COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

INTERIM STATEMENT ON QUANTIFYING THE ASSOCIATION OF LONG-TERM AVERAGE CONCENTRATIONS OF NITROGEN DIOXIDE AND MORTALITY

Summary

1. COMEAP's statement on the health effects of nitrogen dioxide (NO_2) concluded that evidence associating NO_2 with health effects has strengthened substantially in recent years (COMEAP, 2015a). This increase in evidence has led to interest in estimating the mortality effects associated with long-term average concentrations of NO_2.

2. We are currently considering how to quantify this association. We have provided interim recommendations to the Department for Environment, Food and Rural Affairs (Defra), and are now exploring approaches to refining our advice. This statement explains how our thinking is developing.

3. We are carrying out a systematic review and meta-analysis of epidemiological studies of long-term average concentrations of NO_2 and all-cause mortality to derive a new single-pollutant model summary estimate for all-cause mortality. So far this is similar to the single-pollutant model summary estimate recommended in our letter to Defra of 24 July 2015 (Appendix 1), although there remain further studies to check and incorporate. We are also making a detailed appraisal of the results of the small number of two- and three-pollutant models that include NO_2.

4. Further analysis to date has suggested that within the limited number of individual epidemiological studies that examine the effects of long-term exposure to both NO_2 and $PM_{2.5}$, the combined effect of NO_2 and $PM_{2.5}$ estimated using coefficients where each is adjusted for the effects of the other, is either similar to or only a little higher than what would be estimated for either $PM_{2.5}$ or NO_2 alone, using unadjusted single-pollutant coefficients. This suggests that using a single-pollutant coefficient for NO_2 and a single-pollutant coefficient for $PM_{2.5}$, and adding the results, would give an overestimate of the combined effects of the two pollutants.

5. We are considering a number of scientific and methodological challenges in interpreting the extent of the independence of the associations of mortality with concentrations of NO_2 and $PM_{2.5}$. In addition, before producing final recommendations, further work is required on the influence of the spatial scale of modelled NO_2

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concentrations and on a concentration cut-off for quantification. We have not yet completed our work on investigating and summarising the uncertainty around these and other issues. We intend to publish a report in the first half of 2016, once this additional work has been done.

6. In the meantime, we suggest use of the recommendations the working group made in July 2015, for cost-benefit analysis, with additional comment on the evidence in this statement that there is likely to be substantial overlap between NO_2 and $PM_{2.5}$ when single-pollutant models are used in the same analysis.

Background

7. In March 2015, we, the Committee on the Medical Effects of Air Pollutants (COMEAP), published a statement concluding that:

> "Evidence of associations of ambient concentrations of NO_2 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. Although it is possible that, to some extent, NO_2 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 NO_2 as causing some of the health impact found to be associated with it in epidemiological studies."

8. At that time, we neither drew conclusions on specific health outcomes nor looked in detail at the methodological issues relevant to quantifying effects associated with ambient NO_2, but we noted our intention to address these at a later date.

9. At the COMEAP Strategy Group meeting in May 2015, the COMEAP Chair and Assessors from government departments identified estimates of mortality associated with long-term average concentrations of NO_2 as being the highest priority for the Committee's consideration. Feedback from Public Health England's Air Pollution and Public Health Advisory Group and other stakeholders also identified this as a priority.

10. Furthermore, Defra has been quantifying the potential benefits of policy options to reduce NO_2 concentrations as part of its air quality plans for the achievement of EU air quality limit values for NO_2 in the UK. In view of this, the Committee was asked to fast-track its work on quantifying the association between long-term average concentrations of NO_2 and mortality and so, in June 2015, a COMEAP working group was set up.

11. On 24 July 2015, COMEAP's working group provided Defra with interim recommendations for quantifying the association between long-term average concentrations of NO_2 and mortality to assist Defra's initial cost-benefit analyses of measures (policies) to reduce NO_2 (see Appendix 1). The working group's discussions

regarding this are available on the COMEAP website (COMEAP, 2015b). It was explained that these interim recommendations would be subject to change following further analysis by the working group and consultation with the whole committee.

