# *Associations of long-term average concentrations of nitrogen dioxide with mortality*

A report by the Committee on the Medical Effects of Air Pollutants

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# Foreword

In recent years many city dwellers in the United Kingdom have been exposed to illegal concentrations of nitrogen dioxide ($NO_2$). In March 2015 we published a statement on the evidence linking $NO_2$ with health effects, and concluded 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'. Furthermore, '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'.

This increase in evidence led to interest in estimating effects associated with concentrations of $NO_2$. In May 2015, Defra requested advice on how to undertake quantification of the mortality benefits of reducing long-term average concentrations of $NO_2$. This was to assist Defra with quantifying the potential benefits of policy options to reduce concentrations as part of its Air Quality Plans for the achievement of EU air quality limit values for $NO_2$ in the UK. To underpin our advice, we carried 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. We also made a detailed appraisal of the results of the small number of two- and three-pollutant models that include $NO_2$. This work identified 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 $PM_{2.5}$.

Perhaps not surprisingly, in working through these substantive challenges COMEAP Members were unable to reach a consensus view on some of the issues. In order to reflect the full range of views, this report documents those areas on which consensus was reached, as well as expressing the full range of views on the more controversial aspects. This has necessitated the presentation of the more divergent viewpoints in a binary fashion, although the actual views of the Members form a continuum between those extremes. This report progresses our thinking, in terms of its willingness and ability to tackle these difficult areas and to move thinking forward. It will, I believe, generate useful discussion and proactive interest, acting as a springboard for further research into multipollutant model research as requested herein.

The majority of the work in the report was undertaken by a working group under the guidance of Roy Harrison. Given the extensive work required for this report over several years, I am deeply indebted to Roy and working group Members: Richard Atkinson, Mike Holland, Fintan Hurley, Brian Miller, John Stedman and Heather Walton; to other Members who joined the group to help with drafting the report: Bob Maynard and Gavin Shaddick; and to the Secretariat and other Members of COMEAP who contributed their time so generously.

Professor Frank Kelly

Chairman of the Committee on the Medical Effects of Air Pollutants

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Exploratory analyses undertaken using information on $NO_2$ concentrations in London by Dr Heather Walton and Dr David Dajnak of King's College London and John Stedman of Ricardo Energy and Environment.

Calculations of impact of reducing $NO_2$ concentrations, carried out by Dr Clare Heaviside, Public Health England.

An additional face-face meeting of the COMEAP Working Group on $NO_2$.

# Executive Summary

## Introduction

In March 2015, we published a statement recognising the strengthening of the evidence for associations of adverse health effects with ambient concentrations of nitrogen dioxide ($NO_2$). We concluded that:

*'the 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. Nonetheless, it is likely that, to some extent, $NO_2$ acts as a marker of the effects of other traffic-related pollutants' (COMEAP, 2015b).*

We published an interim statement on 15 December 2015 with our initial recommendation for a coefficient to reflect the relationship between long-term average concentrations of $NO_2$ and mortality but we did not quantify the number of deaths attributable to long-term exposure to $NO_2$. We explained that there is uncertainty regarding both the exact causal agent(s) and the extent to which the effects can be attributed to $NO_2$ itself. Associations of long-term average concentrations of $NO_2$ with mortality have been reported in cohort studies, but the extent to which these associations reflect an effect that is additional to the mortality effect found to be associated with fine particulate matter ($PM_{2.5}$) is not clear. It is also not clear whether the association with $NO_2$ is due to $NO_2$ itself or other pollutants. This statement built on earlier advice provided in July 2015 to assist the Department for Environment, Food and Rural Affairs (Defra) with quantifying the potential benefits of policy options to reduce $NO_2$ concentrations as part of its Air Quality Plans.[1]

In further work described in this report, we undertook a systematic review of cohort studies that reported associations of long-term average concentrations of $NO_2$ with all-cause mortality. We have attempted to derive coefficients that allow calculation of the impacts of policies that reduce air pollutant concentrations, and the overall mortality burden attributable to the air pollution mixture as a whole, while commenting on the associated uncertainty of any estimates of effects and benefits. We have given separate consideration to abatement measures that reduce $NO_x$ emissions alone and those that also reduce co-emitted pollutants.

We have examined the epidemiological evidence in more detail, including studies published up to October 2015, paying particular attention to the issues arising out of the use of multi-pollutant models in this context. This has been a challenging task, extending previous work by

[1] We provided updated advice to Defra in July 2017, based on the development of our views on methods for impact assessment as described in this report, to assist in updated impact analyses. This was published as an annex to Defra's Technical Report: https://www.gov.uk/government/publications/air-quality-plan-for-nitrogen-dioxide-no2-in-uk-2017

the World Health Organization (WHO) and the US Environmental Protection Agency (US EPA), and requiring further work in the future to provide more confident quantification of the effects of both individual pollutants and multi-pollutant mixtures. Policy needs have determined the focus on $NO_2$ in this report.

