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)

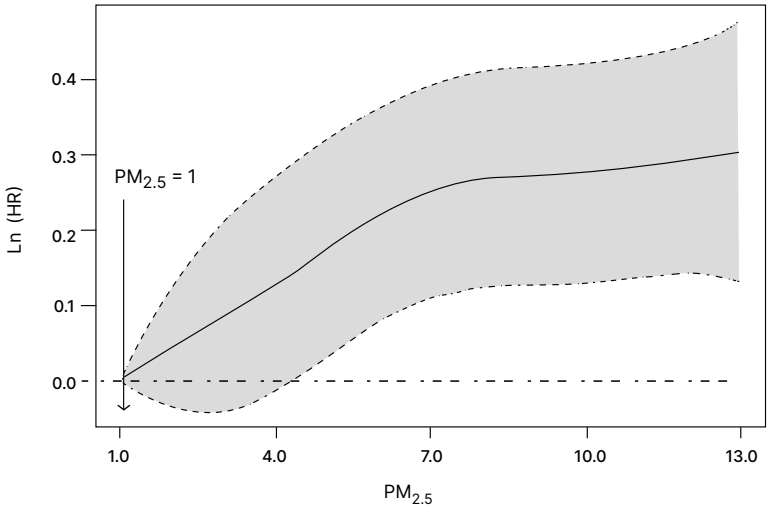
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard deviation using the following formula: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

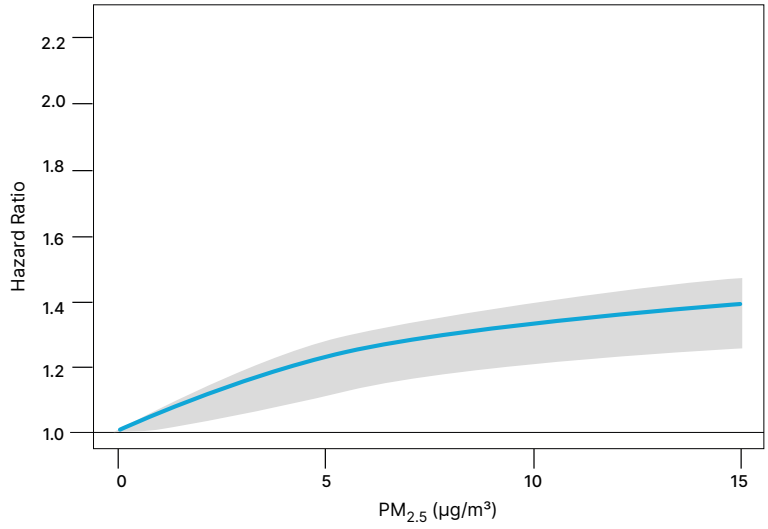
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard deviation using the following formula: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

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



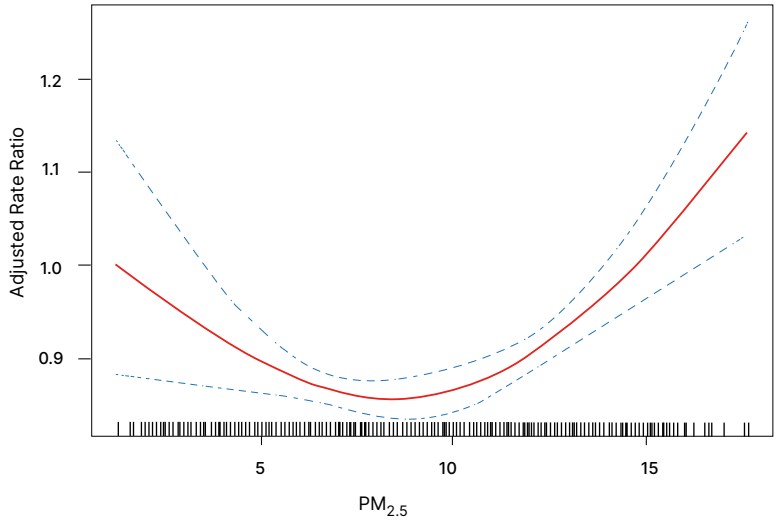
Ln (HR): log HR, with an HR of 1 at a $PM_{2.5}$ concentration of 1 µg/m³.
Source: Pinault et al. (2016).

