

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

STATEMENT ON THE EVIDENCE FOR THE EFFECTS OF NITROGEN DIOXIDE ON HEALTH

Summary

1. Studies have shown associations of nitrogen dioxide (NO₂) in outdoor air with adverse effects on health, including reduced life expectancy. It has been unclear whether these effects are caused by NO₂ itself or by other pollutants emitted by the same sources (such as traffic). Evidence associating NO₂ with health effects has strengthened substantially in recent years and we now think that, on the balance of probability, NO₂ itself is responsible for some of the health impact found to be associated with it in epidemiological studies.

Background

2. NO₂ has been associated with adverse effects on hospital admissions for various diagnoses, decrements in measures of lung function and lung function growth, increases in respiratory symptoms, asthma prevalence and incidence, cancer incidence, adverse birth outcomes and mortality (US EPA, 2013; WHO, 2013). However, it has not been clear whether the effects are caused by NO₂ itself, or by some other pollutant(s) with which it is correlated in ambient air.

3. The UK is currently subject to legal proceedings for failing to meet European Limit Values for NO₂.¹ This is due in part to the failure of Euro standards² to deliver the expected benefits in terms of reductions in emissions of oxides of nitrogen (NO_x) from diesel vehicles, and the increase in the proportion emitted as primary NO₂. The health effects associated with NO₂ are therefore very policy-relevant.

4. COMEAP last reviewed evidence on the health effects associated with NO₂ in its 2009 *Statement on the quantification of the effects of long-term exposure to NO₂ on respiratory morbidity in children* (COMEAP, 2009). Members agreed that whilst, on the basis of epidemiological evidence, a direct effect of NO₂ on respiratory morbidity in children could not be clearly identified (because the possible adverse effects of NO₂ could not be disentangled from those of the other pollutants in the

¹In February 2014, the European Commission started legal proceedings against the UK because the UK Supreme Court made a declaration that the UK was in breach of its obligations to comply with the Limit Values for NO₂ in the Air Quality Directive. http://europa.eu/rapid/press-release_IP-14-154_en.htm

² European emission standards for vehicles <http://ec.europa.eu/environment/air/transport/road.htm>

urban mixture), a small independent effect could not be ruled out. Overall, Members concluded that it was not possible to quantify the direct effects of NO₂ on respiratory morbidity in children.

5. Two authoritative reviews on the health effects from exposure to NO₂ have been published since COMEAP's statement in 2009: the US Environmental Protection Agency's (US EPA) updated Integrated Science Assessment (first and second external review drafts; US EPA, 2013, 2015), and the World Health Organization's (WHO) Review of Evidence on Health Aspects of Air Pollution-REVIHAAP (WHO, 2013). Therefore, we agreed it was timely to re-assess the evidence associating health effects with short- and long-term exposures to NO₂³.

The approach adopted by COMEAP

6. The evidence for all-cause, respiratory and cardiovascular morbidity and mortality for both short- and long-term exposure to NO₂ was summarised in the discussion paper [COMEAP/2014/02: Considering the evidence for the effects of NO₂ on health](#). Evidence on reproductive and developmental effects and cancer was not included. The paper was based on the US EPA (2013)⁴ and WHO REVIHAAP reviews and some papers published more recently, including the results from ESCAPE, the European Study of Cohorts for Air Pollution Effects (ESCAPE, 2014) and a meta-analysis of long-term studies on NO₂ (Faustini et al, 2014).

7. We also considered the results of a systematic review and meta-analysis of time-series epidemiological studies relating to effects associated with short-term variations in concentrations of ambient air pollutants, including NO₂. These were presented to us at our meeting in June 2014. This work was funded by the Department of Health's Policy Research Programme and led by St George's, University of London. The evidence reviewed includes a number of multi-city studies as well as a number of newer results from single-city studies. The meta-analysis provides summary estimates not previously available for some outcomes (Atkinson et al, 2014, Mills et al, in press).

