COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Committee on the Medical Effects of Air Pollutants

Statement on quantifying mortality associated with long-term exposure to $PM_{2.5}$

Summary

1. Quantification of the health impacts of reductions in air pollution provides an important input to policy development. Recommendations for quantification typically consist of a concentration-response function (CRF) representing the relationship between a pollutant and an adverse effect on health, along with advice on how this should be applied. This statement updates COMEAP's recommendations for quantifying mortality associated with long-term exposure to fine particle air pollution ($PM_{2.5}$) in outdoor air.

2. The CRF recommended for use is 1.08 (95% CI: 1.06, 1.09) per 10 μg/m^3 annual average $PM_{2.5}$. This is a summary effects estimate from a meta-analysis of the available global literature by Chen and Hoek (2020). The use of a cut-off value for quantification is not recommended; it is recommended to assume continuing linearity[1] when quantification is performed down to very low or even zero $PM_{2.5}$ concentrations, for example when quantifying the mortality burden attributable to particulate air pollution. As some of the health effects of previous exposure could persist for some time, the full mortality benefits of reductions in concentrations of $PM_{2.5}$ are unlikely to be realised immediately. This delay in the reduction of mortality risk is known as the cessation lag. We recommend use of a cessation lag that assumes that 30% of the risk reduction occurs in the first year after pollution has reduced, 50% occurs across years 2 to 5 and the remaining 20% of the risk reduction is distributed across years 6 to 20 with smoothed annual values. This is the same lag structure that we have previously recommended (COMEAP, 2010).

3. We recommend that quantification using these methods should be accompanied by a discussion of the uncertainties. For example, it should be noted that the recommended CRF is not adjusted for effects of other pollutants[2], which means that:

[1] Linearity on the log scale: log-linearity. Cohort studies of mortality typically relate the natural log of the hazard function to the concentration. In practice, for a small hazard ratio (as found in most air pollution studies) and over a small concentration range (as is usually the case in a health impact assessment) there is little difference between a linear and log-linear relationship. This might not be the case when larger concentration differences are being considered.

[2] There are a number of challenges in interpreting the results of 2-pollutant models. COMEAP (2018a; section 3.2.3) summarises the statistical issues as including: the lack of an interaction term; multi-collinearity (high correlations between pollutant concentrations); transfer of effect arising from exposure misclassification; and overlapping confidence intervals between coefficients reported from

a. mortality estimates will likely include effects caused by other correlated pollutants (such as NO_2) to some extent and
b. if mortality effects estimated using this coefficient are added to estimates of mortality effects associated with other pollutants, this will likely give an overestimate of the effects of the pollution mixture and of the benefits of reducing concentrations.

4. Appendix B presents COMEAP's views on studies in populations with low-level exposures and the shape of the concentration-response curve.

Introduction – background

5. Quantification of the health impacts of reductions in air pollution provides an important input to policy development. It is, for example, carried out as part of cost-benefit analysis (CBA), which values the costs and benefits associated with a given policy option (Defra, 2020). Recommendations for quantification typically consist of a concentration-response function (CRF) representing the relationship between a pollutant and an adverse effect on health, along with advice on how this should be applied. The CBA guidance, published by Defra with the endorsement of the Interdepartmental Group on Costs and Benefits (IGCB) Air, draws on COMEAP recommendations for quantifying health impacts of air pollutants, as well as recommendations made by other organisations. The public health burden associated with existing levels of air pollution can also be estimated (COMEAP, 2010; 2018a).

6. The Committee previously recommended an approach for quantifying mortality associated with long-term exposure to particulate air pollution in its reports on 'Long-term Exposure to Air Pollution: Effect on Mortality' (COMEAP, 2009) and 'Mortality effects of long-term exposure to air pollution in the UK' (COMEAP, 2010). More recently, the Committee revised its recommendation for the CRF to be used in its 'Statement on quantifying mortality associated with long-term average concentrations of fine particulate matter ($PM_{2.5}$)' (COMEAP, 2018b). The CRF recommended in the 2018 statement – 1.06 (95% confidence interval, CI: 1.04, 1.08) per 10 μg/m^3 $PM_{2.5}$ – was based on a meta-analysis of cohort studies of $PM_{2.5}$ and all-cause mortality by Hoek et al (2013).

7. More recently, the World Health Organization (WHO) has commissioned a number of systematic reviews and meta-analyses to inform the review of its Air Quality Guidelines. At its meeting in April 2020, the COMEAP Strategy Group agreed that these reviews might provide a useful basis for COMEAP to consider whether updates were required to some of the Committee's recommendations for quantification of health effects. The reviews undertaken for WHO have been published in a Special Issue of 'Environment International'.[3] At a similar time, Pope et al (2020) reviewed and compiled the findings of cohort studies on fine particulate air pollution and mortality.

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single- and 2-pollutant models. In addition a coefficient for $PM_{2.5}$, even when adjusted for another pollutant (such as NO_2), likely reflects the effects of other pollutants which are more closely correlated with $PM_{2.5}$ than the other pollutant (NO_2 in this example) to some extent (COMEAP, 2018a table 7.1)

[3] Update of the WHO Global Air Quality Guidelines: Systematic Reviews

8. At the COMEAP meeting held on 11th November 2020, the Committee discussed whether these recently published reviews would provide a suitable basis for updating its recommendations for quantifying mortality associated with long-term exposure to fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3).

