistry/exposure assessment; 4. Best practices, interventions and/or health economics; 5. Vulnerable groups, equity, human rights, gender and/or developing country perspective; 6. End-user perspective, policy implications, implementation of the guidelines; 7. Methodology and guideline development.
[b] Deceased 15 June 2020.

Table A1.6. External review group – stakeholder organizations

Organization	Location	Area of expertise specifically sought for guidelines[a]
Abu Dhabi Global Environmental Data Initiative (AGEDI)	Abu Dhabi, United Arab Emirates	2, 3
African Centre for Clean Air (ACCA)	Kampala, Uganda	1, 4
Association for Emissions Control by Catalyst (AECC)	Schaerbeek, Belgium	1, 2, 5
Clean Air Asia (CAA)	Manila, the Philippines	1, 2
ClientEarth	London, England, the United Kingdom	3
Concawe	Brussels, Belgium	2, 4, 6

Table A1.6 contd

Organization	Location	Area of expertise specifically sought for guidelines[a]
European Environment Agency (EEA)	Copenhagen, Denmark	3
European Environmental Bureau (EEB)	Brussels, Belgium	3
European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	Brussels, Belgium	4
European Respiratory Society (ERS)	Lausanne, Switzerland	4
Health and Environment Alliance (HEAL)	Brussels, Belgium	3, 4
International Society for Environmental Epidemiology (ISEE)	Herndon, VA, the United States	3, 4
International Transport Forum (ITF)	Paris, France	5
South Asia Co-operative Environment Programme (SACEP)	Colombo, Sri Lanka	3

[a] Area of expertise/interest: 1. Air quality; 2. Climate change; 3. Environment in general; 4. Health; 5. Transport; 6. Energy.

Table A1.7. Working groups[a]

Working group title	Experts involved	Group membership in the process
Risk of Bias Assessment	Bert Brunekreef	Guideline development group
	Aaron J. Cohen	Guideline development group
	Francesco Forastiere	Guideline development group
	Rebecca Morgan	External methodologists
	Jos Verbeek	External methodologists
Working group title	**Experts involved**	**Group membership in the process**
Certainty of Evidence Assessment	Bert Brunekreef	Guideline development group
	Aaron J. Cohen	Guideline development group
	Francesco Forastiere	Guideline development group
	Nino Künzli	Guideline development group
	Rebecca Morgan	External methodologists
	Jos Verbeek	External methodologists
Derivation of Air Quality Guideline Levels and Interim Targets	Bert Brunekreef	Guideline development group
	Aaron J. Cohen	Guideline development group
	Francesco Forastiere	Guideline development group
	Gerard Hoek[b]	Systematic review team
	Nino Künzli	Guideline development group
	Michał Krzyżanowski	Guideline development group
	Jonathan Samet	Guideline development group
	Jos Verbeek (until 2020)	External methodologists
	Martin Williams[c]	Guideline development group
	Caradee Y. Wright	Guideline development group

Table A1.7 contd

Working group title	Experts involved	Group membership in the process
Good Practice Statements	Francesco Forastiere	Guideline development group
	Michał Krzyżanowski	Guideline development group
	Lidia Morawska	Guideline development group
	Martin Williams[c]	Guideline development group
	Xavier Querol Carceller	External review group
	Massimo Stafoggia	External review group
	Aurelio Tobías Garces	External review group

[a] The working groups were coordinated by the members of the WHO Secretariat, Román Pérez Velasco and Dorota Jarosińska, with general assistance from Hanna Yang and specific support from Pierpaolo Mudu on the good practice statements related to SDS. The work produced by the working groups was reviewed by the GDG and by members of the systematic review team and the ERG, where needed.
[b] Technical consultant who supported the work conducted by the working group.
[c] Deceased 21 September 2020.

Annex 2. Assessment of conflict of interest

All external contributors to the guidelines, including members of the GDG, systematic review team, external methodologists and ERG, completed WHO declaration of interest forms in accordance with WHO's policy for experts. Further, WHO technical staff reviewed curricula vitae of candidates for the groups. At the beginning of the GDG meetings, participants declared or updated their competing interests (Table A2.1).

The conflict-of-interest assessment was done according to WHO procedures. If a conflict was declared, an initial review was undertaken by the WHO Secretariat to assess its relevance and significance. A declared conflict of interest is insignificant or minimal if it is unlikely to affect or to be reasonably perceived to affect the expert's judgement. Insignificant or minimal interests are those unrelated or only tangentially related to the subject of the activity or work and its outcome; nominal in amount or inconsequential in importance; or expired and unlikely to affect current behaviour.

The WHO Secretariat reviewed and assessed the declarations, which were cleared through the Office of Compliance, Risk Management and Ethics when required. WHO was of the opinion that these declarations did not constitute conflicts of interest and that the considered experts could participate in the process subject to disclosure of their interests.

The relevant declared interests of members of the GDG are summarized below. Other participants in the process, such as the systematic review team (see the special issue of *Environment International*: *Update of the WHO global air quality guidelines: systematic reviews* (Whaley et al., 2021; see main reference list)) and external methodologists, did not declare relevant interests. Some individual members of the large ERG declared non-significant, relevant interests. However, these interests – as well as those of the stakeholder organizations – were carefully considered in assessing their inputs and comments.

