COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Committee on Medical Effects of Air Pollutants

Statement on update of recommendations for quantifying hospital admissions associated with short-term exposures to air pollutants

Summary

1. We are updating our recommendations for quantification of hospital admissions associated with short-term exposures to air pollutants, specifically particulate matter (PM), nitrogen dioxide (NO_2) and ozone (O_3). These recommendations are intended to inform cost-benefit analyses that will be undertaken to support the development of air quality targets under the Environment Act 2021 (formerly the Environment Bill 2020). We have therefore adopted an approach to evaluating the evidence which has allowed us to make revised recommendations in a timely manner.

2. We have examined recent meta-analyses of studies evaluating the associations between (total, all-cause) respiratory and cardiovascular hospital admissions and short-term exposures to PM, NO_2 and O_3. We consider summary effects estimates (coefficients) from single pollutant models derived in meta-analyses of the global literature, undertaken by St George's, University of London with funding from the Department of Health, as the most suitable for use as concentration-response functions to quantify hospital admissions associated with short-term exposures to air pollutants. These are summarised in the table below.

3. We recommend that the 24-hour effect estimates for NO_2 are used in health impact assessments of interventions to improve air quality. However, concentration-response functions for 1-hour average concentrations of NO_2 might be appropriate for some uses and therefore have also been included in the table.

4. Concentrations of $PM_{2.5}$ and NO_2 are often highly correlated, meaning that associations reported from epidemiological studies likely reflect the effect of both pollutants to some extent. Therefore, using coefficients for both $PM_{2.5}$ and NO_2 (for the same health end-point) within the same assessment would result in an over-estimation of the effect of the air pollution mixture, or of the benefits of interventions to reduce emissions. However, on balance, we consider that the coefficients for all-year O_3 are likely to be independent of those for either $PM_{2.5}$ or NO_2, meaning that that there is less concern about possible over-estimation when using them in a combined assessment. In addition, policy-makers should be aware that localised interventions designed to reduce NO_2 may have the unintended consequence of increasing localised concentrations of O_3.

5. In this statement, we also draw attention to the uncertainties regarding causality for some pollutant-outcome pairs, notably cardiovascular hospital admissions associated with NO_2; these uncertainties will need to be considered when deciding which pollutant-outcome pairs to include in core assessments or in sensitivity analyses.

Random summary effects estimates (95% confidence intervals) for the percentage increase per 10 μg/m³ reported from meta-analyses of time-series studies

	Overall	**Reference**
$PM_{2.5}$		
Respiratory hospital admissions, all ages	24-hour: 0.96 (-0.63, 2.58)	Atkinson et al (2014) Table 3
CV hospital admissions, all ages	24-hour: 0.90 (0.26, 1.53)	Atkinson et al (2014) Table 3
NO_2		
Respiratory hospital admissions, all ages	24-hour: 0.57 (0.33, 0.82) 1 hour: 0.34 (-0.02, 0.7)	Mills et al (2015) Table S2
CV hospital admissions, all ages	24-hour: 0.66 (0.32, 1.01) 1 hour: 0.36 (-0.16, 0.89)	Mills et al (2015) Table S3
O_3		
Respiratory hospital admissions, all ages	Daily maximum 8 hour running mean 0.75% (0.30, 1.2)	Walton et al (2014)
CV hospital admissions, all ages	Daily maximum 8 hour running mean 0.11% (−0.06, 0.27)	Walton et al (2014)

Introduction

6. COMEAP last made recommendations for quantifying respiratory hospital admissions associated with short term exposure to particulate matter (PM) and nitrogen dioxide (NO_2) in 1998, and its recommendations for quantifying cardiovascular hospital admissions associated with short-term exposure to PM in 2001. In 2015, COMEAP updated its 1998 recommendations for quantifying respiratory hospital admissions associated with short-term exposure to ozone (O_3), and also made recommendations for quantifying cardiovascular hospital admissions.