9. After considering the systematic literature review commissioned by WHO to support the update of its global air quality guidelines (Huangfu and Atkinson, 2020), it was agreed that COMEAP would retain its current recommendations for quantifying mortality associated with long-term exposure to NO_2 and O_3 (CRFs and other aspects, such as cut-offs, cessation lags), as reported in the COMEAP reports on 'Associations of long-term average concentrations of nitrogen dioxide with mortality' (COMEAP, 2018a) and 'Quantification of mortality and hospital admissions associated with ground-level ozone' (COMEAP, 2015a). The Committee has recommended the use of a coefficient within the range of 1.006 to 1.013 per 10 $\mu g/m^3$ annual average NO_2 for the quantification of the mortality benefits of interventions that primarily target emissions of oxides of nitrogen (NO_x) and an unadjusted coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ annual average NO_2 for the assessment of the mortality benefits of interventions that reduce a mixture of traffic-related pollutants. Quantification is not recommended for mortality associated with long-term exposure to O_3.

10. The Committee agreed to set up a working group that would give further consideration to updating COMEAP's recommendations for quantifying mortality associated with long-term exposure to $PM_{2.5}$. The working group met in December 2020 and January 2021 and discussed how best to use the findings of the new reviews to update the quantification recommendations. The working group's recommendations were discussed by COMEAP's sub-group on the quantification of air pollution risks in the UK (QUARK) at its meeting on 5th February 2021 and the full Committee at the COMEAP meetings held on 8th March and 11th May 2021.

11. Specific questions that the working group were asked to consider are:

i). Do you consider that these reviews and meta-analyses provide a suitable basis for updating the Committee's recommendations for quantification of all-cause mortality associated with long-term average concentrations of $PM_{2.5}$?

If so:

ii). What (if any) single-pollutant CRF (and expression of uncertainty) would you recommend for quantification? Should a European or global CRF be chosen?

iii). What cut-off for quantification should be recommended, if calculations are to avoid extrapolation beyond the studied range of concentrations?

iv). What locations / scale of modelling might be most appropriate as the basis for application of these CRFs for quantification?

v). Consideration of an appropriate cessation lag to be used in quantification.

Current practice and recommendations

COMEAP's 2010 quantification of mortality associated with particulate air pollution

12. As well as specifying the CRF, COMEAP's recommendations for quantifying mortality associated with long-term average $PM_{2.5}$ concentrations address other methodological aspects. These are outlined in the report published by COMEAP in 2010 (COMEAP, 2010). We use the term 'cut-off' to refer to a concentration below which there is an absence of evidence for an effect either due to a complete absence of data, or because data are extremely sparse; this does not mean that there is no effect (if there is no threshold, then there will be some effects), just that there is uncertainty about its magnitude.

13. COMEAP recommended that calculations could be undertaken either by extrapolating to zero anthropogenic pollution or, to avoid extrapolation beyond the studied range of concentrations, by applying a cut-off for quantification of 7 $\mu g/m^3$, which represented the lower end of the range of concentrations studied (at that time) in epidemiological studies. COMEAP reported estimates using both of these approaches.

14. The term 'cessation lag' is used to denote the likely time lag between reductions in long-term average $PM_{2.5}$ concentrations and a consequent reduction in mortality risk. The cessation lag distribution used by the US Environmental Protection Agency (2004, 2011) was adopted by COMEAP's (2010) assessments of the mortality impact of reductions of $PM_{2.5}$ concentrations and recommended for subsequent use. This approach suggests that much of the reduction in risk occurs in the first 5 years after pollution concentrations are reduced.

15. Annual mean $PM_{2.5}$ concentrations at "background" sites[4] simulated by the Pollution Climate Mapping (PCM) model[5] at a spatial resolution of 1 km x 1 km across the UK were used by COMEAP (2010) in its calculations. This approach was considered to be a reasonable approximation to the exposure metric used in the epidemiological study from which the CRF was adopted.

16. This statement includes an updated consideration of these methodological aspects, as well as revised recommendations for the CRF itself.

Subsequent COMEAP consideration of particle metrics

17. The Committee has acknowledged that there are variations in toxicity between the various components of $PM_{2.5}$, but has concluded that the evidence available does not give a consistent view of relative toxicity (COMEAP, 2015b)[6].

[4] Background sites as defined by the EU Ambient Air Quality Directive

[5] The Pollution Climate Mapping (PCM) model is an air pollution model that is calibrated using data from monitoring data at background sites in Defra's Automatic Urban and Rural Network (AURN). The PCM model simulated the annual average $PM_{2.5}$ concentrations used by COMEAP (2010, 2018) as the basis of its burden estimates

[6] COMEAP is currently reviewing the evidence for differential toxicity of PM according to source or components, with the intention of updating the Committee's views; finalisation of a revised statement on this topic is expected in 2022.

Also, more recently, COMEAP concluded that there was insufficient evidence to provide a quantitative comment on the risk arising from non-exhaust traffic particle emissions compared with ambient particles (COMEAP, 2020).

18. Despite changes in pollution composition over the last few years, the available epidemiological evidence base does not seem to suggest major changes in CRFs. Similarly, the summary CRF has remained similar despite the increasing number of different methods used to assign exposure in epidemiological studies – from a single monitor in a city to street-scale dispersion models. This suggests that $PM_{2.5}$ mass, even at relatively coarse spatial resolution, remains an effective metric for assessing population-scale health effects of particulate air pollution. Thus, $PM_{2.5}$ mass has remained the preferred metric for quantitative assessments of the health effects of exposure to particulate air pollution.