Table A2.1. Summary of relevant interests declared by members of the GDG

Name	Details of interests
Marwan Al-Dimashki	Employed by the Environment Public Authority of Kuwait
Michael Brauer	Consultant for HEI and the British Columbia Lung Association; research support from HEI; travel expenses to meetings of the European Respiratory Society; expert opinions for the Ministry of Justice, Province of Ontario, for the Greater Vancouver Regional District and, on behalf of EcoJustice, on a lawsuit against the Province of Ontario; chair of the Air Pollution Expert Group of the World Heart Federation (2019–present); honorarium paid for by the Electric Power Research Institute to present at its annual meeting regarding the International Agency for Research on Cancer's air pollution monograph
Bert Brunekreef	Research support from the HEI; Chairman of the European Respiratory Society Environment and Health Committee (2014–2017)
Aaron J. Cohen	Formerly employed by HEI; consulting for HEI and Vital Strategies
Francesco Forastiere	Consultant for HEI, Health Canada, World Bank and WHO; member of the European Respiratory Society Environment and Health Committee
Lu Fu	Employed by Clean Air Asia
Mohammad Sadegh Hassanvand	Research support from the Tehran University of Medical Sciences
Marie-Eve Héroux	Employed by Health Canada and formerly employed by WHO (until 2017)
Wei Huang	Consultant for WHO
Michał Krzyżanowski	Consultant for the Frank Bold Society, Health and Environment Alliance, Health Canada, UN Environment, Vital Strategies and WHO; chair of the Policy Committee at the International Society for Environmental Epidemiology (until 2018); member of the Board of the International Joint Policy Committee of the Societies of Epidemiology (until 2018)

Table A2.1 contd

Name	Details of interests
Nino Künzli	President of the Swiss Federal Commission on Air Hygiene; member of the European Respiratory Society Environment and Health Committee (until 2018)
Thomas J. Luben	Travel expenses to meeting paid for by the American Petroleum Institute; expert opinion for the United States Department of Justice on the lawsuit *United States vs Mountain State Carbon, LLC*
Lidia Morawska	Consultant for WHO (March–July 2019)
Kaye Patdu	Employed by Clean Air Asia (until 2017); expert opinion on behalf of Clean Air Asia in the development of $PM_{2.5}$ standards in the Philippines (2013)
Pippa Powell	Employed by the European Lung Foundation
Jonathan Samet	Chair of the Oversight Committee of Long-Term Epidemiological Studies of Air Pollution, HEI
Martin Williams[a]	Consultant for the World Bank; research support from the European Commission
Caradee Y. Wright	Employed by South African Medical Research Council; research support from National Department of Environmental Affairs of South Africa; vice-President of the National Association for Clean Air (until 2018); founder of the Environmental Health Research Network; member of the Public Health Association of South Africa
André Zuber	Employed by the European Commission (until 2017)

[a] Deceased 21 September 2020.

Annex 3. Summaries of systematic reviews of evidence informing the air quality guideline levels

This annex contains the abstracts and certainty of evidence tables from the systematic reviews published in the special issue of *Environment International*: *Update of the WHO global air quality guidelines: systematic reviews* (Whaley et al., 2021; see main reference list), where additional information can be found. The abstracts and tables are provided in this annex courtesy of *Environment International*.

A3.1 Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis (Chen & Hoek, 2020)

Abstract

As new scientific evidence on health effects of air pollution is generated, air quality guidelines need to be periodically updated. The objective of this review is to support the derivation of updated guidelines by the World Health Organization (WHO) by performing a systematic review of evidence of associations between long-term exposure to particulate matter with diameter under 2.5 μm ($PM_{2.5}$) and particulate matter with diameter under 10 μm (PM_{10}), in relation to all-cause and cause-specific mortality. As there is especially uncertainty about the relationship at the low and high end of the exposure range, the review needed to provide an indication of the shape of the concentration-response function (CRF).

We systematically searched MEDLINE and EMBASE from database inception to 9 October 2018. Articles were checked for eligibility by two reviewers. We included cohort and case-control studies on outdoor air pollution in human populations using individual level data. In addition to natural-cause mortality, we evaluated mortality from circulatory diseases (ischemic heart disease (IHD) and cerebrovascular disease (stroke) also specifically), respiratory diseases (Chronic Obstructive Pulmonary Disease (COPD) and acute lower respiratory

illness (ALRI) also specifically) and lung cancer. A random-effect meta-analysis was performed when at least three studies were available for a specific exposure-outcome pair. Risk of bias was assessed for all included articles using a specifically developed tool coordinated by WHO. Additional analyses were performed to assess consistency across geographic region, explain heterogeneity and explore the shape of the CRF. A GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the body of evidence was made using a specifically developed tool coordinated by WHO.

A large number (N=107) of predominantly cohort studies (N=104) were included after screening more than 3000 abstracts. Studies were conducted globally with the majority of studies from North America (N=62) and Europe (N=25). More studies used $PM_{2.5}$ (N=71) as the exposure metric than PM_{10} (N=42). $PM_{2.5}$ was significantly associated with all causes of death evaluated. The combined Risk Ratio (RR) for $PM_{2.5}$ and natural-cause mortality was 1.08 (95%CI 1.06, 1.09) per 10 μg/m³. Meta analyses of studies conducted at the low mean $PM_{2.5}$ levels (<25, 20, 15, 12, 10 μg/m³) yielded RRs that were similar or higher compared to the overall RR, consistent with the finding of generally linear or supralinear CRFs in individual studies. Pooled RRs were almost identical for studies conducted in North America, Europe and Western Pacific region. PM_{10} was significantly associated with natural cause and most but not all causes of death. Application of the risk of bias tool showed that few studies were at a high risk of bias in any domain. Application of the GRADE tool resulted in an assessment of "high certainty of evidence" for $PM_{2.5}$ with all assessed endpoints except for respiratory mortality (moderate). The evidence was rated as less certain for PM_{10} and cause-specific mortality ("moderate" for circulatory, IHD, COPD and "low" for stroke mortality).

Compared to the previous global WHO evaluation, the evidence base has increased substantially. However studies conducted in low and middle income countries (LMICs) are still limited. There is clear evidence that both $PM_{2.5}$ and PM_{10} were associated with increased mortality from all causes, cardiovascular disease, respiratory disease and lung cancer. Associations remained below the current WHO guideline value of 10 μg/m³ for $PM_{2.5}$.