7. Since COMEAP's 1998, and 2001 recommendations, in particular, a significant number of primary time series studies of hospital admissions associated with PM, NO_2 and O_3, have been published, as well as a number of meta-analyses. It is now considered timely for COMEAP to update its recommendations for quantification of hospital admissions, particularly to inform the cost-benefit analyses of interventions under consideration to support the development of air quality targets under the Environment Act 2021 (formerly the Environment Bill 2020).

Approach taken – review of the evidence

DH-funded systematic reviews by SGUL

8. The Department of Health previously supported the Committee's work programme on the health effects of short-term exposure to air pollution by funding St George's, University of London (SGUL) to undertake systematic reviews and meta-analyses of time-series studies on mortality and hospital admissions. The reviews cover studies published/indexed to May 2011 and focus on all-year, single pollutant model estimates from time-series studies on $PM_{2.5}$ (Atkinson et al, 2014); components of particles (nitrate (NO_3^-); sulphate (SO_4^{2-}); elemental carbon (EC) and organic carbon (OC); particle number concentrations (PNC), metals) (Atkinson et al, 2015); NO_2 (Mills et al, 2015); and O_3 (Walton et al, 2014)[1].

9. The reviews by SGUL provide an overview of the evidence for hazard and summary estimates calculated by meta-analysis for a range of cardiovascular and respiratory diagnoses in different age groups. An overview of evidence from different geographical regions is also provided. The reviews of associations with $PM_{2.5}$, fine particle components and NO_2 are published in the peer-reviewed literature. A systematic review and meta-analysis of the two-pollutant model evidence relating to short-term exposure to NO_2 adjusted for particles has also been published (Mills et al, 2016) but making recommendations which take into account multi-pollutant approaches and the extent of potential confounding is beyond the scope of our current considerations. The SGUL review on PM (Atkinson et al, 2014) covers associations with fine particles ($PM_{2.5}$) only. The SGUL reviews present summary effects estimates for mortality and hospital admissions for a range of specific respiratory and cardiovascular endpoints, as well as for hospital admissions for all cardiovascular and all respiratory conditions.

Other systematic reviews available and commentary

10. The quantification sub-group (QUARK), on behalf of COMEAP, undertook a systematic literature review to establish whether there were meta-analyses for all cause respiratory and all cause cardiovascular hospital admissions associated with short-term exposure to PM, NO_2 and O_3, that were more recent than the SGUL meta-analyses. In order to support QUARK's discussion of the available evidence, the Public Health England (PHE) library was asked to undertake a literature search to identify systematic reviews of epidemiological studies linking short-term exposure to air pollutants with hospital admissions. The Secretariat then conducted preliminary screening. The literature search terms used are presented in Annex A. The results of the search and screening are also illustrated within Annex A, as Figure 1.

11. The search and screening process identified a large number of systematic reviews of epidemiological studies of air pollution and hospital admissions. Some reviews focused either on individual components of PM, rather than $PM_{2.5}$, or on specific events such as wildfires or desert dust events. Many reviews were of studies of hospital admissions for specific health endpoints (such as asthma), rather than for the broader categories of cardiovascular or respiratory admissions which correspond

[1] This formed the basis of COMEAP's (2015) recommendations for O_3

to COMEAP's current recommendations. Others were exclusively of studies in specific geographical regions other than Europe. While these contribute valuable information – for example regarding causality – they were not considered to provide a suitable basis for updating COMEAP's current recommendations for quantification. Therefore, QUARK Members focused on the available systematic reviews of studies of PM_{10}, $PM_{2.5}$, NO_2 and O_3 and the overall categories of cardiovascular and respiratory hospital admissions, which drew on either the global literature or focused on studies in Europe.

12. Of the remaining seven reviews, three were SGUL DH-funded systematic reviews (Atkinson 2014, Mills 2015, Mills 2016)[2]. The other four systematic reviews, and QUARK's views on their suitability as a basis for updating our recommendations, are summarised below.