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



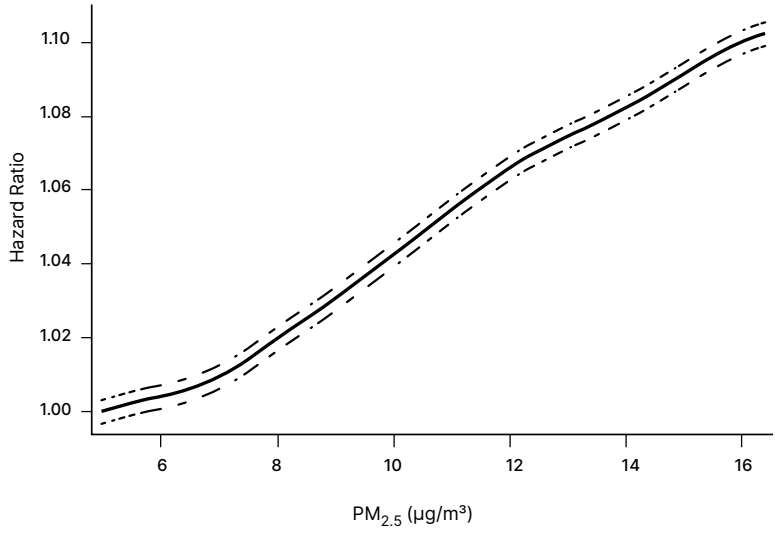
Source: reprinted from Pinault et al. (2017) with permission from Elsevier.

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



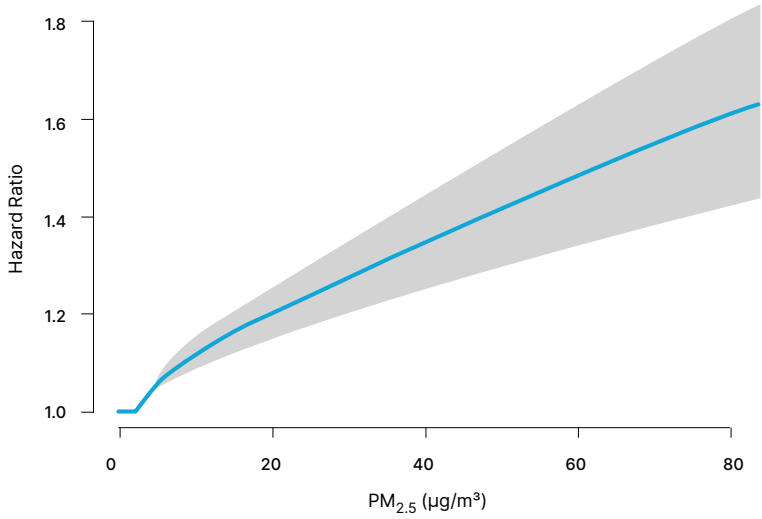
Source: reprinted from Villeneuve et al. (2015) with permission from the publisher. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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.