12. Since then, we have been carrying out a systematic review and meta-analysis of epidemiological studies of long-term average concentrations of NO_2 and all-cause mortality. In interpreting these, there have been a number of scientific and methodological challenges to consider. For example, consideration of the extent of the independence of the associations of mortality with NO_2 and $PM_{2.5}$ to inform thinking about whether and how mortality estimates calculated on the basis of NO_2 and $PM_{2.5}$ concentrations should be combined.

13. We have not yet completed our work on investigating and summarising the uncertainty around these issues. Nonetheless, given the current interest in this issue, we felt it important to provide information, in the form of this interim statement, on how the Committee's views are developing. We intend to publish a report in 2016, once the ongoing additional work has been completed. The report will provide a more detailed discussion of the evidence considered in coming to the Committee's views and the results of further analyses.

Committee discussions

14. Associations of mortality with long-term average concentrations of NO_2 have been reported in cohort studies. However, the extent to which these associations reflect an effect that is additional to the mortality effect found to be associated with $PM_{2.5}$ is not clear; this is part of our ongoing considerations.

15. In addition, there is uncertainty in the extent to which the association between long-term average concentrations of NO_2 and mortality is causal. It is likely that some of the reported effect is due to NO_2, but other, less studied, particulate metrics such as particle number concentration or other co-varying pollutants could also be responsible to some extent. Therefore, the uncertainty in applying a coefficient to assess the health benefit of measures (policies) to reducing NO_2 will depend on the extent to which the measure is specific to reducing NO_2, versus also reducing other co-varying pollutants.

16. In July 2015, the working group made an interim recommendation to Defra that a coefficient of 1.025 (95% confidence interval 1.01–1.04) per 10 $\mu g/m^3$ NO_2 could be used to reflect associations between long-term average concentrations of NO_2 and all-cause mortality. This coefficient took into account two published meta-analyses of studies of associations with NO_2 and mortality (Hoek et al, 2013; Faustini et al, 2014), and more recently published studies. At that time it was noted that it would be important for the Committee to run its own meta-analysis to incorporate all recently published studies.

17. A systematic review, carried out by St George's, University of London, to inform the Committee's considerations, has so far identified 30 publications, which reported results for all-cause mortality and NO_2. After excluding studies of cohorts with pre-existing disease, cohorts defined by occupational and other lifestyle factors or reporting associations for oxides of nitrogen, nine separate cohorts, including the summary estimate from the European Study of Cohorts for Air Pollution Effects (ESCAPE) study (meta-analysis of 22 individual cohorts), provided single-pollutant hazard ratios (HR) for the association between NO_2 and all-cause mortality. There was substantial heterogeneity between effect estimates. The magnitude of the summary HRs was broadly insensitive to the selection of studies. Successive exclusion of studies in selective age subgroups and non-European studies gave meta-analytical HRs in the range 1.02–1.027 per 10 $\mu g/m^3$ increase in NO_2 concentrations.

18. So far four European studies in adults (~30+ years old) have been selected for meta-analysis. These include three large cohorts (Carey et al, 2013; Cesaroni et al, 2013; Fischer et al, 2015) and the meta-analytical estimate from the 22 cohorts in ESCAPE (Beelen et al, 2014). All of the cohorts are from the general adult population.

19. We note that this is a small amount of evidence from which it is difficult to draw firm conclusions. So far the analysis has been dominated by one study that is particularly large, ie Fischer et al (2015) and two of the studies did not include individual confounding factors in the analysis, eg smoking.

20. Calculations should focus on the benefits likely to be delivered by changes in concentrations of NO_2. However, there is likely to be more uncertainty when the measure is specific for a reduction in NO_2, compared to when an intervention aims to reduce the whole mixture of air pollutants by controlling combustion sources. We wish to consider further the uncertainties associated with such calculations in our report.