Multi-pollutant considerations

19. Because concentrations of different air pollutants are often strongly correlated, it is difficult to ascribe causality of associated health outcomes to individual pollutants within the air pollution mixture. When considering the many studies reporting associations of mortality with long-term average concentrations of NO_2, COMEAP (2018a) noted that associations of NO_2 with mortality likely represent a causal effect of NO_2 and also effects of closely correlated pollutants, including $PM_{2.5}$. Similarly, mortality effects associated with $PM_{2.5}$ are likely, in part, to represent the effects of other correlated pollutants (COMEAP, 2009), possibly including NO_2, as well as effects caused by particles. COMEAP (2018a) noted that, given the good evidence and plausibility of causality for $PM_{2.5}$, it was reasonable to regard the majority of the mortality effect associated with $PM_{2.5}$ as likely to be causally related to $PM_{2.5}$. Nonetheless, correlation between pollutants has implications for the interpretation and application of CRFs from epidemiological studies, which are discussed in COMEAP (2018a). A number of scientific and methodological challenges in understanding the extent of the independence of the associations of mortality with concentrations of NO_2 and $PM_{2.5}$ were also identified (COMEAP, 2018a). QUARK is currently undertaking work to consider the appropriate use of results of multi-pollutant models to inform approaches to quantification of effects associated with air pollutants. Therefore, we do not address this issue further in this statement, which focuses on recommendations for quantification using a CRF from single-pollutant models.

Recent systematic reviews, meta-analyses and studies

20. Chen and Hoek (2020) systematically searched MEDLINE and EMBASE from database inception (1966 for MEDLINE and 1974 for EMBASE) to 9 October 2018 for cohort and case-control studies on associations of $PM_{2.5}$ and PM_{10} with all-cause and cause-specific mortality. A random-effects meta-analysis was performed when at least 3 studies were available for a specific exposure-outcome pair. The authors also performed additional analyses to assess consistency across geographic region, explain heterogeneity and explore the shape of the CRF.

21. Pope et al (2020) reviewed previous cohort studies of mortality and fine particulate matter air pollution conducted in the US and other countries around the world from the last 25 years. The findings of these cohort studies were compiled and summarised using meta-analysis.

22. Vodonos et al (2018) undertook a systematic review and meta-analysis of cohort studies (indexed before April 21, 2017) which reported associations between long-term exposure to $PM_{2.5}$ and mortality. Multi-variate approaches to meta-analysis and meta-regression techniques were used to examine whether study characteristics modified the association between $PM_{2.5}$ and mortality, and to estimate the shape of the concentration-response curve.

23. As well as these reviews, studies in cohorts exposed to low levels of $PM_{2.5}$ are emerging. These have arisen from a Request for Applications (RFA) issued by the Health Effects Institute (HEI) on 'Assessing Health Effects of Long-term Exposure to Low Levels of Ambient Air Pollution'[7]. Three studies have been funded under this RFA and are currently underway:

- MAPLE: Mortality-Air Pollution Associations in Low Exposure Environments, Principal Investigator (PI) Michael Brauer, University of British Columbia, Canada. Identifying the shape of the association between long-term exposure to low levels of ambient air pollution and the risk of mortality: An extension of the Canadian Census Health and Environment Cohort using innovative data linkage and exposure methodology
- ELAPSE: an analysis of European cohorts Effects of Low-Level Air Pollution: A Study in Europe, PI Bert Brunekreef, University of Utrecht. Mortality and morbidity effects of long-term exposure to low-level $PM_{2.5}$, Black Carbon, NO_2 and O_3
- Assessing adverse health effects of long-term exposure to low levels of ambient pollution, PIs Francesca Dominici and Antonella Zanobetti, Harvard T.H. Chan School of Public Health

24. It should be noted that these HEI-funded studies, while clearly important, are still in-progress. The working group considered early findings from some of the studies, but its main focus was on available syntheses of the full published literature, rather than on individual studies.

Discussion

Comparison of reviews and selected coefficient

25. The Vodonos et al (2018) meta-regression analysis suggested that the effect estimate varied depending on the $PM_{2.5}$ concentration. COMEAP discussed this meta-regression, and other studies, when considering the shape of the exposure-response curve at low-level exposures. It did not consider the evidence sufficient, at this time, to recommend any change from the current assumption of a linear[1] CRF for use in quantification (see paragraph 37 and Appendix B), and therefore the Vodonos et al analysis was not considered further by the working group.

[7] Assessing Health Effects of Long-term Exposure to Low Levels of Ambient Air Pollution

26. The 2 other reviews – Chen and Hoek (2020) and Pope et al (2020) – included 25 and 33 studies respectively in the main meta-analyses for the association between $PM_{2.5}$ and all-cause mortality, with 17 studies used in common in both analyses (Table A1, Appendix A). Although Pope et al included some additional studies in the meta-analysis, not all of these were based on exposure to $PM_{2.5}$; some examined associations with other particle metrics such as PM_{10} or total suspended particles.

27. Chen and Hoek (2020) undertook a domain-based risk of bias (RoB) assessment to evaluate all the studies included in their meta-analyses. This RoB assessment included evaluation of the exposure assessment. Chen and Hoek considered exposure assessment methods to be appropriate when studies had documented validity such as good agreement between model predictions and measurements.

28. A summary effects estimate of 1.08 (95% CI: 1.06, 1.09) per 10 $\mu g/m^3$ long-term average concentration of $PM_{2.5}$ was reported by Chen and Hoek (2020). Pope et al (2020) reported a similar summary effects estimate of 1.08 (95% CI: 1.06, 1.11) per 10 $\mu g/m^3$ long-term average concentration of $PM_{2.5}$ when including only "selected" studies [8] in the meta-analysis. A slightly higher summary effects estimate of 1.09 (95% CI: 1.07, 1.11) per 10 $\mu g/m^3$ $PM_{2.5}$ was obtained by Pope et al from a meta-analysis of all studies. We consider this latter meta-analysis to be less suitable as a potential basis for adoption as a CRF for quantification purposes than meta-analyses using studies selected for relevance to the general population and to avoid cohort overlap.