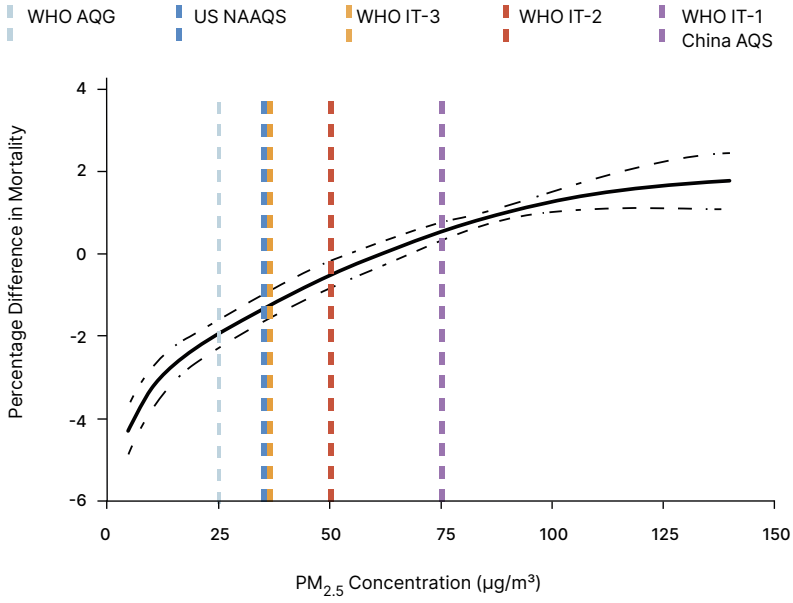
Table 3.6. Recommended short-term (24-hour) AQG level and interim targets for $PM_{2.5}$[a]

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**

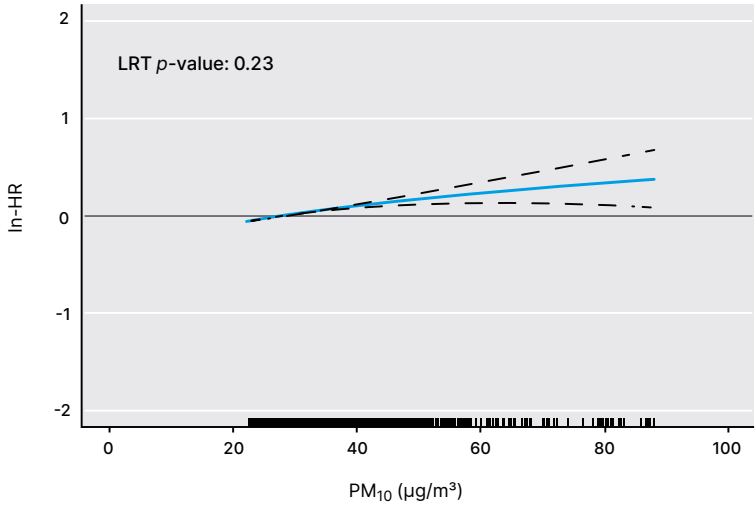
If mortality in a population exposed to PM_{10} at the AQG level were arbitrarily set at 100, then it will be 122, 114, 106 and 102, respectively, in populations exposed to PM_{10} at the interim target 1, 2, 3 and 4 levels. These projections are based on the linear HR of 1.04 per 10-μg/m³ increase in 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)

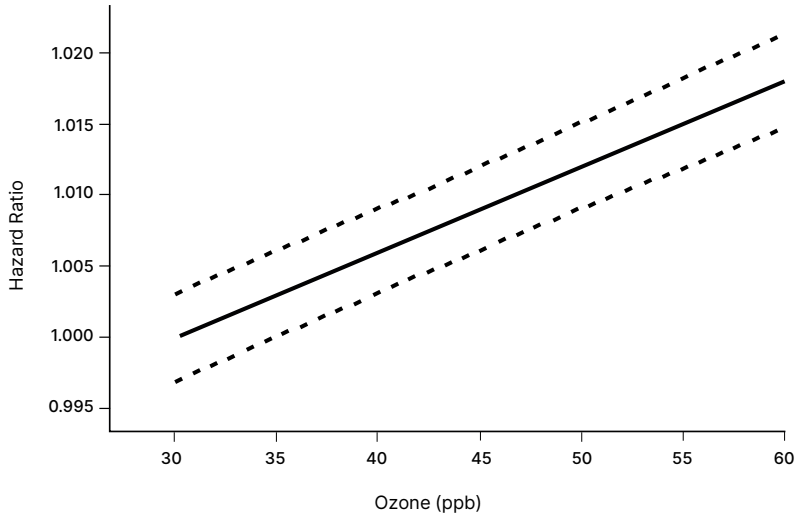
–, data unavailable; CCHS: Canadian Community Health Survey; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.
[c] Calculated from mean and standard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