Systematic review registration number (PROSPERO ID): CRD42018082577.

Table A3.1. Certainty of evidence profile for each exposure–outcome combination

	Reasons for downgrading									Reasons for upgrading				Overall	Final certainty assessment
	A1	Rationale	A2	Rationale	A3	Rationale	A4	Rationale	A5	Rationale	B1	Rationale	B2	Rationale	B3	Rationale	
$PM_{2.5}$ and natural cause	0	Little influence on the overall effect	0	No evidence of indirectness	0	Prediction interval does not include unity	0	Sample size large enough to assess RR with sufficient precision	0	No evidence of publication bias	0	Insufficient basis for upgrading	0	Confounders would shift the RR in both directions	+1	Evidence of increase in risk with increasing exposure	+1	High
PM_{10} and natural cause	0	Little influence on the overall effect	0	No evidence of indirectness	0	Prediction interval does not include unity	0	Sample size large enough to assess RR with sufficient precision	0	No evidence of publication bias	0	Insufficient basis for upgrading	0	Confounders would shift the RR in both directions	+1	Evidence of increase in risk with increasing exposure	+1	High
$PM_{2.5}$ and circulatory	0	Little influence on the overall effect	0	No evidence of indirectness	0	Prediction interval does not include unity	0	Sample size large enough to assess RR with sufficient precision	0	No evidence of publication bias	0	Insufficient basis for upgrading	0	Confounders would shift the RR in both directions	+1	Evidence of increase in risk with increasing exposure	+1	High
PM_{10} and circulatory	0	Little influence on the overall effect	0	No evidence of indirectness	-1	Prediction interval includes unity and larger than twice the CI	0	Sample size large enough to assess RR with sufficient precision	0	No evidence of publication bias	0	Insufficient basis for upgrading	0	Confounders would shift the RR in both directions	+1	Evidence of increase in risk with increasing exposure	0	Moderate

A1 = limitations in studies (risk of bias); A2 = indirectness; A3 = inconsistency; A4 = imprecision; A5 = publication bias.
B1 = large RR; B2 = all confounding decreases observed RR; B3 = concentration–response gradient.
Note: "+" indicates an increase in the confidence level; "–" indicates a decrease in the confidence level; "0" indicates no change in the confidence level.

A3.2 Long-term exposure to NO_2 and O_3 and all-cause and respiratory mortality: a systematic review and meta-analysis (Huangfu & Atkinson, 2020)

Abstract

Background: WHO has published several volumes of Global Air Quality Guidelines to provide guidance on the health risks associated with exposure to outdoor air pollution. As new scientific evidence is generated, air quality guidelines need to be periodically revised and, where necessary, updated.

Objectives: The aims of the study were 1) to summarise the available evidence on the effect of long-term exposure to ozone (O_3) and nitrogen dioxide (NO_2) on mortality; 2) and to assess concentration response functions (CRF), their shape and the minimum level of exposures measured in studies to support WHO's update of the air quality guidelines.

Data sources: We conducted a systematic literature search of the Medline, Embase and Web of Science databases following a protocol proposed by WHO and applied Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for reporting our results.

Study eligibility criteria: Cohort studies in human populations (including sub-groups at risk) exposed to long-term concentrations of NO_2 and O_3. Outcomes assessed were all-cause, respiratory, Chronic Obstructive Pulmonary Disease (COPD) and Acute Lower Respiratory Infection (ALRI) mortality.

Study appraisal and synthesis methods: Studies included in the meta-analyses were assessed using a new risk of bias instrument developed by a group of experts convened by WHO. Study results are presented in forest plots and quantitative meta-analyses were conducted using random effects models. The certainty of evidence was assessed using a newly developed adaptation of GRADE.

Results: The review identified 2068 studies of which 95 were subject to review with 45 meeting the inclusion criteria. An update in September 2018 identified 159 studies with 1 meeting the inclusion criteria. Of the 46 included studies, 41 reported results for NO_2 and 20 for O_3. The majority of studies were from the USA and Europe with the remainder from Canada, China and Japan. Forty-two studies reported results for all-cause mortality and 22 for respiratory mortality.

Associations for NO_2 and mortality were positive; random-effects summary relative risks (RR) were 1.02 (95% CI: 1.01, 1.04), 1.03 (1.00, 1.05), 1.03 (1.01, 1.04) and 1.06 (1.02, 1.10) per 10 μg/m³ for all-cause (24 cohorts), respiratory (15 cohorts), COPD (9 cohorts) and ALRI (5 cohorts) mortality respectively. The review identified high levels of heterogeneity for all causes of death except COPD. A small number of studies investigated the shape of the concentration–response relationship and generally found little evidence to reject the assumption of linearity across the concentration range.

Studies of O_3 using annual metrics showed the associations with all-cause and respiratory mortality were 0.97 (0.93, 1.02) and 0.99 (0.89, 1.11) per 10 μg/m³ respectively. For studies using peak O_3 metrics, the association with all-cause mortality was 1.01 (1.00, 1.02) and for respiratory mortality 1.02 (0.99, 1.05), each per 10 μg/m³. The review identified high levels of heterogeneity. Few studies investigated the shape of the concentration–response relationship.

Certainty in the associations (adapted GRADE) with mortality was rated low to moderate for each exposure-outcome pair, except for NO_2 and COPD mortality which was rated high.

Limitations: The substantial heterogeneity for most outcomes in the review requires explanation. The evidence base is limited in terms of the geographical spread of the study populations and, for some outcomes, the small number of independent cohorts for meta-analysis precludes meaningful meta-regression to explore causes of heterogeneity. Relatively few studies assessed specifically the shape of the CRF or multi-pollutant models.

Conclusions: The short-comings in the existing literature base makes determining the precise nature (magnitude and linearity) of the associations challenging. Grade assessments were moderate or low for both NO_2 and O_3 for all causes of mortality except for NO_2 and COPD mortality where the certainty of the evidence was judged as high.