29. The review by Chen and Hoek was systematic, and followed a protocol developed by WHO. The paper provides more detailed information on the selection of studies for inclusion in meta-analyses than that by Pope et al. Furthermore, Chen and Hoek analysed a number of factors affecting the CRF, such as heterogeneity between studies, possible publication bias, the shape of the CRF and adjustment for other pollutants. Therefore, we regard the review by Chen and Hoek as a more suitable basis for updating COMEAP's recommendations.

European or global literature?

30. As well as meta-analyses of the global literature, both Chen and Hoek (2020) and Pope et al (2020) undertook meta-analyses restricted to studies in specific geographical regions. We discussed whether it might be appropriate to adopt a Europe-specific summary effects estimate for quantification of effects in the UK, rather than an estimate based on the global literature. Pope et al (2020) reported a summary effects estimate of 1.12 (95% CI: 1.06, 1.19) per 10 $\mu g/m^3$ $PM_{2.5}$ from a meta-analysis of 10 European studies. This included several studies which reported associations with particle metrics other than $PM_{2.5}$. Chen and Hoek (2020) combined the 5 European studies identified by their search and sifting, to produce an effects estimate of 1.07 (95% CI: 1.03, 1.11). As this estimate lies within the 95%

[8] Studies were selected to avoid using multiple studies of the same or similar cohorts (usually only the study with the largest and longest follow-up was used) and to exclude studies of cohorts which are not representative of the general population (for example studies undertaken in specific patient groups).

confidence intervals of the global summary estimate, it is not clear that the European effects estimate is significantly different from the global analysis. The authors noted that combined effects were similar across all 3 WHO regions where studies had been conducted, reducing concerns about the applicability of results from (in the past) primarily North-American studies to assess health risks in Europe and other regions.

31. Taking all these factors into account, we recommend adoption of the summary effects estimate of 1.08 (95% CI: 1.06, 1.09) per 10 μg/m^3 annual average $PM_{2.5}$ drawn from Chen and Hoek's (2020) global evidence base, for use in quantification.

Multi-pollutant analyses

32. COMEAP has previously highlighted the challenge of recommending concentration-response functions for the effects of individual pollutants in the face of the uncertainty in the interpretation of concentration-response functions from multi-pollutant models (COMEAP, 2018a). Chen and Hoek (2020) found that the summary effect estimates for the 5 studies reporting 2-pollutant results were reduced from 1.07 (95% CI: 1.05, 1.08) per 10 μg/m^3 for single-pollutant CRFs to 1.02 (95% CI: 1.00, 1.04) for CRFs adjusted for NO_2. We note that the sources and relative concentrations of pollutants differ considerably in Europe compared to US and other areas in the world, which might be important for the transferability of CRFs for $PM_{2.5}$ from elsewhere to the UK situation. While having made some progress on the topic of interpretation and use of CRFs from 2-pollutant models, QUARK considers that there is further work to be done before the challenges can be addressed quantitatively. Therefore, we have not considered pollutant adjustments when updating the recommended quantification method.

Cut-off values and shape of CRF

33. When quantifying health effects associated with air pollutants, COMEAP has previously chosen to undertake calculations using both a cut-off for quantification representing the lower end of the studied range and also by extrapolating to zero anthropogenic pollution (COMEAP, 2010; 2018a). COMEAP has regarded the portion of a burden estimate above the cut-off as that in which there is greatest confidence, while further extrapolation to zero estimates the additional effect that is likely under an assumption of the same concentration-response relationship down to zero anthropogenic pollution.

34. The use of the anthropogenic fraction of particulate pollution, rather than total particulate pollution, was because anthropogenic particulate matter can be considered as the theoretical maximum that could potentially be influenced by policy interventions.[9] However, the concentration of $PM_{2.5}$ corresponding to zero anthropogenic pollution is not straightforwardly defined in practice. The concentrations of $PM_{2.5}$ derived from sources that might initially be considered 'natural' are also affected by anthropogenic activities: for example, both wind-blown

[9] The air pollution indicator currently included in the Public Health Outcomes Framework (PHOF) – the fraction of mortality attributable to particulate air pollution – is based on the levels of anthropogenic particulate air pollution.

dust and emissions of biogenic volatile organic compounds from vegetation (precursors of secondary organic aerosol) are influenced by the cultivation of crops. Primary biological material (for instance, pollen), natural dust from arid areas and sea salt might be considered non-anthropogenically derived particles but may also act as carriers of toxic anthropogenic emissions. However, many of these latter particles may be too coarse to appear in the $PM_{2.5}$ size fraction, meaning that the non-anthropogenic proportion of $PM_{2.5}$ may be very small. In addition, it may be difficult to accurately and unambiguously quantify concentrations of non-anthropogenic $PM_{2.5}$ to enable its subtraction from total $PM_{2.5}$ mass concentration, in order to estimate the anthropogenic fraction. This relies on accurate 'mass closure' of $PM_{2.5}$ in the available measurements or models. In practice, sea salt is the only one of these components that can be easily identified for exclusion. Recent assessments from the PCM model[5] are that the contribution of sea salt to UK population-weighted annual mean $PM_{2.5}$ in 2018 and 2019 is of the order of 0.5 $\mu g/m^3$ (Brookes et al, 2020; 2021). The outputs from the PCM model are calibrated against the AURN[10] data using a 'residual'. This residual represents the contribution from sources that are not explicitly included in the model, and is also assigned as non-anthropogenic (along with the sea salt). However, in recent years, a residual has not been needed to calibrate the model (the residual has been zero) as a result of improved emission inventories and modelling methods.[11]