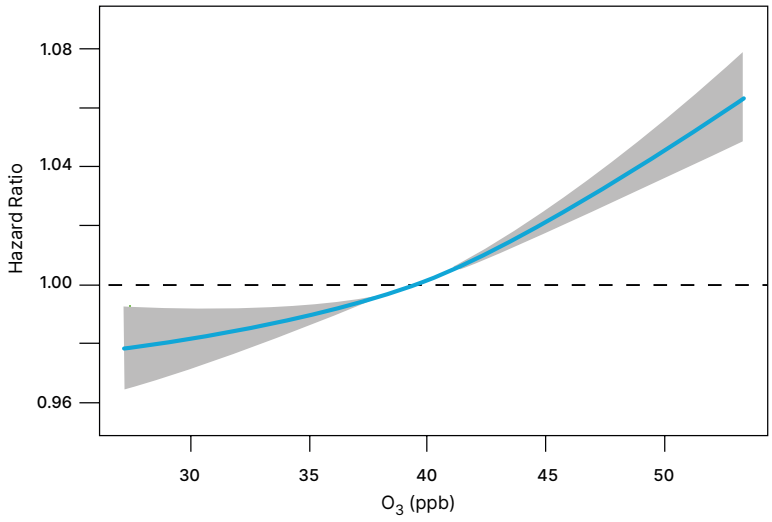
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.

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



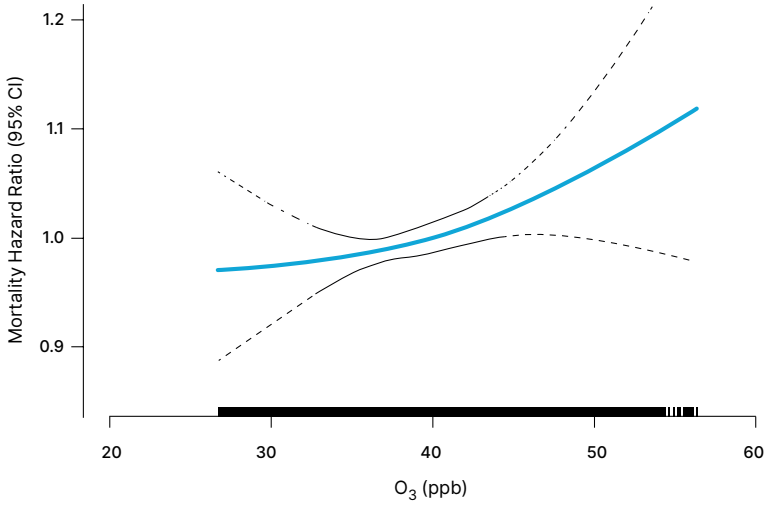
[a] Note that the units for ozone are in ppb; these need to be multiplied by 2 to arrive at concentrations expressed in μg/m³. HR is expressed relative to the 5th percentile of the distribution of ozone concentrations, which was 30 ppb. *Source:* reprinted from Di et al. (2017a) with permission from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

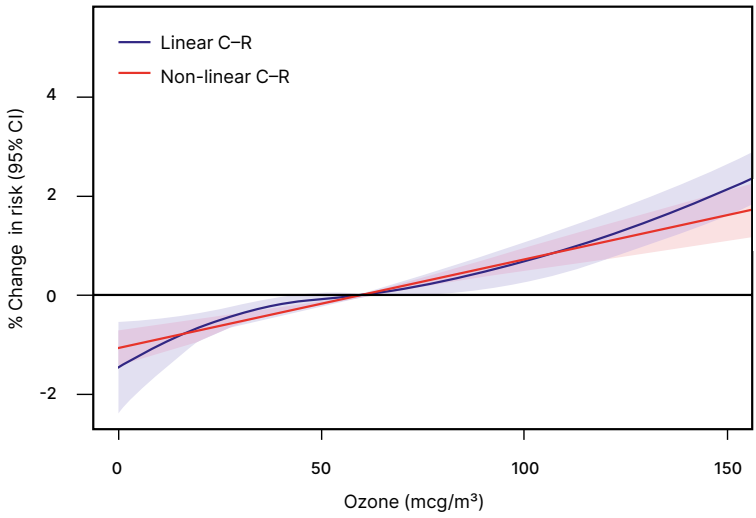
Table 3.15. Recommended short-term (8-hour) daily maximum AQG level and interim targets for ozone[a]