Table A3.2. Certainty of evidence profile for NO_2 and all-cause mortality

Domain	Judgement	Down/up grade
Limitations in studies	Twenty-four included studies. Risk of bias moderate because although not all studies adjusted for all confounders, exclusion of high risk of bias studies did not reduce the summary RR	No downgrading
Indirectness	All studies included the desired population, exposures and outcomes	No downgrading
Inconsistency	The 80% prediction interval included 1 & > twice CI. High level of heterogeneity in general population studies. Studies controlling for individual measures of BMI, smoking, SES gave slightly higher, less precise summary RR. Exclusion of patient cohorts (6) did not change summary RR & CI	Downgrade one level
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	According to the funnel plot and Egger's test (P<0.1), there were sign of publication bias/funnel plot asymmetry	No downgrading
Large effect size	Summary RR = 1.02. Precision reduced for cohorts with all individual confounder adjustment but not summary estimate. Insufficient information on unmeasured potential confounders available	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	A linear dose–response relationship was assumed in all studies. 5 studies investigated the shape of the dose–response relationship with no evidence to suggest non-linear. 95% CI for linear RR excluded 1	Upgrade one level
GRADE conclusion	Downgrade one level and upgrade one level	MODERATE CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 1.02 PER 10 μg/m³

Table A3.3. Certainty of evidence profile for NO_2 and respiratory mortality

Domain	Judgement	Down/up grade
Limitations in studies	Fifteen included studies. Risk of bias moderate because although not all studies adjusted for all confounders, exclusion of high risk of bias studies did not alter summary RR	No downgrading
Indirectness	All studies included the desired population, exposures and outcomes	No downgrading
Inconsistency	The 80% prediction interval included 1; PI = 2 x CI. Studies controlling for individual measures of BMI, smoking, SES gave lower summary RR and CI included 1. Exclusion of single patient cohort did not change summary RR & CI. High level of heterogeneity in general population studies	Downgrade one level
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	According to the funnel plot little evidence of publication bias	No downgrading
Large effect size	Summary RR = 1.03. Insufficient information on unmeasured potential confounders available	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	A linear dose–response relationship was assumed in all studies, 95% CI for linear RR excluded 1. No evidence to confirm shape of the dose–response relationship	Upgrade one level
GRADE conclusion	No downgrade and no upgrade	MODERATE CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 1.03 PER 10 µg/m^3

Table A3.4. Certainty of evidence profile for NO_2 and COPD mortality

Domain	Judgement	Down/up grade
Limitations in studies	Nine included studies. Risk of bias moderate because although not all studies adjusted for all confounders, exclusion of 2 high risk of bias studies did not alter summary RR	No downgrading
Indirectness	All studies included the desired population, exposures and outcomes	No downgrading
Inconsistency	The 80% prediction interval did not include 1	No downgrading
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	No analysis of publication bias – too few studies (n=9)	No downgrading
Large effect size	Summary RR = 1.02. Insufficient information on unmeasured potential confounders available	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	A linear dose–response relationship was assumed in all studies, 95% CI for linear RR excluded 1. 2 studies investigated the shape of the dose–response relationship with no evidence to suggest non-linear	Upgrade one level
GRADE conclusion	No downgrade and upgrade one level	HIGH CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 1.03 PER 10 µg/m³

Table A3.5. Certainty of evidence profile for NO_2 and ALRI mortality

Domain	Judgement	Down/up grade
Limitations in studies	Five included studies. Risk of bias moderate for all studies, not all studies adjusted for all confounders	No downgrading
Indirectness	All studies included the desired population, exposures and outcomes	No downgrading
Inconsistency	The 80% prediction interval included 1 but the PI was not > 2 x CI. Substantial heterogeneity amongst small number of studies	Downgrade one level
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	No analysis of publication bias – too few studies	No downgrading
Large effect size	Summary RR = 1.02. Insufficient information on unmeasured potential confounders available	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	No information on shape. 95% CI for linear RR excluded 1	Upgrade one level
GRADE conclusion	No downgrade and no upgrade	MODERATE CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 1.06 PER 10 μg/m³

Table A3.6. Certainty of evidence profile for O_3 annual exposure and all-cause mortality

Domain	Judgement	Down/up grade
Limitations in studies	Nine included studies. Three studies with a total weight of 28% in the meta-analysis had high risk of bias. Excluding these studies did not change significantly the summary RR	No downgrading
Indirectness	One study with study sample of stroke patients based in London. However, it was a small study and only carried 1% weight	No downgrading
Inconsistency	The 80% prediction interval included 1 & PI > 2 x CI	Downgrade one level
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	No analysis of publication bias – too few studies (n=9)	No downgrading
Large effect size	Summary RR=0.97	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	A linear dose–response relationship was assumed in all studies. 95% CI for linear RR included 1. None of the studies reported the dose–response relationship	No upgrading
GRADE conclusion	Downgrade one level and no upgrade	LOW CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 0.97 PER 10 µg/m³

Table A3.7. Certainty of evidence profile for O_3 annual exposure and respiratory mortality

Domain	Judgement	Down/up grade
Limitations in studies	Only 4 studies; all rated low or moderate risk of bias	No downgrading
Indirectness	All studies included the desired population, exposures and outcomes	No downgrading
Inconsistency	The 80% prediction interval included 1 & PI > 2 x CI. Substantial heterogeneity amongst small number of studies	Downgrade one level
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	No analysis of publication bias – too few studies (n=4)	No downgrading
Large effect size	Summary RR=0.99	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	A linear dose–response relationship was assumed in all studies. 95% CI for linear RR included 1. None of the studies reported dose–response relationship	No upgrading
GRADE conclusion	Downgrade one level and no upgrade	LOW CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 0.99 PER 10 µg/m³