35. If a cut-off for quantification were to be selected, the range of concentrations which has been studied needs to be considered. Previously, the cut-offs for quantification used for estimating the annual UK mortality burden attributable to the current air pollution mixture were 7 $\mu g/m^3$ for $PM_{2.5}$ and 5 $\mu g/m^3$ for NO_2 (COMEAP, 2018a). Recent studies have included cohorts exposed to $PM_{2.5}$ concentrations lower than 7 $\mu g/m^3$ meaning that this cut-off no longer seems appropriate. In addition, policies implemented in recent years have led to improvements in air quality meaning that this cut-off would be relevant to estimates of the impacts of further interventions, as well as to burden estimates (Dajnak et al, 2020). The concentrations experienced by cohorts in the available epidemiological studies vary considerably. Table A2 (Appendix A) provides information on the range of concentrations in the studies included in the meta-analysis of $PM_{2.5}$ and all-cause mortality by Chen and Hoek (2020). Some studies do not report the distribution of exposure values but only mean (or median) values. The lowest value reported as a 5^{th} percentile of population exposure from the studies included in the Chen and Hoek meta-analysis was 3 $\mu g/m^3$ from Pinault et al (2016) (the study contributed 3.40% of the weight to the meta-analysis). Hence, the current evidence demonstrates associations between mortality and $PM_{2.5}$ concentrations considerably lower than previously.

36. We acknowledge the considerable uncertainties involved in extrapolating above the range of studied concentrations. However, there is less uncertainty when extrapolating below studied concentrations: this can be regarded as interpolation between the studied effects and there being zero effects at zero exposure.

[10] The Automatic Urban and Rural Network (AURN) is the UK's largest automatic monitoring network and is the main network used for compliance reporting against the Ambient Air Quality Directives.
[11] If a small residual is required, in the future, to calibrate the PCM model, regarding this as non-anthropogenic would be consistent with current practice.

37. QUARK has discussed studies in populations with low-level exposures. A summary of QUARK's views on these studies, and the shape of the CRF, is attached (Appendix B). Some primary studies, as well as reviews/meta-regressions, have suggested that the exposure-response function might be supra-linear (that is, with a bigger effect, per unit change in concentration, at lower exposures than higher exposures). However, it is not clear to what extent these results may be due to differences in populations and/or the statistical methods used. Therefore we do not consider the evidence sufficient, at this time, to recommend any change from the current assumption of a linear[1] CRF relationship when quantifying the effects associated with long-term exposure to $PM_{2.5}$, particularly as a supra-linear CRF could have important implications for quantification (see Appendix B). QUARK recognises the importance of these issues and intends to keep the literature on this topic under review, and will continue to explore relevant methodological issues, as part of its future work programme.

38. Therefore, we consider that the most appropriate approach to quantification of the mortality effects associated with long-term average concentrations of $PM_{2.5}$, based on the current evidence and methodological understanding, is to extrapolate to low or zero $PM_{2.5}$ using an assumption of continuing linearity.[1] This recommendation takes into account the uncertainties in attributing $PM_{2.5}$ to anthropogenic or non-anthropogenic sources, the low concentrations which have now been studied and the fact that extrapolation below these low concentrations is unlikely to introduce more error than would result from restricting quantification to the studied ranges. This is particularly the case for CBA where quantification of the population exposed above and below a (necessarily arbitrary) cut-off could be a major sensitivity for the analysis, given uncertainty in exposure assessment. For the reasons discussed above we think that it would be appropriate, when conducting health impact assessments or CBA, to assume continuing linearity[1] even at very low exposures. If a sensitivity analysis of estimates obtained without extrapolation is required, the information on the lower ends (such as 5^{th} percentiles) of exposure ranges in Table A2 might provide an appropriate basis for selecting a cut-off for quantification. We note that the recently updated WHO air quality guideline (5 $\mu g/m^3$) for long-term exposure to $PM_{2.5}$ was derived from the average of the 5^{th} percentiles of exposures in studies which reported associations with mortality in populations exposed to low levels of pollution.

39. Similarly, we also think it would be appropriate to extrapolate using an assumption of continuing linearity[1] to zero $PM_{2.5}$ when estimating mortality burdens associated with long-term average $PM_{2.5}$ concentrations. We note that this is a change from previous and current practice (for example COMEAP, 2010; 2018a,b and PHOF air pollution indicator[9]). The use of other counterfactuals might be appropriate in some situations, depending on the aims of the burden estimate. For example, there might be interest in estimating the burden attributable to PM arising from specific activities or sectors, or by concentrations exceeding guidelines or regulatory limit values. A sensitivity analysis of an estimate without extrapolation beyond the studied range could also be made, if desired. Again, the information on the lower ends of exposure ranges in Table A2 might provide an appropriate basis for selecting a cut-off for quantification in this case.

Cessation lag

40. There is likely to be a lag between exposure to pollution and consequent adverse health effects such as mortality (inception lag). Similarly, cessation lag is a term used to denote the time pattern of reductions in mortality risk following a reduction in pollution. We recommend continuing to use the cessation lag recommended by the US Environmental Protection Agency (US EPA), as described in US EPA (2004; 2011) and COMEAP (2010). According to this, 30% of the risk reduction occurs in the first year after pollution reduction, 50% occurs across years 2 to 5 (12.5% per year) and the remaining 20% of the risk reduction is distributed across years 6 – 20 with smoothed annual values. These 3 components of the lag distribution were suggested to reflect short-term, cardiovascular, and lung cancer effects, respectively.