13. Ji et al (2011) studied the association between short term ambient O_3 exposure and respiratory hospital admissions. This review was limited to studies in English from 1990 to 2008, converted studies to a 24-hour metric or an 8-hour metric, separated general and emergency admissions and did not combine single-city and multi-city study results. The Ji et al (2011) results for all respiratory admissions all ages per 10 ppb ozone (roughly twice a 10 μg/m^3 increment) was a 1.45% increase (95% CI: −0.04%, 2.95%) (general admissions) or a 1.24% increase (95% CI: 0.48%, 1.99%) (emergency admissions) for studies converted to an 8-hour average metric and a 2.03% increase (95% CI: −0.21%, 4.31%) (general admissions) or a 1.9% increase (95% CI 0.74%, 3.07%) (emergency admissions) for the same studies converted to a 24-hour average metric. This compares with the SGUL results of 0.75% (95% CI: 0.30%, 1.20%) and 0.69% (95% CI: 0.17%, 1.21%) per 10 μg/m^3 ozone for 8-hour average and 24-hour average ozone respectively. The estimates are similar to those found by SGUL, taking into account the different scales, but the SGUL results had 95% confidence intervals above zero. This was probably due to the additional statistical power provided by the inclusion of multi-city study results. It was decided that, although the Ji et al (2011) review provides corroborative evidence, it does not supersede the SGUL systematic review and meta-analysis which included studies in all languages, all dates up to indexing in May 2011, used the original study averaging times, and combined single and multi-city study results and general and emergency admissions.

14. Requia et al (2018) conducted a systematic review and meta-analysis of studies on air pollutants, including NO_2, O_3 and PM, and cardiorespiratory diseases (hospital admissions and mortality) of studies published between 2006 and 11 May 2016. The QUARK members who reviewed the paper considered that it did not provide a suitable basis for updating COMEAP's recommendations: it used novel meta-regression methods, and it appeared that the effects of short-term exposure (time-series and case-crossover studies) had been combined with the effects of

[2] Walton et al 2014 was not identified by the search because, while peer-reviewed, it is not published in a format that allows it to be indexed by databases such as PubMed. Mills et al (2016) includes only studies which report results from both single-pollutant and two-pollutant models (adjusting for PM). It therefore does not include all the single-pollutant estimates reviewed in Mills et al (2015).

long-term exposure (from cohort studies) within the pooled estimates presented within the paper.

15. Bell et al (2014) conducted a systematic review of the epidemiological evidence (1988 to 2013) regarding the factors that might make individuals more susceptible to mortality or hospital admissions following short-term O_3 exposure, and performed a meta-analysis. QUARK considered that this study was good quality in terms of approach, and noted that it includes primary studies up to June 2013 (slightly beyond the DH-funded systematic reviews). However, it was not considered a suitable basis for updating our recommendations for quantification because it was designed for a different purpose (examining evidence for effect modification). This meant that the authors only included papers that examined potential effect modifiers and not more general papers that studied associations between ozone and mortality or hospital admissions/emergency room visits. Hence, it is not a systematic identification of all papers relevant to a coefficient for hospital admissions. In addition, the meta-analyses combine studies of hospital admissions and emergency room visits. This means that, while the results can be used to draw qualitative conclusions about the importance of individual variables, they cannot be used quantitatively in impact assessments, as it is not clear what baseline rate would be appropriate to use.

16. Ab-Manan et al (2018) reviewed primary studies conducted between 2010 and 2016 looking at the relationship between hospital admission and air pollutants, including $PM_{2.5}$, PM_{10}, NO_2 and O_3. QUARK did not consider this study a suitable basis for updating COMEAP's recommendations because the search strategy and combination of terms used was not sufficiently comprehensive and because the study did not derive pooled estimates.