Independence from particulate matter

21. When the recommended coefficient for long-term average concentrations of NO_2 and all-cause mortality is included in an assessment that also includes assessment of health impacts on the basis of $PM_{2.5}$ or PM_{10}, a percentage reduction needs to be applied to the coefficient to avoid double-counting and overestimation of the combined mortality effect of NO_2 and PM. In July 2015, it was recommended that when included in an assessment that also includes assessment of health impacts on the basis of $PM_{2.5}$, the NO_2 coefficient should be reduced by up to 33% to take account of double-counting of effects associated with PM. This was suggested by the World Health Organization's health risks of air pollution in Europe – HRAPIE – project (WHO, 2013).

22. A literature search identified six studies reporting two-pollutant model results for NO_2 and PM, four from Europe and two from the US [both analyses from the American Cancer Society (ACS) Cancer Prevention Study II cohort (Krewski et al, 2000; Jerrett et al, 2013)].

23. In the four European studies, adjusting the NO_2 HRs for PM and vice versa resulted in a wide range by which the HRs were reduced. The unadjusted HR for NO_2 was reduced by between 10% (Cesaroni et al, 2013) and 95% (Carey et al, 2013) after inclusion of PM in the model. Similarly, the unadjusted PM HRs reduced by between 0% (Carey et al, 2013) and 83% (Cesaroni et al, 2013) upon adjustment for NO_2 (see Appendix 2).

24. Comparison of HRs expressed on the basis of interquartile range (see Table 1 in Appendix 2) suggests that the combined effect of NO_2 and $PM_{2.5}$ using adjusted HRs is either similar to or only a little higher than that estimated for either $PM_{2.5}$ or NO_2 alone, using unadjusted single-pollutant coefficients. This finding strongly suggests that it is incorrect to estimate separately an effect associated with NO_2 and an effect associated with $PM_{2.5}$, using coefficients from single-pollutant models, and add the results, because the overall total will give an overestimate.

25. Furthermore, high correlations between NO_2 and PM are reported in the two-pollutant models, especially in the Carey et al (2013) and Cesaroni et al (2013) studies. Correlation between the two pollutants ranged from –0.08 to 0.85 (0.2 to 0.85 in the European studies) as shown in Appendix 2, Table 1. This means that there is additional uncertainty and instability making it difficult to draw firm conclusions about the possible overestimation of effect or to ascribe effects of the overall mixture to one pollutant or the other.

26. Because the epidemiological evidence base is limited, and correlation between the pollutants is high, it is also difficult to draw conclusions on the relative importance of the two pollutants and the overall size of their joint effect, other than that the joint effect is not smaller than we have estimated previously attributed to $PM_{2.5}$ alone.

27. We have been discussing possible methods for refining the approach to accounting for overestimation of the reported associations with NO_2, and intend to develop our thinking on this in our report. It is not straightforward to meta-analyse the two-pollutant model results in Appendix 2, Table 1, without knowledge of the covariance between the multi-pollutant estimates within each study and differences in measurement error. We are working on this but are reliant on receiving information from the original study authors.

28. There is also possible overestimation of mortality effects calculated on the basis of single-pollutant model estimates of associations with $PM_{2.5.}$ Further work is needed before we can comment on what the additional overestimate for PM is likely to be. This includes consideration of whether using the coefficients from the two-pollutant models identified above would be a representative subset of the larger body of evidence on PM. We intend to review our 2009 recommendation for long-term exposure to $PM_{2.5}$ and all-cause mortality of 1.06 (95% confidence interval 1.02–1.11) per 10 $\mu g/m^3$ $PM_{2.5}$ at a later date (COMEAP, 2009).

Spatial scale

29. The Committee acknowledges that concentrations of NO_2 vary more over small spatial scales than is the case for $PM_{2.5}$. Because it is likely that higher concentrations occur near sources, eg roads that are also associated with more densely populated urban areas, modelling at a 1 km x 1 km scale may average concentrations over a wider area, changing some of the underlying assumed exposure characteristics.