8. The main tasks of the WHO REVIHAAP review were to consider whether there was sufficient new evidence to justify revising the WHO Air Quality Guidelines for each pollutant, and to make recommendations for health endpoints that could be included in health impact assessments. A Member of the REVIHAAP working group on NO₂ gave a presentation to the Committee, which dealt with some of the specific issues considered for this pollutant: (1) whether effects have been observed in chamber studies at environmentally relevant concentrations, (2) the findings of

³ When we refer to studies of the effects of short- or long-term exposure to NO₂, we are referring to studies investigating associations of health effects with variations in ambient concentrations of NO₂ averaged over a short-time period (often between an hour and 24-hours, e.g. time-series studies) or long-term differences in concentrations (often annual averages, e.g. in cohort studies)

⁴ Since the COMEAP meeting in November 2014, the US EPA has published its second external review draft of this Integrated Science Assessment. This has been considered in the drafting of this statement. The Committee notes that the first and second reviews are draft versions and that the current view of the US EPA is based on its 2008 integrated science assessment. We have taken this into account when considering the evidence.

epidemiological studies using multi-pollutant models and (3) the concentrations at which effects have been observed in toxicology studies.

Summary of the evidence and Members' views

9. We discussed the information in paper [COMEAP/2014/02](#) at a meeting in June 2014, considered a draft statement in November 2014 (COMEAP/2014/06) and agreed this statement in March 2015. Points raised during the discussions can be found in the minutes of these meetings: 16 June 2014 ([COMEAP/2014/MIN2](#)) and 3 November 2014 ([COMEAP/2014/MIN3](#)). Our evaluation focused on:

- a. Whether the evidence suggests that reported associations between ambient concentrations of NO₂ and effects on health are causal
- b. Whether the reported associations between ambient concentrations of NO₂ and effects on health should be considered as distinct from, and thus additional to, those reported for regulated metrics of particulate matter (PM)
- c. The emerging evidence from the European ESCAPE studies and how this compares with earlier data from Europe and the US.

Short-term exposure to NO₂

10. We note that there is consistent evidence from short-term epidemiological studies of effects on respiratory morbidity, and this is supported by chamber-study and toxicological evidence. Robustness of the associations with short-term average concentrations of NO₂ to adjustment for particles (mainly PM₁₀, and sometimes PM_{2.5} or Black Smoke) and other pollutants has been demonstrated in studies from various geographic locations, including Europe. REVIHAAP concluded that it is reasonable to infer that short-term exposure to NO₂ has some direct effects on respiratory morbidity. The US EPA's (2015) current draft conclusion is that the evidence for respiratory effects reflects a *causal relationship*.

11. There are positive associations between short-term exposure to NO₂ and hospital admissions and emergency room visits for cardiovascular and/or cardiac diagnoses. REVIHAAP commented that findings for these outcomes are mixed after adjustment for co-pollutants and suggested the association with cardiovascular hospital admissions could be included in sensitivity analysis of assessments of health impacts. REVIHAAP did not review studies of other cardiovascular-related morbidity end-points associated with short-term exposure to NO₂. The EPA did review other cardiovascular events and its current (2015) draft conclusion is that the evidence *is suggestive but not sufficient to infer a causal relationship* with cardiovascular effects.

12. Positive and statistically significant associations of short-term ambient concentrations of NO₂ with all-cause and cause-specific mortality have been reported. These associations with mortality are not confounded by PM₁₀. In some studies, the associations also remained significant after adjustment for PM_{2.5} and Black Smoke. REVIHAAP concluded that, because of the limited number of studies which assessed confounding by ultrafine particles, firm conclusions could not be

drawn about whether associations with NO₂ may reflect an effect of ultrafine particles. NO₂ could also act as a marker for other traffic-related pollutants such as volatile organic compounds, aldehydes and organic compounds bound to primary particles. The EPA's (2015) draft conclusion is that the evidence is *suggestive but not sufficient to infer a causal relationship* between short-term exposure to NO₂ and all-cause mortality.

13. The systematic review and meta-analysis of time-series studies funded by the Department of Health (Atkinson et al, 2014, Mills et al, in press) found considerable geographical heterogeneity between summary estimates of mortality and hospital admissions associated with ambient NO₂ concentrations. Nonetheless, the global summary estimates consistently indicate associations of NO₂ with mortality and hospital admissions for a range of respiratory and cardiovascular endpoints, and we consider that this work further contributes to the evidence suggesting that NO₂ is associated with adverse health effects.