17. As a result of this review, we accepted QUARK's recommendation that the coefficients derived within the SGUL meta-analyses from single pollutant models were the most appropriate to recommend for quantification of hospital admissions associated with short-term exposure to NO_2 (Mills et al, 2015) and PM (Atkinson et al, 2014), and that the current recommendations for CRFs for O_3, which are already derived from the SGUL study (Walton et al, 2014), should remain the same. It is noted that the Atkinson et al 2014 review presents coefficients for $PM_{2.5}$, whereas our previously recommended coefficients for PM were for PM_{10}.[3]

Discussion

Global or regional effects estimates

18. The SGUL reviews present summary estimates of all studies (regardless of where they have been conducted) and also summary estimates by WHO region. For some pollutant-outcome pairs the reviews found considerable heterogeneity between regions (for example, respiratory hospital admissions associated with $PM_{2.5}$ concentrations, I^2=80%).

[3] COMEAP (2020) has noted that recommendations for quantification of effects using associations reported with a metric of particulate matter ($PM_{2.5}$ or PM_{10}) are usually regarded as indicating effects of particulate matter pollution more generally. Therefore, coefficients for the same health effect associated with $PM_{2.5}$ and PM_{10} should not be used together in the same assessment.

19. Nonetheless, we recommend that the coefficients drawn from the full global evidence base, rather than solely from European studies, should be used for quantification of hospital admissions associated with short-term exposure to PM and NO_2. This is consistent with the approach taken to the selection of the O_3 coefficients recommended by COMEAP in its 2015 report, taken from the review by Walton et al (2014). Global estimates draw on a larger evidence base than Europe-only estimates. In addition, the observed heterogeneity between regions may reflect methodological, and other, differences between studies, rather than necessarily differences between locations/regions.

Uncertainty regarding causality

20. In making its 1998 and 2001 recommendations, COMEAP acknowledged the likelihood that PM is causally related to the respiratory and cardiovascular effects associated with it in epidemiological studies. It has therefore been considered appropriate to include respiratory and cardiovascular hospital admissions associated with short-term exposure to PM in core analyses (such as burden estimates or health impact analyses)[4]. Nonetheless, the comparison of effects estimates from single- and two-pollutant models demonstrated considerable attenuation on adjustment for effects associated with NO_2 (Mills et al, 2016).

21. Due to the doubts about the causal role of NO_2, COMEAP's 1998 recommendation for a coefficient linking NO_2 with respiratory hospital admissions was intended for use in sensitivity analyses. We considered the increase in the strength of the evidence for causality since the previous COMEAP recommendations, including the REVIHAAP review (WHO, 2013a), the HRAPIE project (WHO, 2013b), the SGUL review itself (Mills et al, 2015), the SGUL adjustment for PM mass in two-pollutant models (Mills et al, 2016), and current USEPA Integrated Science Assessments (ISAs: USEPA 2016; 2019). We noted that the evidence suggesting a causal role for NO_2 in both respiratory and cardiovascular effects has strengthened in recent years. It is, however, stronger for respiratory effects than for cardiovascular effects, for which there remains a higher level of uncertainty. In addition, the evidence available for plausible biological mechanisms for cardiovascular effects is greater for PM than for NO_2 (COMEAP 2018).

Independence of epidemiological associations

22. Concentrations of pollutants are often correlated spatially and temporally, and this is particularly true of PM and NO_2. This results in uncertainty in attribution of causality of effects estimates, reported in epidemiological studies, to individual pollutants within the air pollution mixture. We have been asked to update COMEAP's previous recommendations for coefficients from single-pollutant models, in which there has been no adjustment for effects associated with correlated pollutants. This means that recommended coefficients will, to some extent, likely include effects caused by other correlated pollutants. Therefore, if effects on hospital admissions estimated using the recommendations for coefficients from single pollutant models

[4] Quantification of mortality associated with short-term exposure to PM is only included if the assessment does not also include quantification of mortality associated with long-term exposure to PM.

for PM and NO_2 are added to each other, this would give an over-estimate of the effects of the pollution mixture (or of the reduction in the pollution mixture) as a whole.

