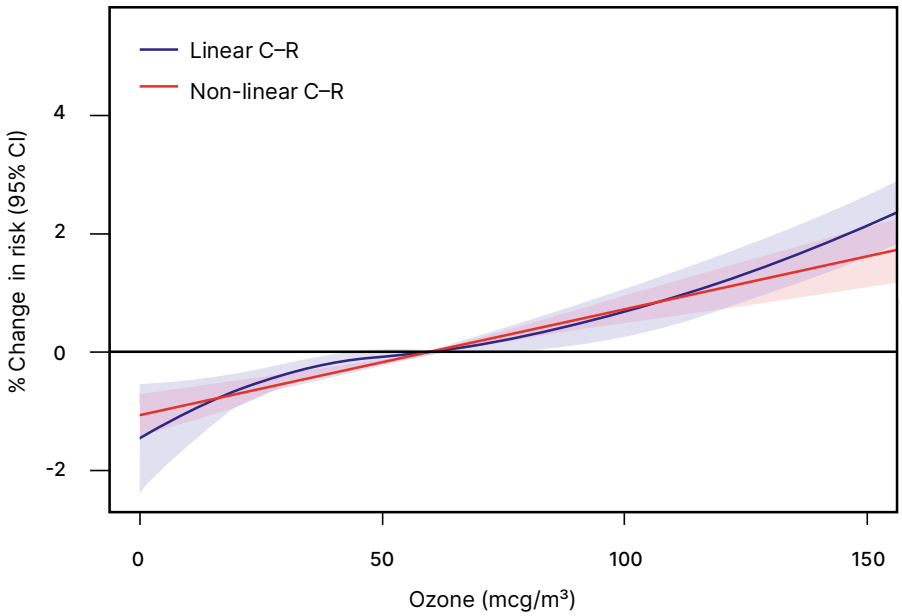
**Fig. 3.11.** Exposure–response curve for 8-hour ozone exposure (µg/m³) and all-cause mortality[a]




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) |

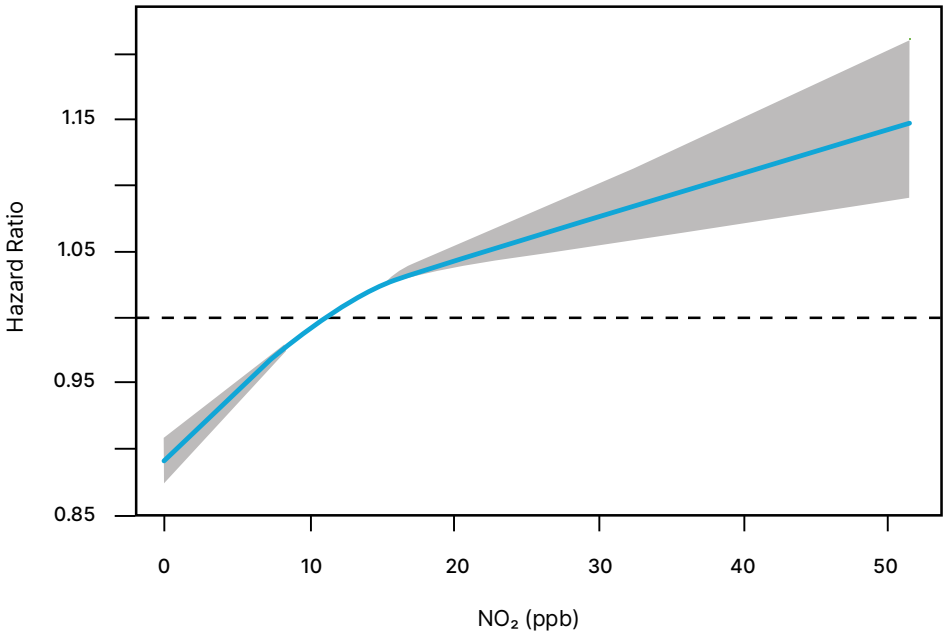
–, data unavailable; CCHS: Canadian Community Health Survey; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Calculated from the mean and SD using the following formula: Me(di)an – 1.645 * SD.
[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 | 0.990 (0.960–1.010) |
| Hvidtfeldt et al. (2019) | 25.0 | – | 17.9[b] | – | 1.070 (1.040–1.100) |
| Eum et al. (2019) | 26.7 | – | – | 18.2 | 1.027 (1.027–1.029) |

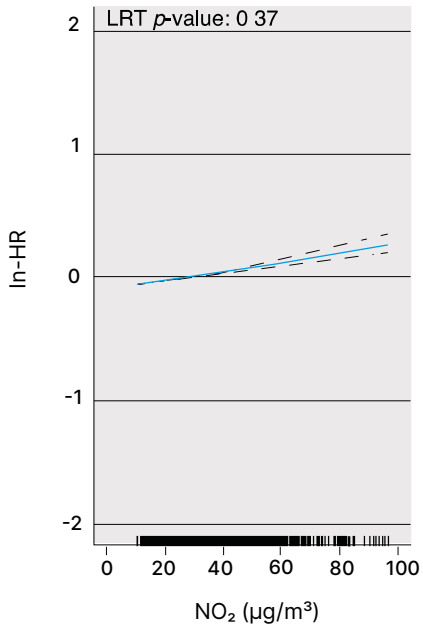
–, data unavailable; P5: 5th percentile (of the distribution of concentrations assigned to study participants); P25: 25th percentile; SD: standard deviation.
[a] Per 10 μg/m³.
[b] Reported in paper or by authors on request.

**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/m³ 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/m³ 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 µg/m$^3$ is proposed – which is roughly comparable to the existing 1-hour 2005 air quality guideline of 200 µg/m$^3$. An interim target 2 of 50 µg/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.**

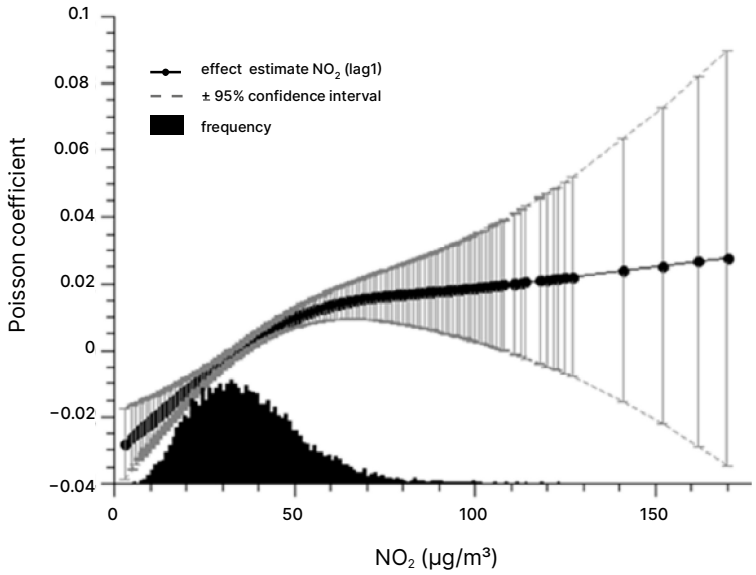
**Table 3.21.** Recommended short-term (24-hour) AQG level and interim targets for nitrogen dioxide[a]

| 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.