14. There is evidence of an effect on mortality which is independent of the effects of PM mass but we note that, in the vast majority of studies, the main source of NO₂ is road traffic. NO₂ in these studies may also represent other constituents of the air pollution mixture not represented by currently regulated PM metrics, such as ultrafine particles. However, we note that the RAPTES⁵ project, in which volunteers undertook exercise in a range of locations, included a very comprehensive characterisation of pollutants including ultrafine particles. It found strong associations, robust to adjustment for PM metrics, of short-term exposure to NO₂ with both respiratory effects (reductions in lung function) and an indicator of cardiovascular risk (thrombin generation) though not with some other markers (acute vascular inflammation and coagulation) (Strak et al, 2012, Strak et al 2013a, Strak et al, 2013b). Overall in this study, the largest number of positive associations was with NO₂, rather than particle metrics, and NO₂ appeared unlikely to be a surrogate for ultrafine particulate matter (Harrison, 2014). In addition, effects of NO₂ may be under-estimated in epidemiological studies unless analyses include adjustment for ozone, due to its often negative correlation with ozone, as highlighted by Williams et al (2014).

Long-term exposures to NO₂

15. Studies of long-term exposure to NO₂ report associations with all-cause, respiratory and cardiovascular mortality, children's respiratory symptoms and lung function. There are still uncertainties about causality, due to strong correlations with other pollutants meaning that NO₂ may be an indicator for other pollutants. However, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence for associations of short-term exposure with morbidity and mortality led REVIHAAP to conclude that these associations with long-term exposures to NO₂ are *suggestive of a causal relationship*. The US EPA's (2015) current draft conclusion is that there is *likely to be a causal relationship* for long-term exposure and respiratory effects but that the evidence for cardiovascular effects and total mortality is only *suggestive but not sufficient to infer a causal relationship*.

⁵ RAPTES: Risk of Airborne Particulate matter: a Toxicological and Epidemiological hybrid Study

16. The European ESCAPE studies have reported statistically significant associations between long-term exposure to NO₂ and lung function in children, respiratory infections in early childhood and effects on adult lung function. For mortality, lung cancer, and cardiovascular and cerebrovascular effects in adults, reported associations are predominately with PM mass and not with NO₂ (studies cited in COMEAP/2014/06 Annex B). However, it is not clear to what extent the approach used in this study to assess exposure to pollutants may have reduced its ability to detect associations.

17. Similar pooled effect estimates for total/natural mortality per 10 µg/m³ PM_{2.5} and NO₂ were found in the meta-analysis by Faustini et al (2014). However, because of the greater range of NO₂ concentrations (e.g. the median interquartile range (IQR) was 14.1 µg/m³ for NO₂ and 5.4 µg/m³ for PM_{2.5} across the natural/total mortality studies) greater effects of NO₂ (6%) than of PM_{2.5} (3%) were found on total mortality when the results were expressed using IQR as the exposure metric. The authors concluded that the magnitude of the effect of long-term exposure to NO₂ on mortality is at least as important as that of PM_{2.5}.

Conclusions

18. From our consideration of authoritative reviews and additional evidence we have reached the following conclusions:

- i. Evidence of associations of ambient concentrations of NO₂ with a range of effects on health has strengthened in recent years. These associations have been shown to be robust to adjustment for other pollutants including some particle metrics.
- ii. Although it is possible that, to some extent, NO₂ acts as a marker of the effects of other traffic-related pollutants, the epidemiological and mechanistic evidence now suggests that it would be sensible to regard NO₂ as causing some of the health impact found to be associated with it in epidemiological studies.

19. We have not drawn conclusions on specific health outcomes nor looked in detail at the methodological issues relevant to quantification of effects associated with ambient NO₂ at this stage. We intend to do this and, if appropriate, to consider recommendations for coefficients associating NO₂ with specific health effects, as part of separate work items to be addressed later.

Recommendations for research

20. A Department of Health-funded workshop in 2011 to identify needs for research on the health effects of NO₂ (HPA, 2011) and the WHO REVIHAAP project (WHO, 2013) made recommendations to address data gaps in relation to the health effects of NO₂. We agree that the studies recommended, and other research, would be valuable, in particular the following:

Studies to investigate whether the health effects associated with ambient concentrations of NO₂ are explained by associations with other pollutants, particularly currently regulated particle metrics