41. Some UK studies have suggested that a small element of the estimate for black smoke has similar (Elliott et al, 2007 (12 to 16 years)) or longer (Hansell et al, 2016 (>30 years)) lags than previously considered. Pollution levels were reducing considerably over the time of these studies, so this may reflect a mixture of inception and cessation lags. We have decided to retain the recommendation to use the US EPA lag at the current time, but plan to keep information relating to lags (including mechanistic information) under review.

42. In COMEAP (2010), the evidence on cessation lag was reviewed thoroughly (summarised in Table 16 of the COMEAP (2010) working paper 'COMEAP: development of proposals for cessation lags for use in total impact calculations'). Various alternative lag structures were explored based on evidence in the literature and it was concluded that a categorical evidence-based choice between them was not possible. Sensitivity analyses were undertaken to understand the possible influence of alternative lag structures on the results of health impact assessments, using a range from no lag to a 30-year phased-in lag. In assessments of the mortality impact over the 106 years[12] following reductions in $PM_{2.5}$ concentrations, the cessation lag was found to have much less influence on estimated benefits (an 11% reduction using the 30 year phased-in lag compared with benefits estimated using the US EPA cessation lag structure) than assumptions about economic discounting (which ranged from a 55% reduction for a discount rate of 1.5% to a 91% reduction for a discount rate of 6%, compared with no discounting).[13]

43. Therefore, when assessing mortality benefits, the relative influence of the cessation lag chosen will be affected by the length of time period considered and the discount rate used. Where assessments are concerned with the mortality benefits that accrue over a short (20 to 30 year) time period after pollution concentrations are reduced, the choice of cessation lag will have more influence – and discount rate less influence – than for assessments of benefits over 106 years.

[12] It is common practice to use a follow-up period of 106 years which is a period long enough to allow the current population to die out. This ensures that the full extent of mortality benefits to those alive at the time of the intervention is reflected in the assessment.

[13] Weighting factors are commonly used in cost-benefit analyses to discount future mortality impacts in economic terms. For health effects, this discounting largely reflects Social Time Preference Rates, STPR (see for example The Green Book: appraisal and evaluation in central government).

44. The influence of the cessation lag was also found to be small compared with the uncertainty around the CRF that was used in COMEAP's (2010) estimates. The uncertainty around the summary effects estimate from the meta-analysis by Chen and Hoek (2020), which is the basis of our current revised recommendation, is much less. This means that the possible influence of the cessation lag is, therefore, relatively larger in comparison with the uncertainty around our new recommended CRF, but is still small compared with the likely influence of discounting in economic analysis.

Exposure assessment – spatial scale

45. The scale, and locations, of the pollutant modelling used as the basis for predicting health impacts of interventions, or estimating burdens, might have an important influence on the results[14] (COMEAP, 2018a; Maiheu et al, 2017). Therefore, specification of the exposure assessment characteristics (such as spatial scale of modelling, location of measurement points) for application of the CRFs for quantification might be required. In principle, it would seem desirable to use exposures that reflect the exposure assessments used in the studies from which the CRF is derived. However, the different epidemiological studies use a variety of exposure assessment methods: methods include exposure assigned to the nearest monitoring station, land use regression and dispersion models; spatial scales vary from residential address to US county.

46. The studies contributing to the Chen and Hoek summary estimate were not dominated by studies using exposure metrics of one particular spatial scale. This means that it is not possible to recommend a particular spatial scale for use in health impact assessment or burden estimates. The authors did not stratify studies of the exposure metric to assess whether the coefficient varied by spatial scale. Although there was heterogeneity across the reviewed studies, this could be due to a number of factors in addition to exposure assessment, such as differences in methods, the concentration and composition of PM, population, geographic location and time period. The factors which drive heterogeneity in reported associations of health effects with air pollutants is an issue currently being considered by QUARK. However, this work is on-going.

47. We note that spatial scale of exposure assessment is likely to have a less important influence on quantification of effects associated with $PM_{2.5}$ than for NO_2, as it is less spatially variable. Nonetheless, very broad spatial scales (for example, 10 km by 10 km and above), are unlikely to pick up variations in $PM_{2.5}$ from locally emitted sources, which would likely have been reflected in the exposure metrics for many of the studies included in Chen and Hoek's meta-analysis.

Estimation of mortality burdens and interpretation of "attributable deaths"

48. We anticipate that the main use of our recommendations will be in assessing the impacts of the mortality benefits of reducing concentrations of $PM_{2.5}$, for example in cost-benefit analyses of policies and interventions. However, CRFs can also be

[14] Finer scale modelling is likely to lead to greater exposure contrasts and reduced misclassification of exposures. It may also indirectly represent other pollutants to a greater degree than broader scale modelling.

used to estimate the mortality burden associated with long-term exposure to current levels of air pollutants. COMEAP has discussed appropriate methods for this in its previous reports (COMEAP, 2010; 2018a).

49. The interpretation of mortality burden estimates is also discussed at some length in both of these reports. COMEAP (2018a) explains why we consider it more appropriate to estimate the mortality burden of an air pollution mixture, rather than attempting to attribute the burden to specific pollutants. COMEAP (2010) discusses how to interpret estimates of the annual number of "attributable deaths" associated with long-term average concentrations of pollutants. This is not an estimate of the number of people whose untimely death is caused entirely by air pollution. Instead, it is a way of representing the effect of air pollution across the whole population: air pollution is considered to act as a contributory factor to many more individual deaths. This is why we recommend expression of the results of burden estimates as "an effect equivalent to a specific number of deaths at typical ages".