Table A3.8. Certainty of evidence profile for O_3 peak exposure and all-cause mortality

Domain	Judgement	Down/up grade
Limitations in studies	Seven included studies. One study with high risk of bias – exclusion did not change summary RR	No downgrading
Indirectness	One study might have introduced some selection bias due to the volunteering sample chosen. However, it was only weighted at less than 2% among all studies	No downgrading
Inconsistency	The 80% prediction interval included 1; PI = 2 x CI	No downgrading
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	No analysis of publication bias – too few studies (*n*=6)	No downgrading
Large effect size	Summary RR = 1.01. All critical confounders were adjusted for. Insufficient information on unmeasured potential confounders available	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	A linear dose–response relationship was assumed in all studies. 95% CI for linear RR included 1. One study investigated the shape of the dose–response relationship with no evidence to suggest non-linear	No upgrading
GRADE conclusion	No downgrade and no upgrade	MODERATE CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 1.01 PER 10 µg/m³

Table A3.9. Certainty of evidence profile for O_3 peak exposure and respiratory mortality

Domain	Judgement	Down/up grade
Limitations in studies	Four included studies. One study high risk of bias. Exclusion did not alter significantly the RR and CI	No downgrading
Indirectness	All studies included the desired population, exposures and outcomes	No downgrading
Inconsistency	The 80% prediction interval included 1; PI = 2 x CI. Substantial heterogeneity amongst small number of studies	Downgrade one level
Imprecision	The number of person years in the included studies was greater than 940 000	No downgrading
Publication bias	No analysis of publication bias – too few studies (n=3)	No downgrading
Large effect size	Summary RR = 1.02. Insufficient information on unmeasured potential confounders available	No upgrading
Plausible confounding towards null	Confounding direction unknown but precision may be affected	No upgrading
Dose–response relation	A linear dose–response relationship was assumed in all studies. 95% CI for linear RR included 1. One study investigated the dose–response relationship. No evidence to confirm shape of the dose–response relationship for ozone exposure	No upgrading
GRADE conclusion	No downgrade and no upgrade	LOW CERTAINTY EVIDENCE MEAN RR UNADJUSTED FOR CO-POLLUTANTS EQUALS 1.02 PER 10 µg/m³

A3.3 Short-term exposure to particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) and all-cause and cause-specific mortality: systematic review and meta-analysis (Orellano et al., 2020)

Abstract

Background: Air pollution is a leading cause of mortality and morbidity worldwide. Short-term exposure (from one hour to days) to selected air pollutants has been associated with human mortality. This systematic review was conducted to analyse the evidence on the effects of short-term exposure to particulate matter with aerodynamic diameters less or equal than 10 and 2.5 μm (PM_{10}, $PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3), on all-cause mortality, and PM_{10} and $PM_{2.5}$ on cardiovascular, respiratory, and cerebrovascular mortality.

Methods: We included studies on human populations exposed to outdoor air pollution from any source, excluding occupational exposures. Relative risks (RRs) per 10 μg/m³ increase in air pollutants concentrations were used as the effect estimates. Heterogeneity between studies was assessed using 80% prediction intervals. Risk of bias (RoB) in individual studies was analysed using a new domain-based assessment tool, developed by a working group convened by the World Health Organization and designed specifically to evaluate RoB within eligible air pollution studies included in systematic reviews. We conducted subgroup and sensitivity analyses by age, sex, continent, study design, single or multicity studies, time lag, and RoB. The certainty of evidence was assessed for each exposure-outcome combination. The protocol for this review was registered with PROSPERO (CRD42018087749).

Results: We included 196 articles in quantitative analysis. All combinations of pollutants and all-cause and cause-specific mortality were positively associated in the main analysis, and in a wide range of sensitivity analyses. The only exception was NO_2, but when considering a 1-hour maximum exposure. We found positive associations between pollutants and all-cause mortality for PM_{10} (RR: 1.0041; 95% CI: 1.0034-1.0049), $PM_{2.5}$ (RR: 1.0065; 95% CI: 1.0044-1.0086), NO_2 (24-hour average) (RR: 1.0072; 95% CI: 1.0059-1.0085), and O_3 (RR: 1.0043; 95% CI: 1.0034-1.0052). PM_{10} and $PM_{2.5}$ were also positively associated with cardiovascular, respiratory, and cerebrovascular mortality. We found some degree of heterogeneity between studies in three exposure-outcome combinations, and this heterogeneity could not be explained after subgroup analysis. RoB was low or moderate in the majority of articles.

The certainty of evidence was judged as high in 10 out of 11 combinations, and moderate in one combination.

Conclusions: This study found evidence of a positive association between short-term exposure to PM_{10}, $PM_{2.5}$, NO_2, and O_3 and all-cause mortality, and between PM_{10} and $PM_{2.5}$ and cardiovascular, respiratory and cerebrovascular mortality. These results were robust through several sensitivity analyses. In general, the level of evidence was high, meaning that we can be confident in the associations found in this study.

Table A3.10 Certainty of evidence profile for each exposure–outcome combination

Exposure – outcome	Limitations in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
			Downgrade			Upgrade			
PM_{10} – all-cause mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias detected, but no difference between multicity and single-city studies was observed.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠
PM_{10} – cardiovascular mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias detected, but no difference between multicity and single-city studies was observed.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠
PM_{10} – respiratory mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias was not detected.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠

Certainty of evidence, starting from moderate certainty (⊠⊠⊠); CRFs, concentration–response functions; (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk.