30. A preliminary analysis in London has suggested that when 20 m x 20 m modelling of NO_2 concentrations in 2010 is averaged to 1 km grid squares or to output areas (generally much smaller), and weighted by the population aged 30+ years at 1 km grid square or output area level, the overall population-weighted mean for London is similar for the two methods. However, the underlying distributions are very different, with grid squares dominated by relatively low populations and lower concentrations in outer London, with a long tail to higher populations and higher concentrations in inner London. Output areas showed more fine scale variation within inner and outer London.

31. For our report, we intend to undertake work to explore this, by comparing annual mean population-weighted NO_2 concentrations estimated at a spatial resolution of 20 m x 20 m averaged up to 1 km grid squares across London, with modelling done only at 1 km grid square level. It may also be possible to compare preliminary 20 m x 20 m national modelling with 1 km grid square modelling. Consideration will also be given to the spatial scale of age group distributions and mortality data, and if sufficient variation is demonstrated, variation in coefficients in individual epidemiological studies by spatial scale.

Concentration cut-off for quantification

32. In July 2015, the working group recommended that no cut-off should be used for quantification for the main analysis, as there is an absence of evidence for a threshold for effect at the population level. For a sensitivity analysis it was recommended that a cut-off of the lowest concentration reported in the epidemiological studies used to derive the coefficient could be used. However, when discussing this at a Committee meeting, others thought it preferable to stay within the range of data in the epidemiological studies rather than extrapolate to zero. The reason being that, since there is an absence of evidence as to the nature of the exposure response below the range of data in the various studies, any extrapolation to zero is based on an untested assumption rather than empirical evidence and thus subject to additional uncertainty.

33. The lowest concentration reported in the studies included in our meta-analysis to derive the coefficient for long-term average concentrations of NO_2 and all-cause mortality was 1.5 $\mu g/m^3$. This concentration was reported for a Swedish cohort, in the ESCAPE study (Beelen et al, 2014). An alternative suggestion was to use a similar approach to that followed in the Global Burden of Disease project for $PM_{2.5}$ in which

the 5th percentile from the largest cohort study was used to derive the coefficient, with the minimum value and 5th percentile as the confidence intervals (Lim et al, 2012). In our meta-analysis, the largest study was Fischer et al (2015) (with over 7 million subjects), which had a minimum concentration of 11 μg/m^3 and the 5th percentile was 19 μg/m^3. These, and other, options require further discussion by the Committee.

34. Members held divergent views on the appropriateness of extrapolating beyond the studied range of concentrations. We agreed that calculations based on both no (zero) cut-off and restricting calculations to concentrations in the studied range, should be undertaken when quantifying effects of mortality from long-term average concentrations of NO_2. Further discussion on the cut-off for use in quantification will be included in the report.

Cessation lag

35. Cessation lag denotes the time pattern of reductions in mortality hazards following a reduction in pollution. There is little direct evidence about what these time patterns are likely to be. We have not re-examined any evidence on cessation lag structure and so the recommendation remains unchanged as given in July 2015. It is the same as that used for the $PM_{2.5}$ calculations in COMEAP's 2010 report: 30% of the effect occurs in the first year after pollution reduction, 50% is distributed across years 2–5 and the remaining 20% distributed across years 6–20 (COMEAP, 2010).

Conclusions

36. We have been investigating whether it is possible to quantify the association of long-term average concentrations of NO_2 and mortality. There are a number of scientific and methodological challenges to consider, including interpreting the extent of the independence of the associations of mortality with concentrations of NO_2 and PM. Using both a single-pollutant coefficient for NO_2 and a single-pollutant coefficient for $PM_{2.5}$ is likely to give an overestimate.