23. Concentrations of O_3 reflect a complex atmospheric chemistry. O_3 is formed by photochemical reactions between chemical precursors in the atmosphere. The concentration of O_3 is determined by the balance between these formation reactions and other physical and chemical processes that disperse O_3 or remove it from the atmosphere. As noted in COMEAP (2015), correlations between O_3 and other pollutants can vary in both size and direction according to the concentration of O_3, which varies spatially and temporally. Correlations may vary with season and/or temperature; these effects may be independent of each other and depend upon the climate of the location.

24. Correlations between concentrations of O_3 and NO_2 are also complex, as oxides of nitrogen (NO_x) are involved in both the formation and destruction of O_3; which of these processes dominates depends upon the concentration of NO_x. In the UK, O_3 is often negatively correlated with $PM_{2.5}$ at lower O_3 concentrations but positively correlated with $PM_{2.5}$ at higher O_3 concentrations; this pattern is more marked for $PM_{2.5}$ than for PM_{10} because of the secondary inorganic aerosol (SIA) component of $PM_{2.5}$.

25. The varying correlations of O_3 with other pollutants make it difficult to interpret associations of health effects with O_3 reported from single-pollutant models: there may be under-estimation or over-estimation depending on the specific study and its location. The global summary effects estimates for O_3 from the SGUL meta-analyses include studies conducted throughout the whole year and in a variety of climates. Therefore, they are likely to include periods of both positive and negative correlations between ozone and co-pollutants, and hence it does not seem likely that they are greatly affected by confounding due to correlated PM or NO_2 concentrations. Therefore, despite the uncertainty, we consider that the commonly used approach – of regarding associations of health effects with short-term variations in O_3 as independent of those with other pollutants – is likely to be appropriate. This means that quantification using the O_3 coefficient along with those for other pollutants, in assessments of effects over the long-term (for instance, at least a year), is unlikely to result in an important over-estimation of effects due to double-counting. Nonetheless, those undertaking assessments should be aware of the uncertainty around this. We also note that mitigation measures designed to reduce NO_x emissions (and NO_2 concentrations) may result in a local increase in O_3 close to source, which might be important for population exposure to O_3.

Limitations of the recommended approach

26. We are aware that a more in-depth examination of the available reviews, and of the wider epidemiological and mechanistic evidence base, might have allowed us to make more robust, up-to-date and detailed recommendations for quantification of hospital admissions associated with short-term exposures to air pollutants. However, this is beyond our current resources, particularly as updated recommendations were required in a timescale that would allow them to inform planned policy development by Defra (derivation of Environment Act $PM_{2.5}$ targets). We consider that adopting

coefficients from existing systematic reviews, and recommending that they be used in assessments in place of COMEAP's previously recommended coefficients (COMEAP, 1998; 2001), is an appropriate, pragmatic approach to updating COMEAP's previous recommendations.

27. Making recommendations which take into account multi-pollutant approaches and the extent of potential confounding is beyond the scope of our current considerations. Instead, we have updated our recommendations for single-pollutant coefficients. We anticipate that the revised recommendations will be used by Defra in its cost-benefit assessments to derive Environment Act $PM_{2.5}$ targets. We have not undertaken any new quantification estimates (burden or impact).

Research Recommendations

28. We recommend that further research into the implications of correlations between O_3 and both NO_2 and $PM_{2.5}$, and how these may affect use of the O_3 coefficients within a combined health impact assessment, should take place. This should include evaluating the possible role of these correlations in the apparent effect modification by temperature of O_3 coefficients that has been sometimes been reported.

29. We note that primary reviews only up until 2011 are included in the meta-analyses by SGUL on which our recommended coefficients are based. We would therefore recommend that the meta-analyses should be updated. In our view, this should be commissioned and undertaken by others for COMEAP/QUARK to review, rather than undertaken by us directly. Undertaking such a review is unlikely to be a priority for ourselves (COMEAP/QUARK) because of the small contribution of hospitalisations to cost-benefit assessments.

Overall conclusions and recommendations

30. Our view is that meta-analyses of associations from single pollutant models undertaken by SGUL provide the most appropriate source of coefficients for quantification of all cause cardiovascular and all cause respiratory hospital admissions associated with short-term exposures to air pollutants.