Table A3.10 contd

Exposure – outcome	Limitations in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
	Downgrade					Upgrade			
PM_{10} – cerebrovascular mortality	(0) No differences between studies with low/ moderate and high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias detected, but no difference between multicity and single-city studies was observed.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High**
$PM_{2.5}$ – all-cause mortality	(0) Statistical differences between studies with low/ moderate versus high RoB, but studies showing high RoB had small weight on the results	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias detected, but no difference between multicity and single-city studies was observed.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High**
$PM_{2.5}$ – cardiovascular mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias was not detected.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High**

Certainty of evidence, starting from moderate certainty (⊠⊠⊠); CRFs, concentration–response functions; (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk.

Table A3.10 contd

Exposure–outcome	Limitations in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
	Downgrade					Upgrade			
$PM_{2.5}$ – respiratory mortality	(0) No differences between studies with low/moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval included unity, but is not twice the confidence interval.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias was not detected.	(0) Unmeasured confounding could influence the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠
$PM_{2.5}$ – cerebrovascular mortality	(-1) Statistical differences between studies with low/moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval included unity, but is not twice the confidence interval.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias was not detected.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠
NO_2 (24-hour average) – all-cause mortality	(-1) Statistical differences between studies with low/moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias detected, but no difference between multicity and single-city studies was observed.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠

Certainty of evidence, starting from moderate certainty (⊠⊠⊠); CRFs, concentration–response functions; (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk.

Table A3.10 contd

Exposure – outcome	Limitations in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
	Downgrade					Upgrade			
NO_2 – (1-hour max.) – all-cause mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias was not detected.	(0) Unmeasured confounding could influence the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(0) No significant association detected in the main analysis.	**Moderate** ⊠⊠⊠□
O_3 – all-cause mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the original question.	(0) 80% prediction interval did not include unity.	(0) Number of mortality cases higher than 100,000.	(0) Publication bias detected, but no difference between multicity and single-city studies was observed.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠

Certainty of evidence, starting from moderate certainty (⊠⊠⊠); CRFs, concentration–response functions; (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk.

A3.4 Short-term exposure to sulfur dioxide (SO_2) and all-cause and respiratory mortality: a systematic review and meta-analysis (Orellano, Reynoso & Quaranta, 2021)

Abstract

Background: Many studies have assessed the harmful effects of ambient air pollution on human mortality, but the evidence needs further exploration, analysis, and refinement, given the large number of studies that have been published in recent years. The objective of this study was to evaluate all the available evidence of the effect of short-term exposure to ambient sulphur dioxide (SO_2) on all-cause and respiratory mortality.

Methods: Articles reporting observational epidemiological studies were included, comprising time-series and case-crossover designs. A broad search and wide inclusion criteria were considered, encompassing international and regional databases, with no geographical or language restrictions. A random effect meta-analysis was conducted, and pooled relative risk for an increment of 10 μg/m³ in SO_2 concentrations were calculated for each outcome. We analysed the risk of bias (RoB) in individual studies for specific domains using a new domain-based RoB assessment tool, and the certainty of evidence across studies with an adaptation of the Grading of Recommendations Assessment, Development and Evaluation approach. The certainty of evidence was judged separately for each exposure-outcome combination. A number of subgroup and sensitivity analyses were carried out, as well as assessments of heterogeneity and potential publication bias. The protocol for this review was registered with PROSPERO (CRD42019120738).

Results: Our search retrieved 1,128 articles, from which 67 were included in quantitative analysis. The RoB was low or moderate in the majority of articles and domains. An increment of 10 μg/m³ in SO_2 (24-hour average) was associated with all-cause mortality (RR: 1.0059; 95% CI: 1.0046–1.0071; p-value: <0.01), and respiratory mortality (RR: 1.0067; 95% CI: 1.0025–1.0109; p-value: <0.01), while the same increment in SO_2 (1-hour max.) was associated with respiratory mortality (RR:1.0052; 95% CI: 1.0013–1.0091; p-value: 0.03). Similarly, the association was positive but non-significant for SO_2 (1-hour max.) and all-cause mortality (RR: 1.0016; 95% CI: 0.9930–1.0102; p-value: 0.60). These associations were still significant after the adjustment for particulate matter, but not for other pollutants, according to the results from 13 articles that evaluated co-pollutant models. In general, linear concentration-response functions with no thresholds were found for the two outcomes, although this was only evaluated in a small number of studies. We found signs of heterogeneity for SO_2 (24-hour average) – respiratory mortality and SO_2 (1-hour max.) – all-cause mortality, and funnel plot asymmetry

for SO_2 (24-hour average) – all-cause mortality. The certainty of evidence was high in two combinations, i.e. SO_2 (24-hour average) – all-cause mortality and SO_2 (1-hour max.) – respiratory mortality, moderate in one combination, i.e. SO_2 (24-hour average) – respiratory mortality, and low in the remaining one combination.

Conclusions: Positive associations were found between short-term exposure to ambient SO_2 and all-cause and respiratory mortality. These associations were robust against several sensitivity analyses, and were judged to be of moderate or high certainty in three of the four exposure-outcome combinations.

Table A3.11. Certainty of evidence profile for each exposure–outcome combination

Exposure – outcome	Limitations in studies in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
	Downgrade					Upgrade			
SO_2 (24-hour average) – all-cause mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the PECO question.	(0) 80% prediction interval did not include unity.	(0) At least one multicity study showed a clinically meaningful association.	(0) Publication bias possibly detected, but a positive significant association was estimated when using multicity studies only.	(+1) Unmeasured confounding would not suffice to explain away the effect estimate.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant association detected in the main analysis.	**High** ⊠⊠⊠
SO_2 (24-hour average) – respiratory mortality	(0) No differences between studies with low/ moderate versus high RoB	(0) The research question in the studies reflects the PECO question.	(-1) 80% prediction interval included unity, and was twice the size of the 95% CI.	(0) At least one multicity study showed a clinically meaningful association.	(0) Publication bias was not detected.	(0) According to the analysis of the E-value, the presence of unmeasured confounders is plausible.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant association detected in the main analysis.	**Moderate** ⊠⊠□

Certainty of evidence, starting from moderate certainty (⊠⊠□); (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk; CI, 95% confidence interval; PECO, population, exposure, comparator, and outcomes.