37. Until we publish our full report, we suggest use of the recommendations made in July 2015, for cost-benefit analysis, with additional comment on the evidence in this statement that there is likely to be substantial overlap between NO_2 and $PM_{2.5}$ when single-pollutant models are used in the same analysis. The range in reductions in the NO_2 coefficients is wider in the newly identified studies but further work is needed on how to pool these results. We have also not yet completed our work on investigating and summarising the uncertainty around a number of other scientific and methodological issues. We intend to publish a report in the first half of 2016, once this additional work has been done.

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References

Beelen R, Raaschou-Nielsen O, Stafoggia M, et al (2014). Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383(9919):785-795.

Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG and Anderson HR (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med 187(11):1226-1233.

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M and Forastiere F (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ Health Perspect 121(3):324-331.

COMEAP (2009). Long-term exposure to air pollution: effect on mortality. Committee on the Medical Effects of Air Pollutants. Available at https://www.gov.uk/government/publications/comeap-long-term-exposure-to-air-pollution-effect-on-mortality [Accessed November 2015]

COMEAP (2010). Mortality effects of long-term exposure to particulate air pollution in the UK. Committee on the Medical Effects of Air Pollutants. Available at https://www.gov.uk/government/publications/comeap-mortality-effects-of-long-term-exposure-to-particulate-air-pollution-in-the-uk [Accessed November 2015]

COMEAP (2015a) Statement: The evidence for the effects of nitrogen dioxide on health. Committee on the Medical Effects of Air Pollutants. Available at https://www.gov.uk/government/publications/nitrogen-dioxide-health-effects-of-exposure [Accessed November 2015]

COMEAP (2015b). NOTE NO_2 working group. Working group on the quantification of mortality associated with long-term average concentrations of nitrogen dioxide (NO_2) Note of the Meeting held on Monday 6 July 2015. Available at https://www.gov.uk/government/groups/committee-on-the-medical-effects-of-air-pollutants-comeap#minutes [Accessed November 2015]

Faustini A, Rapp R and Forastiere F (2014). Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. Eur Respir J 44(3):744-753.

Fischer PH, Marra M, Ameling CB, Hoek G, Beelen R, de Hoogh K, Breugelmans O, Kruize H, Janssen NA and Houthuijs D (2015). Air pollution and mortality in seven million adults: the Dutch Environmental Longitudinal Study (DUELS). Environ Health Perspect Jul;123(7):697-704.

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B and Kaufman JD (2013). Long-term air pollution exposure and cardio-respiratory mortality: a review. Environ Health 12(1):43.

Jerrett, M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, Martin RV, van Donkelaar A, Hughes E, Shi Y, Gapstur SM, Thun MJ and Pope CA, 3rd (2013). Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med 188(5):593-599.

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Abrahamowicz M and White WH (2000). Part I: Replication and Validation. In: Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. A Special Report of the Institute's Particle Epidemiology Reanalysis Project. Health Effects Institute, Cambridge MA.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet Dec 15;380(9859):2224-2260.

WHO (2013). Health risks of air pollution in Europe – HRAPIE project. Recommendations for concentration–response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide. Copenhagen, World Health Organization.

Glossary of terms and abbreviations

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
Concentration-response coefficient	A quantitative relationship between the concentration of a pollutant and an increased risk of an effect on health (in this case, mortality)
Confidence intervals	If it is possible to define two statistics t_1 and t_2 (functions of sample values only) such that, being a parameter $$p\ (t_1 \leq \theta > t_2) = \alpha$$ where α is some fixed probability (eg 0.95 or 95%), the interval between t_1 and t_2 is called a confidence interval. The assertion that θ lies in this interval will be true, on average, in a proportion of the cases when the assertion is made
Defra	Department for Environment, Food and Rural Affairs
Epidemiological studies	Investigations of diseases conducted at a population level
ESCAPE	European Study of Cohorts for Air Pollution Effects
Meta-analysis	A statistical technique used to combine the results of individual studies
Mortality	Death
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 produced during combustion that can be inhaled into the lungs
PM	Particulate matter
$PM_{2.5}$	$PM_{2.5}$ 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 $PM_{2.5}$

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APPENDIX 1

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

COMEAP'S WORKING GROUP ON NITROGEN DIOXIDE

Previous interim recommendations for quantifying the association of long-term average concentrations of nitrogen dioxide and mortality

Interim recommendations made by COMEAP's working group were provided to Mr Rory Stewart, the parliamentary under-secretary of Defra on 24 July 2015.