Main conclusions and recommendations

50. The main points covered in the statement are summarised below:

i. Our recommendations for quantification of mortality associated with long-term average concentrations of exposure to NO_2 and O_3 remain as before

ii. An updated CRF (and expression of uncertainty) from single-pollutant models is recommended for quantification of mortality associated with long-term average concentrations of $PM_{2.5}$: 1.08 (95% CI: 1.06, 1.09) per 10 $\mu g/m^3$ annual average $PM_{2.5}$. This is the summary effects estimate from a meta-analysis of the global literature by Chen and Hoek (2020)

iii. We do not recommend the use of a cut-off value for quantification. We suggest quantification to zero $PM_{2.5}$, using an assumption of continuing linearity[1]. The lowest value reported as a 5^{th} percentile of population exposure in a study included in the meta-analysis from which the CRF is adopted is 3 $\mu g/m^3$ total (rather than anthropogenic only) $PM_{2.5}$. This, and other information on the range of exposures studied, might inform the choice of cut-off value for use in sensitivity analysis, if desired

iv. We recommend that the cessation lag developed by the US EPA, and used in our previous work (COMEAP, 2010), be used in assessments of the impact of reductions in $PM_{2.5}$. This assumes that 30% of the risk reduction occurs in the first year after pollution reduction, 50% occurs across years 2 to 5 (i.e. 12.5% per year) and the remaining 20% of the risk reduction is distributed across years 6 – 20 with smoothed annual values

v. Due to the different exposure methods used in the available epidemiological studies, we are not able to specify what spatial scale is most appropriate when applying this CRF for use in quantification. Nonetheless, we recommend that very broad spatial scales (for example 10 km x 10 km or higher) that are unlikely to reflect variations in $PM_{2.5}$ from

local emission sources should be avoided if effects of local sources are the primary concern

vi. Quantifications made using these methods should be accompanied by a discussion of uncertainties. One of these uncertainties arises from the heterogeneity in associations reported in the available epidemiological studies. This heterogeneity is likely due to various factors, such as differences in methodology and exposure assessments, concentration and composition of PM, population, geographic location and time period. Another uncertainty relates to attribution of causality to exposure to particulate matter and other components of the air pollution mixture, given the correlation between $PM_{2.5}$ concentrations and those of other pollutants in the populations studied. It should be noted that the suggested coefficient is not adjusted for effects of other pollutants, which means that:
   a. mortality estimates will likely include effects caused by other correlated pollutants (such as NO_2) to some extent and
   b. if mortality effects estimated using this coefficient are added to estimates of mortality effects associated with other pollutants, this will likely give an overestimate of the effects of the pollution mixture and of the benefits of reducing concentrations.

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Statement on quantifying mortality associated with long-term exposure to $PM_{2.5}$

Appendix A

This appendix includes:

a. Table A1: Comparison of studies included in the meta-analyses by Chen and Hoek (2020) and Pope et al (2020) and
b. Table A2: Details of the studies included in the meta-analysis of $PM_{2.5}$ exposure and all-cause mortality by Chen and Hoek (2020).

Table A1. All-cause mortality and $PM_{2.5}$ – comparison of studies included in meta-analyses by Pope et al (2020) and Chen and Hoek (2020)

Country	**Cohort**	**Pope et al "selected"**	**Chen and Hoek meta-analysis**
Americas			
USA	Harvard Six Cities	Lepeule et al 2012	Lepeule et al 2012
	CA-CPS I	**Not included (no CA CPS I studies selected)**	**Enstrom et al, 2005**
	ACS CPS-II	**Pope et al 2015**	**Turner et al, 2016**
	AHSMOG	McDonnell et al 2000	McDonnell et al 2000
	US Medicare	Di et al, 2017	Di et al, 2017
	US Nurses (NHS)	Hart et al, 2015	Hart et al, 2015
	US California Teachers	Ostro et al, 2015	Ostro et al, 2015
	US Male Health Professionals	Puett et al, 2011	Puett et al, 2011
	US Truckers	Hart et al, 2011	Hart et al, 2011
	US Agricultural Health (AHS)	Weichenthal et al, 2014	Weichenthal et al, 2014
	US NIS-AARP	Thurston et al 2016	Thurston et al 2016
	US CA Elderly	**Garcia et al, 2016**	**Not included (not mentioned in the review)**
	US NJ Department of Health	**Wang et al, 2016**	**Not included (not mentioned in the review)**
	US National Health (NHIS)	**Pope et al, 2019**	**Parker et al, 2018**
	US Veterans	**Not included (not mentioned in review)**	**Bowe, 2018**
Canada	CanCHEC	**Crouse et al, 2015**	**CanCHEC 1991: Cakmak et al, 2018**
			CanCHEC 2001: Pinault et al, 2017
	Canada Breast Screening (CNBSS)	Villeneuve et al, 2015	Villeneuve et al, 2015
	Canada Com Health (CCHS)	Pinault et al, 2016	Pinault et al, 2016
Europe			
France	PAARC	**Filleul et al, 2005**	**Not included (not mentioned in review)**
	Electric and Gas (Gazel)	Bentayeb et al 2,015	Bentayeb et al, 2015
Germany	Urban Women	**Gehring et al, 2006**	**Not included (mentioned in review but not included in list of studies reporting association between $PM_{2.5}$ and all-cause mortality. PM_{10} was studied)**
Netherlands	NLCS-Air	Beelen et al, 2008	Beelen et al, 2008