Table A3.11 contd

Exposure – outcome	Limitations in studies in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
	Downgrade					Upgrade			
SO_2 (1-hour max.) – all-cause mortality	(0) Not enough studies to detect differences in the RoB.	(0) The research question in the studies reflects the PECO question..	(-1) 80% prediction interval included unity, and was twice the size of the 95% CI	(0) At least one multicity study showed a clinically meaningful association.	(0) Not enough studies to analyse publication bias.	(0) Unmeasured confounding was not analysed, because the association was not significant.	(0) Several potential confounders that would shift the RR in both directions.	(0) The association was not significant.	**Low** ⊠⊠□□
SO_2 (1-hour max.) – respiratory mortality	(0) Not enough studies to detect differences in the RoB.	(0) The research question in the studies reflects the PECO question.	(0) 80% prediction interval did not include unity.	(0) At least one multicity study showed a clinically meaningful association..	(0) Not enough studies to analyse publication bias.	(0) According to the analysis of the E-value, the presence of unmeasured confounders is plausible.	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant association detected in the main analysis.	**High** ⊠⊠⊠⊠

Certainty of evidence, starting from moderate certainty (⊠⊠⊠); (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk; CI, 95% confidence interval; PECO, population, exposure, comparator, and outcomes.

A3.5 Short-term exposure to ozone, nitrogen dioxide, and sulphur dioxide and emergency department visits and hospital admissions due to asthma: a systematic review and meta-analysis (Zheng et al., 2021)

Abstract

Background: Air pollution is a major environmental hazard to human health and a leading cause of morbidity for asthma worldwide.

Objectives: To assess the current evidence on short-term effects (from several hours to 7 days) of exposure to ozone (O_3), nitrogen dioxide (NO_2), and sulphur dioxide (SO_2) on asthma exacerbations, defined as emergency room visits (ERVs) and hospital admissions (HAs).

Methods: We searched PubMed/MEDLINE, EMBASE and other electronic databases to retrieve studies that investigated the risk of asthma-related ERVs and HAs associated with short-term exposure to O_3, NO_2, or SO_2. We evaluated the risks of bias (RoB) for individual studies and the certainty of evidence for each pollutant in the overall analysis. A subgroup analysis was performed, stratified by sex, age, and type of asthma exacerbation. We conducted sensitivity analysis by excluding the studies with high RoB and based on the E-value. Publication bias was examined with the Egger's test and with funnel plots.

Results: Our literature search retrieved 9,059 articles, and finally 67 studies were included, from which 48 studies included the data on children, 21 on adults, 14 on the elderly, and 31 on the general population. Forty-three studies included data on asthma ERVs, and 25 on asthma HAs. The pooled relative risk (RR) per 10 μg/m³ increase of ambient concentrations was 1.008 (95%CI: 1.005, 1.011) for maximum 8-hour daily or average 24-hour O_3, 1.014 (95%CI: 1.008, 1.020) for average 24-hour NO_2, 1.010 (95%CI: 1.001, 1.020) for 24-hour SO_2, 1.017 (95%CI: 0.973, 1.063) for maximum 1-hour daily O_3, 0.999 (95%CI: 0.966, 1.033) for 1-hour NO_2, and 1.003 (95%CI: 0.992, 1.014) for 1-hour SO_2. Heterogeneity was observed in all pollutants except for 8-hour or 24-hour O_3 and 24-hour NO_2. In general, we found no significant differences between subgroups that can explain this heterogeneity. Sensitivity analysis based on the RoB showed certain differences in NO_2 and SO_2 when considering the outcome or confounding domains, but the analysis using the E-value showed that no unmeasured confounders were expected. There was no major evidence of publication bias.

Based on the adaptation of the Grading of Recommendations Assessment, Development and Evaluation, the certainty of evidence was high for 8-hour or 24-hour O_3 and 24-hour NO_2, moderate for 24-hour SO_2, 1-hour O_3, and 1-hour SO_2, and low for 1-hour NO_2.

Conclusion: Short-term exposure to daily O_3, NO_2, and SO_2 was associated with an increased risk of asthma exacerbation in terms of asthma-associated ERVs and HAs.

Table A3.12. Certainty of evidence profile for each exposure–outcome combination

Exposure – outcome	Limitations in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
			Downgrade			Upgrade			
O_3 (8-h or 24-h) – ERV or HA	(0) Statistical differences between studies with low/moderate versus high RoB, but the pooled effect in low/moderate RoB articles is significant	(0) The research question in the studies reflects the original question	(0) 80% prediction interval did not include unity	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not detected	(+1) Unmeasured confounding would not suffice to explain away the effect estimate	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠
NO_2 (24-h) – ERV or HA	(0) Statistical differences between studies with low/moderate versus high RoB, but the pooled effect in low/moderate RoB articles is significant	(0) The research question in the studies reflects the original question	(0) 80% prediction interval did not include unity	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not detected	(+1) Unmeasured confounding would not suffice to explain away the effect estimate	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**High** ⊠⊠⊠⊠
SO_2 (24-h) z– ERV or HA	(-1) Statistical differences between studies with low/ moderate versus high RoBt	(0) The research question in the studies reflects the original question	(-1) 80% prediction interval included unity, and was twice the width of the 95%CI	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not detected	(+1) Unmeasured confounding would not suffice to explain away the effect estimate	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	**Moderate** ⊠⊠⊠□

Certainty of evidence, starting from moderate certainty (⊠⊠⊠); (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk.