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

c/o COMEAP Secretariat
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Mr Rory Stewart
Parliamentary Under Secretary
Department for Environment, Food & Rural Affairs
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24th July 2015

Dear Mr Stewart,

The Committee on the Medical Effects of Air Pollutants (COMEAP) is currently undertaking work to quantify the association between long-term average concentrations of nitrogen dioxide (NO_2) and mortality. The committee has been asked to fast-track this work and to publish its findings by the end of this year. A working group of the committee, set up to undertake this work, met on Monday 6th July.

Defra Officials requested that an interim recommendation of a coefficient, to be used in cost-benefit analyses of measures to reduce NO_2, be provided to Defra to assist with the on-going development of plans to improve air quality. Views on other aspects relevant to this quantification were also requested.

The interim recommendations made by COMEAP's working group are summarised below. It must be noted that these recommendations are subject to change following further analysis by the working group and consultation with the whole committee.

Interim Recommendations:

The working group agreed that there is uncertainty in the extent to which the association between long-term average concentrations of NO_2 and mortality is causal. It is likely that some of the effect is due to NO_2, but other co-emitted pollutants could also be responsible to some extent. Therefore, the uncertainty in applying a coefficient to assess the health benefit of measures to reducing NO_2 will depend on the extent to which the measure is specific to NO_2, or also reduces concentrations of other co-emitted pollutants. There is likely to be more uncertainty when the measure is specific for a reduction in NO_2, compared to when an intervention aims to reduce the whole mixture of air pollutants.

A coefficient of 1.025 (1.01–1.04) is recommended. However, you should note that the group intends to run a new meta-analysis to obtain an updated coefficient for use in its own calculations. When included in an assessment which also includes assessment of health impacts on the basis of $PM_{2.5}$, a reduction of this coefficient by up to 33% is proposed to take account of possible overestimation due to double counting of effects associated with PM. However, there will also be a need to consider possible overestimation of effects calculated on the basis of single-pollutant model estimates of associations with $PM_{2.5}$. The group is not in a position at this stage to say what this additional overestimate is likely to be.

We are aware that Defra will be using 1 km by 1 km modelling using 2013 data, population weighted, across the UK. Because of its availability across the whole of the UK, the working group also plans to use this modelling in its calculations. However, this approach is likely to under-estimate population exposure, so the group plans to perform a sensitivity analysis using modelling at a 20 m by 20 m scale for one city.

As there is no clear evidence for a threshold of effect at the population level, a zero cut-off for quantification is recommended for use in the main calculation. For sensitivity analysis, the working group intends to use the lowest concentration in studies in which associations were found, as a cut-off (to be determined). Similarly, zero will also be used as the main counterfactual for calculating estimates of the mortality burden and, for sensitivity analysis, the lowest concentration in studies in which associations were found will be used.

The recommended cessation lag structure is the same as that used for the $PM_{2.5}$ calculations: 30% of the effect in the first year, 50% across years 2–5 and remaining 20% across years 6–20.

We hope these interim recommendations are useful for your cost-benefit analyses of measures to reduce NO_2.

Yours sincerely

Professor Frank Kelly	Professor Roy Harrison
COMEAP Chair	COMEAP NO_2 working group Chair

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APPENDIX 2

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Hazard ratios and summary estimates for unadjusted and adjusted NO_2 and $PM_{2.5}$

Independence from particulate matter

Table 1 shows the hazard ratios (HRs) from single- and two-pollutant models including NO_2 and $PM_{2.5}$ in the cohorts reporting results for all-cause mortality. None of the cohorts assessed the independence of NO_2 from traffic-related particles (ultrafine, elemental carbon, etc). Figure 1 presents the unadjusted and adjusted HRs per interquartile range (IQR) for European cohorts as forest plots.