- i. Understanding the reasons for the observed heterogeneity in coefficients associating NO₂ with adverse health effects remains important. We suggest examining whether there has been a change, over time, in coefficients representing associations of health effects with NO₂ concentrations. This is of interest given the changing ratio between NO₂ and particulate matter. In particular, the marked reduction in ultrafine particulate matter (particle number concentration) as a result of the introduction of low sulphur fuel, whilst NO₂ concentrations have remained similar (Jones et al, 2012), provides an opportunity to disentangle the effects of NO₂ and ultrafine particles.
- ii. The study by McConnell et al (2003; discussed in COMEAP/2014/02) is an important paper on increased respiratory symptoms associated with long-term exposure to NO₂. The authors reported significant associations with bronchitic symptoms in asthmatic children. It would be valuable to replicate this study elsewhere and provide more information on associations of NO₂ with these effects in two-pollutant models.
- iii. New epidemiological studies using two- or multi-pollutant models to examine health effects associated with between-community and within-community⁶ variations in NO₂ concentrations, as used by McConnell et al (2003), would be valuable. This approach reduces correlations between NO₂ and PM metrics.

Studies to help investigate whether the reported associations of health effects with ambient concentrations of NO₂ are likely to be causal

- iv. Chamber studies to compare the effects of different constituents of traffic-related pollution.
- v. Toxicological studies comparing the potency of ultrafine particles, other pollutants and NO₂ in the same experimental system to allow appropriate comparisons to be drawn.
- vi. Studies on the effects of combinations of pollutants (e.g. adding or removing NO₂ to/from filtered and unfiltered diesel exhaust exposures).

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⁶ Between-community refers to comparisons across communities in relation to spatial variations in NO₂; here within-community refers to year to year variations in NO₂ concentrations within the different communities, a spatio-temporal measure.

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Glossary of Terms and Abbreviations

Ambient air	Outdoor air
Association	A statistical relationship between two measured quantities. In the context of this statement, an association is a statistical relationship between measured concentrations of an air pollutant and a health endpoint.
Black Smoke	A metric used to measure carbonaceous (“sooty”) particles. Black Smoke measurements have largely been superseded by metrics such as Black Carbon or Elemental Carbon.
Chamber studies	Controlled exposure studies in which human volunteers are exposed to air pollutants within an experimental chamber.
Confounding	In this context: robustness to adjustment for confounding means that an effect of NO ₂ remains after adjustment for the effect of particles, demonstrating that the reported relationship between NO ₂ and the health outcome under study cannot be attributed to the particle metric used. (More generally, confounding: interference by a third variable so as to distort the association being studied between two other variables, because of a strong relationship with both of the other variables.)
Epidemiological studies	Studies of the causes of diseases in populations.
ESCAPE	European Study of Cohorts for Air Pollution Effects
Incidence	The number of new cases of a disease in a population in a given time period.
Interquartile Range, IQR	A measure of the spread/dispersion of values. The IQR is the difference between the upper and lower quartiles of the range of values (i.e. the 75 th – the 25 th percentile).

Meta-analysis	A statistical technique used to combine the results of individual studies.
Multi-pollutant models	Statistical approaches used in epidemiological studies of ambient air pollution to differentiate the health effects of multiple pollutants.
NO ₂	Nitrogen dioxide. A gas that can be inhaled into the lungs.
NO _x , oxides of nitrogen	Nitrogen dioxide (NO ₂) and nitric oxide (NO)
PM _{2.5}	PM _{2.5} is defined as the mass per cubic metre of airborne particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of 2.5 µm. In practice, PM _{2.5} represents the mass concentration of all particles of generally less than 2.5 µm aerodynamic diameter. Often referred to as fine particles. This fraction can penetrate deep into the lungs.
PM ₁₀	PM ₁₀ is the mass concentration of particles of generally less than 10 µm aerodynamic diameter. This fraction can enter the lungs. PM ₁₀ includes PM _{2.5} .
Prevalence	The proportion of a population with a disease at a given time.
Primary NO ₂	NO ₂ emitted directly to the air. NO ₂ can also be formed in the air from nitric oxide (NO) which is also emitted in diesel engine exhaust.
Primary particles	Particles emitted directly to the air.
RAPTES	Risk of Airborne Particulate matter: a Toxicological and Epidemiological hybrid Study
REVIHAAP	Review of Evidence on Health Aspects of Air Pollution
Ultrafine particles	Nanosized particles, ≤ 100 nanometres (≤ 0.1 µm) in diameter. Ultrafine particles are usually measured as particle number concentration, because they contribute little to particle mass.
US EPA	United States Environmental Protection Agency
WHO	World Health Organization