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)

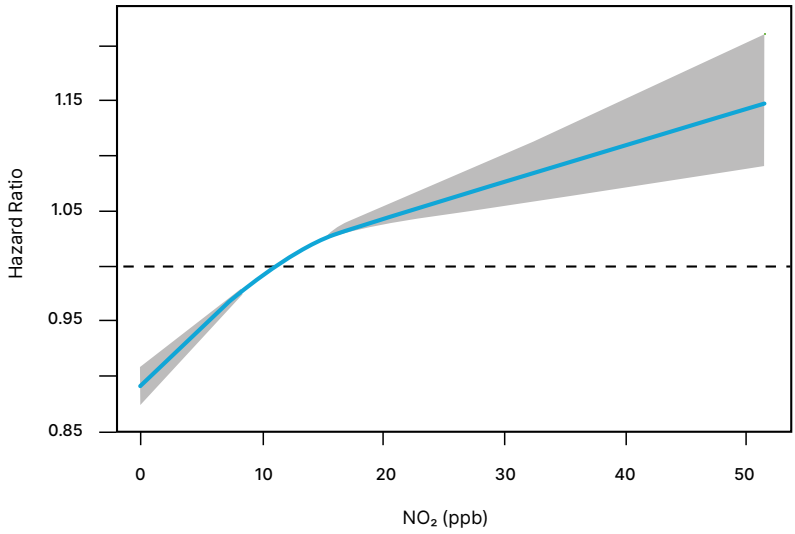
–, data unavailable; CCHS: Canadian Community Health Survey; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Calculated from the mean and SD using the following formula: Me(di)an – 1.645 * SD.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

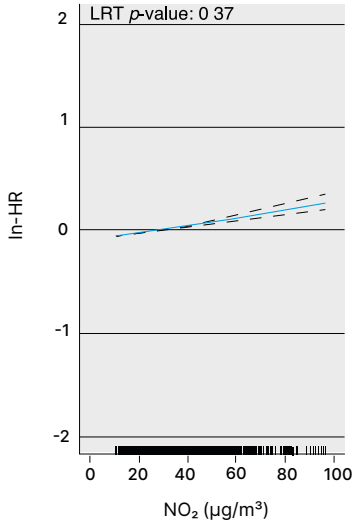
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 µg/m³.
[b] Reported in paper or by authors on request.

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.

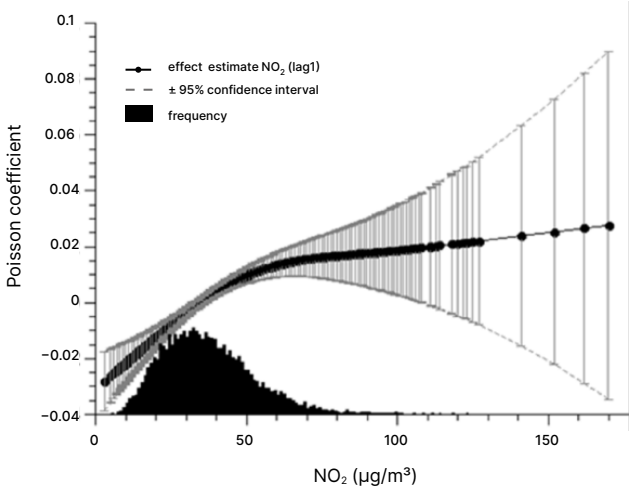
Table 3.21. Recommended short-term (24-hour) AQG level and interim targets for nitrogen dioxide[a]

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.