31. We recommend that the global effects estimates from these meta-analyses are used to quantify respiratory and cardiovascular hospital admissions associated with short-term exposure to PM, NO_2 and O_3. For NO_2, we recommend use of the coefficients based on 24-hour average concentrations for use in cost-benefit assessment of proposed interventions (we note that there may be some assessments in which the use of the 1-hour coefficient is appropriate). The concentration-response functions recommended are summarised in the table below.

32. Users should consider the uncertainties regarding causality, notably for cardiovascular hospital admissions associated with NO_2, when deciding which pollutant-outcome pairs to include in assessments or sensitivity analyses. They should also give appropriate consideration to the likelihood of overlap between the effects estimates reported for PM and NO_2, which means that combining them within an assessment would result in an over-estimation of effects/benefits. We consider

that associations reported with all-year O_3 are likely to be independent of those reported with other pollutants. Therefore, there is less concern regarding possible double-counting of effects (or benefits) if O_3 is included with other pollutants in a long-term assessment.

Random summary effects estimates (95% confidence intervals) for the percentage increase per 10 µg/m^3 reported from meta-analyses of time-series studies

	Overall	**Reference**
$PM_{2.5}$		
Respiratory hospital admissions, all ages	24-hour: 0.96 (-0.63, 2.58)	Atkinson et al (2014) Table 3
CV hospital admissions, all ages	24-hour: 0.90 (0.26, 1.53)	Atkinson et al (2014) Table 3
NO_2		
Respiratory hospital admissions, all ages	24-hour: 0.57 (0.33, 0.82) 1 hour: 0.34 (-0.02, 0.7)	Mills et al (2015) Table S2
CV hospital admissions, all ages	24-hour: 0.66 (0.32, 1.01) 1 hour: 0.36 (-0.16, 0.89)	Mills et al (2015) Table S3
O_3		
Respiratory hospital admissions, all ages	Daily maximum 8 hour running mean 0.75% (0.30, 1.2)	Walton et al (2014)
CV hospital admissions, all ages	Daily maximum 8 hour running mean 0.11% (−0.06, 0.27)	Walton et al (2014)

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COMEAP statement on update of recommendations for quantifying hospital admissions associated with short-term exposures to air pollutants

Annex A

The literature search information is summarised in this annex.

Search question:

Systematic reviews and meta-analyses of epidemiological studies on hospital admissions associated with air pollution.

Terms used:

(Air pollut* or PM10 or "PM2.5" or Nitrogen dioxide* or NO2 or Ozone or O3 or Ultrafine particulate* or Black Carbon or ultrafine particle* or ultra-fine particulate* or ultra-fine particle* or particulate pollut* or PM pollut* or ambient pollut*) OR (air adj2 (quality or ambient)) OR (atmospher* adj2 pollut*) OR (vehicle adj emission*) OR ((coarse or fine) adj particle*) OR particulate matter OR (PM0* or PM1* or PM2* or PM10*) OR (nitrogen adj dioxid*) OR (NO2 or NOx or "NO(x)") OR (particulate adj2 pollut*) OR ((sulphur or sulfur) adj dioxide*) OR SO2 OR (carbon adj monoxide*) OR (air adj stagn*) OR (oxidant adj air adj pollut*) OR (airborne adj acidity)
AND
(hospital adj3 (visit or visits or attendance* or admit*)) OR (hospitalization or hospitalisation) OR (hospital adj3 admission*) OR ("accident and emergency" or emergency department* or "a&e" or "a and e") OR (physician* or consultation*) OR general practi*

Limits applied:

Age group	Language	Publication type	Time limit
	English	Systematic Reviews	2010-Dec 2020

Figure 1 presents the PRISMA diagram which illustrates the screening and review process carried out during the literature search.

Figure 1: PRISMA flowchart illustrating the numbers of papers on hospital admissions associated with air pollution