Country	**Cohort**	**Pope et al "selected"**	**Chen and Hoek meta-analysis**
	DUELS	**Fischer et al, 2015**	**Not included (mentioned in review but not included in list of studies reporting association between $PM_{2.5}$ and all-cause mortality. PM_{10} was studied)**
England	Clinical Practice	Carey et al, 2013	Carey et al, 2013
Italy	Rome register/Rome longitudinal	**Cesaroni et al, 2013**	**Badaloni et al, 2017**
Spain	Small area	**Keijzer et al, 2017**	**Not included (Not mentioned in review).**
Denmark	DCH	**Hvidtfeldt et al, 2019**	**Not included (Mentioned as being published after the cut-off date for the review)**
Europe	ESCAPE	Beelen et al, 2014	Beelen et al, 2014
Asia			
China	Hypertension	**Cao et al, 2011**	**Not included (Not mentioned in the review. TSP studied)**
	Chinese Men	Yin et al, 2017	Yin et al, 2017
	CLHLS	**Li et al, 2018**	**Not included (Mentioned as being published after the cut-off date for the review)**
Hong Kong	Hong Kong Elderly	**Wong et al, 2015**	**Yang, 2018**
Taiwan	Taipei (Civil Servants)	Tseng et al, 2015	Tseng et al, 2015
Japan	Nippon	**Ueda et al, 2012**	**Not included (Mentioned in review but not included in list of studies reporting association between $PM_{2.5}$ and all-cause mortality. PM_{7} was studied)**
Iran	Tehran	**Yarahmadi et al, 2018**	**Not included. (Not mentioned in the review). This appears to be a burden estimate using AirQ+ software)**
Number of papers included		**33**	**25**

Table A2. Details of studies on all-cause mortality and $PM_{2.5}$ included in the meta-analysis by Chen and Hoek (2020)

First author	Year of publication	Study name	Study period	Study location	Year of exposure	5-95th percentiles of population exposure	Mean concentration	Standard deviation	Median concentration
Badaloni	2017	Rome longitudinal study	2001-2010	Rome, Italy	2010	17.6-24.2	19.6	1.9	19.1
Beelen	2008	NLCS-AIR	1987-1996	the Netherlands	1987-1996		28.3	2.1	
Beelen	2014	ESCAPE	1990s-2008	Europe	2008-2011				
Bentayeb	2015	Gazel	1989-2013	France	1989		17	4.3	16.8
Bowe	2018	U.S. veterans	2003-2012	U.S.	2004	25-75th: 10.1-13.6			11.8
Cakmak	2018	1991 CanCHEC	1991-2011	Canada	satellite estimates for 1998-2011 assigned to each year for 1984-2011				
Carey	2013	English national cohort	2002-2007	England	2002		12.9	1.4	
Di	2017	Medicare	2000-2012	continental USA	2000-2012	6.21-15.64	11		
Enstrom	2005	CA CPS I	1973-2002	11 counties in California	1979-1983		23.4		
Hart	2011	trucking companies	1985-2000	continental USA	2000		14.1	4	
Hart	2015	NHS	2000-2006	U.S.	2000-2006		12	2.8	
Lepeule	2012	Harvard Six Cities	1974-2009	6 cities in U.S.	1979-2009		15.9		
Mcdonnell	2000	AHSMOG	1977-1992	California, USA	1973-1977		31.9	10.7	

First author	Year of publication	Study name	Study period	Study location	Year of exposure	5-95th percentiles of population exposure	Mean concentration	Standard deviation	Median concentration
Ostro	2015	California Teachers Study	2001-2007	California, USA	2000-2007	13.1-22.8 (25-75th)	17.9		18.2
Parker	2018	NHIS	1997-2011	US	2004	10-90%: 8.7-14.7			11.8
Pinault	2016	CCHS-Mortality Cohort	2000-2011	Canada	1998-2012 (3-yr avg. prior to follow-up year)	3.0-11.3	6.32	2.54	5.9
Pinault	2017	2001 CanCHEC	2001-2011	Canada	2004-2012 estimates extended to 1998-2010, 3-yr average prior to follow-up	3.51-11.97	7.37	2.6	7.12
Puett	2011	Health Professionals FollowUp Study	1986-2003	U.S.	12-month ave, before each outcome (1988-2002)		17.8	3.4	
Thurston	2016a	NIH-AARP	2000-2009	6 US states and Atlanta and Detroit	2000-2008	10.7-15.9 (20-80th)	12.2	3.4	
Tseng	2015	civil servants cohort	1989-2008	29 districts within the Greater Taipei, Taiwan	2000-2008	27.3-30.9 (20-80th)			
Turner	2016	ACS-CPS II	1982-2004	USA, esp. Iowa and North Carolina	1999-2004	8.2-17.1	12.6	2.9	12.5
Villeneuve	2015	CNBSS	1980-2005	Canada	1998-2006	6.4-12.4 (25-75th)		3.4	9.1

First author	Year of publication	Study name	Study period	Study location	Year of exposure	5-95th percentiles of population exposure	Mean concentration	Standard deviation	Median concentration
Weichenthal	2014	AHS	1993-2009	Iowa and North Carolina, USA	2001-2006 average		9.52	1.66	
Wong	2015	Hong Kong elderly	1998-2011	Hong Kong	2000-2011				35.3
Yang	2018	Hong Kong elderly	1998-2011	Hong Kong	moving ave. of con, one year before and one year after the recruitment date (baseline 1998-2001)				42.2
Yin	2017	Chinese men	1990-2006	45 districts in China	ave, between 2000 and 2005		43.7		