Table 1: Hazard ratios (HRs) from single- and two-pollutant models for NO_2 and $PM_{2.5}$ (HRs are expressed per interquartile range, IQR)

Study	Corr NO_2/$PM_{2.5}$	NO_2 IQR ($\mu g/m^3$)	NO_2	LCL	UCL	NO_2 adj $PM_{2.5}$	LCL	UCL	$PM_{2.5}$ IQR ($\mu g/m^3$)	$PM_{2.5}$	LCL	UCL	$PM_{2.5}$ adj NO_2	LCL	UCL
Cesaroni et al (2013)	0.79	10.7	1.029	1.022	1.036	1.026	1.015	1.037	5.7	1.023	1.016	1.031	1.004	0.994	1.015
Carey et al (2013)[1]	0.85	10.7	1.022	0.995	1.049	1.001	0.959	1.044	1.9	1.023	1.000	1.460	1.023	0.989	1.060
Beelen et al (2014)[2]	0.2–<0.7	10.0	1.012	0.993	1.031	1.01	0.97	1.05	5.0	1.07	1.01	1.13	1.06	0.98	1.15
Fischer et al (2015)[3]	0.58[4]	10.0	1.027	1.023	1.030	1.019	1.015	1.023	2.4	1.029	1.025	1.033	1.015	1.011	1.020
Krewski et al (2000)[5]	–0.08	43.3	0.95	0.89	1.01	0.90	0.84	0.96	24.5	1.15	1.05	1.25	1.22	1.11	1.33
Jerrett et al (2013)	0.55	7.7	1.031	1.008	1.056	1.025	0.997	1.054	5.3	1.032	1.002	1.062	1.015	0.980	1.050

Corr correlation, IQR interquartile range, LCL lower confidence interval, UCL upper confidence interval, adj adjusted for

Notes:

1 $PM_{2.5}$ results –personal communication

2 Based on 14 cohorts

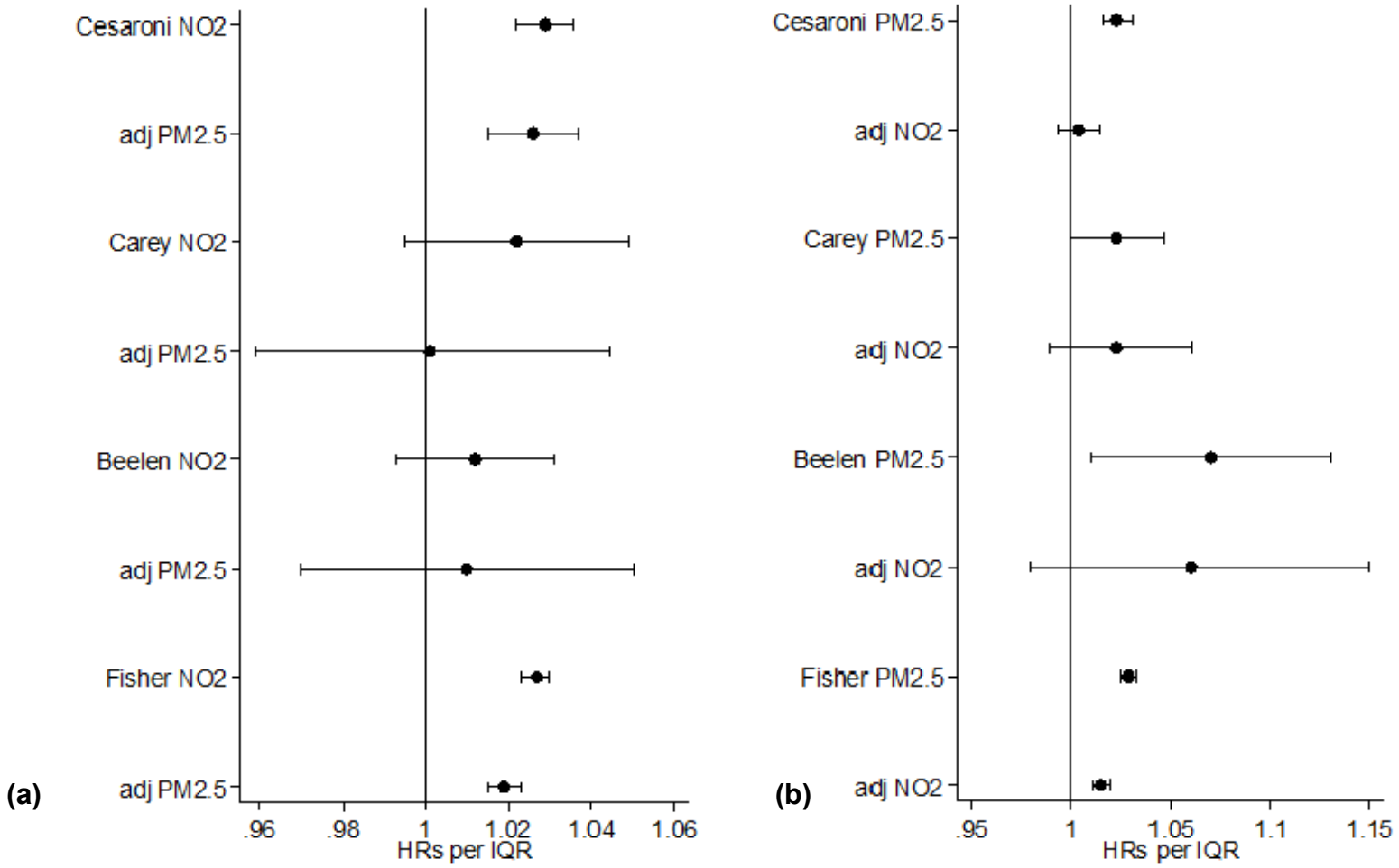
3 $PM_{2.5}$ results scaled from PM_{10} (0.66 and assuming all toxicity within $PM_{2.5}$ fraction)

4 Correlation with PM_{10}

5 HR (95% CI) for min-max range of average concentrations in fine particulate cohort (41 cities)

Additional significant figures for the HRs obtained from the authors

Figure 1: Unadjusted and adjusted hazard ratios of NO_2 (a) and $PM_{2.5}$ (b) per interquartile range, IQR, for European cohorts



Notes:

For Fischer et al (2015), the $PM_{2.5}$ results were scaled from PM_{10} (0.66 and assuming all toxicity within $PM_{2.5}$ fraction)

The scales on the y-axis are slightly different for (a) and (b) to best illustrate the results

References

Beelen R, Raaschou-Nielsen O, Stafoggia M, et al (2014). Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383(9919):785-795.

Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG and Anderson HR (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med 187(11):1226-1233.

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M and Forastiere F (2013). Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ Health Perspect 121(3):324-331.

Fischer PH, Marra M, Ameling CB, Hoek G, Beelen R, de Hoogh K, Breugelmans O, Kruize H, Janssen NA and Houthuijs D (2015). Air pollution and mortality in seven million adults: the Dutch Environmental Longitudinal Study (DUELS). Environ Health Perspect Jul;123(7):697-704.

Jerrett, M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, Martin RV, van Donkelaar A, Hughes E, Shi Y, Gapstur SM, Thun MJ and Pope CA, 3rd (2013). Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med 188(5):593-599.

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Abrahamowicz M and White WH (2000). Part I: Replication and Validation. In: Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. A Special Report of the Institute's Particle Epidemiology Reanalysis Project. Health Effects Institute, Cambridge MA.