Table A3.12 contd

Exposure – outcome	Limitations in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
	Downgrade					Upgrade			
O_3 (1-h) – ERV or HA	(0) Differences between studies with low/moderate versus high RoB were not evaluated.	(0) The research question in the studies reflects the original question	(0) 80% prediction interval included unity, but is not twice the 95%CI	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not evaluated	(0) E-value was not calculated, because the pooled RR is not significant.	(0) Several potential confounders that would shift the RR in both directions.	(0) No significant association detected in the main analysis.	**Moderate** ⊠⊠⊠□
NO_2 (1-h) – ERV or HA	(0) No differences between studies with low/moderate versus high RoB.	(0) The research question in the studies reflects the original question	(0) 80% prediction interval included unity, but is not twice the 95%CI	(-1) Number of asthma exacerbations lower than 150,000.	(0) Publication bias was not evaluated	(0) E-value was not calculated, because the pooled RR is not significant.	(0) Several potential confounders that would shift the RR in both directions.	(0) No significant association detected in the main analysis.	**Low** ⊠⊠□□
SO_2 (1-h) – ERV or HA	(0) Differences between studies with low/moderate versus high RoB were not evaluated.	(0) The research question in the studies reflects the original question	(0) 80% prediction interval included unity, but is not twice the 95%CI	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not evaluated	(0) E-value was not calculated, because the pooled RR is not significant.	(0) Several potential confounders that would shift the RR in both directions.	(0) No significant association detected in the main analysis.	**Moderate** ⊠⊠⊠□

Certainty of evidence, starting from moderate certainty (⊠⊠⊠); (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk.

A3.6 Short-term exposure to carbon monoxide and myocardial infarction: a systematic review and meta-analysis (Lee et al., 2020)

Abstract

Background: Previous studies suggest an association between short-term exposure to carbon monoxide and myocardial infarction. We performed a systematic review and meta-analysis to assess current evidence on this association to support the update of the World Health Organization (WHO) Global Air Quality Guidelines.

Methods: We searched Medline, Embase and Cochrane Central Register of Controlled Trials to update the evidence published in a previous systematic review up to 30th September 2018 for studies investigating the association between short-term exposure to ambient carbon monoxide (up to lag of seven days) and emergency department visits or hospital admissions and mortality due to myocardial infarction. Two reviewers assessed potentially eligible studies and performed data extraction independently. Random-effects meta-analysis was used to derive the pooled risk estimate per 1mg/m³ increase in ambient carbon monoxide concentration. Risk of bias in individual studies was assessed using a domain-based assessment tool. The overall certainty of the body of evidence was evaluated using an adapted certainty of evidence assessment framework.

Results: We evaluated 1,038 articles from the previous review and our updated literature search, of which, 26 satisfied our inclusion criteria. Overall, myocardial infarction was associated with exposure to ambient carbon monoxide concentration (risk ratio of 1.052, 95% confidence interval 1.017 – 1.089 per 1mg/m³ increase). A third of studies were assessed to be at high risk of bias (RoB) due to inadequate adjustment for confounding. Using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, the overall evidence was assessed to be of moderate certainty.

Conclusions: This review demonstrated that the pooled risk ratio for myocardial infarction was 1.052 (95% CI 1.017–1.089) per 1mg/m³ increase in ambient carbon monoxide concentration. However, very few studies originated from low- and middle-income countries.

Table A3.13. Certainty of evidence profile for CO and myocardial infarction

Domain	Judgement	Down/up grade
Limitations in studies	Ten studies were assessed to be high risk of bias due to inadequate adjustment for confounding. Subgroup analysis did not demonstrate a statistically significant difference in risk estimates between studies at low/moderate risk of bias versus those at high risk of bias	No downgrading
Indirectness	All included studies were consistent with the prespecified PECOS	No downgrading
Inconsistency	The 80% prediction interval was 0.871–1.271. However, most of this is driven by 3 studies that reported outlying results. Sensitivity analysis excluding these studies had a 80% prediction interval of 1.002–1.030	No downgrading
Imprecision	Although the number of participants included in the review (1.5 million) was significantly lower than the estimated sample size required (12.1 million), risk estimates reported by the studies are sufficiently precise	No downgrading
Publication bias	Visual inspection of the funnel plot does not indicate significant asymmetry	No downgrading
Large effect size	Overall relative risk was 1.052. Based on this, an E-value of 1.29 was calculated. However there is insufficient information to determine strength of unmeasured confounders	No upgrading
Plausible confounding towards null	Direction of effect of other confounding is unknown	No upgrading
Dose–response relation	None of the studies reported the dose–response relationship	No upgrading
GRADE conclusion		MODERATE CERTAINTY OF EVIDENCE

The main objective of these updated global guidelines is to offer health-based air quality guideline levels, expressed as long- or short-term concentrations, for six key air pollutants: $PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. In addition, the guidelines provide interim targets to guide reduction efforts for these pollutants, as well as good practice statements for the management of certain types of PM (i.e. black carbon/elemental carbon, ultrafine particles, and particles originating from sand and dust storms). These guidelines are not legally binding standards; however, they provide WHO Member States with an evidence-informed tool they can use to inform legislation and policy. Ultimately, the goal of these guidelines is to help reduce levels of air pollutants in order to decrease the enormous health burden resulting from exposure to air pollution worldwide.

Compared with previous WHO guidelines, these guidelines:

- use new methods for evidence synthesis and guideline development;
- reinforce previous evidence on the adverse health effects of air pollution; and
- provide evidence of adverse health effects from air pollution at lower levels than previously known.

The guidelines are a critical tool for the following three main groups of users:

- policy-makers, lawmakers and technical experts at the local, national and international levels who are responsible for developing and implementing regulations and standards for air quality, air pollution control, urban planning and other policy areas;
- national and local authorities and nongovernmental organizations, civil society organizations and advocacy groups such as patients, citizen groups, industrial stakeholders and environmental organizations; and
- academics, health and environmental impact assessment practitioners, and researchers in the broad field of air pollution.

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