## Approach to deriving associations between mortality and long-term exposure to $NO_2$

There are now several cohort studies that report estimates of associations between long-term (annual average) concentrations of $NO_2$ and mortality. This does not automatically mean that the associations represent the effects of $NO_2$ alone. These are estimates of the association with $NO_2$ without reference to the effect of other pollutants, i.e. they are estimates from single-pollutant models. Some studies also include estimates for associations with $NO_2$ after adjustment for other pollutants, notably PM mass, i.e. they provide estimates from multi-pollutant models.

Our approach was to derive a summary coefficient linking long-term average concentrations of $NO_2$ with all-cause mortality by undertaking a meta-analysis of the findings of studies which had reported results from single-pollutant models. We then considered whether or not the evidence allowed a further step: adjusting the summary estimate to account for confounding by other pollutants. Unadjusted coefficients will typically over-estimate the associations with an individual pollutant.

## Approach to analysing single pollutant model evidence

St George's, University of London undertook a systematic review and meta-analysis of cohort studies of $NO_2$ and all-cause mortality to inform the considerations of the $NO_2$ working group. Publications were identified from the period 1996 to the first week of October 2015. Studies were excluded if the cohorts comprised sub-groups defined by pre-existing disease or specific age groups and if the cohorts had been analysed in other publications included in this review. Only one result from each study was selected for meta-analysis.

If the concentrations of a group of pollutants are correlated with each other, and if each pollutant has an effect on mortality, then the statistical associations of each individual pollutant with mortality will, to some extent, also reflect the effects of other pollutants in the group. For example, use of a single-pollutant coefficient to estimate the impact upon mortality of changes in $NO_2$ concentrations would risk attributing some of the mortality effect of co-varying (eg other traffic-generated) pollutants to the association with $NO_2$.

Ideally, associations with each individual pollutant should be adjusted for correlated pollutants to give the independent associations with each pollutant. The application of multi-pollutant models allows such adjustments. However, there are difficulties in interpreting the results of multi-pollutant models when pollutants are highly correlated. In addition, if one pollutant has greater exposure misclassification[2] than another then some of its effect can 'transfer' to the other more precisely measured pollutant. Known as 'effect transfer', this may result in the effects associated with a causal relationship being under-estimated whilst non-causal associations are spuriously overestimated. These and other complications are discussed in the report.

[2] Exposure misclassification (measurement error) is explained in Section 3.2.3.1

## Approach to analysing multi-pollutant model evidence

We examined evidence from two- or multi-pollutant models. The first step was to identify the studies, from the review of single-pollutant model evidence, that also presented results from multi-pollutant models. We concentrated on adjustments for PM mass ($PM_{2.5}$ or $PM_{10}$). We then investigated combining the adjusted log hazard ratios (HRs) within each study ($NO_2$ adjusted for $PM_{2.5}$ or $PM_{10}$ and vice versa). We did this because within any study, even if effect transfer occurs, the total across the hazard ratios per interquartile range of each pollutant should indicate the total association.

We then considered possible approaches to combining the information from two-pollutant models. We explored several approaches to account for possible confounding of the $NO_2$-mortality associations by associations of mortality with $PM_{2.5}$. However, we concluded that none of these potential approaches was appropriate and we have decided against formally deriving an $NO_2$ coefficient adjusted for effects associated with $PM_{2.5}$. Instead we have applied our judgement, informed by the available evidence, to propose a reduced coefficient which may be used to quantify the mortality benefits of reductions in concentrations of $NO_2$ alone, where this is necessary.

The scientific and methodological challenges we encountered when deriving a coefficient to reflect the association between mortality and long-term average concentrations of $NO_2$ are discussed in the report. These include heterogeneity of the studies, effects of other pollutants, potential small study bias, and limitations of the evidence base.

We have described the interpretation of the coefficients and make recommendations for their appropriate application (or not) in quantification with a description of the uncertainties. We have also made recommendations for future research which we think would help to resolve some of the difficulties we encountered during our work.

# Discussion of the evidence

## Single pollutant model evidence

Eleven study estimates for mortality associated with long-term exposure to $NO_2$ were selected for meta-analysis. Meta-analysis of the results of these single pollutant studies resulted in a summary coefficient from a random-effects model of the association with mortality of 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ $NO_2$ as an annual average[3]. There was substantial heterogeneity between the estimates from different studies ($I^2$, a measure of heterogeneity, was 97%). There was some suggestion of small study bias towards a higher estimate than would otherwise be the case. However, the results of formal tests for small study bias were not statistically significant, and the substantial heterogeneity observed could be an alternative explanation for higher estimates in smaller studies. We noted that those studies with individual level control for smoking and social economic status (SES) tended to report smaller coefficients than those where control for these variables was at the area level.

[3] Subsequent updating of the meta-analysis has resulted in a slightly smaller summary coefficient, see Chapter 2 and Working Paper 1. However, the work in this report was based on the original meta-analysis.

## Multi-pollutant model evidence

Six studies identified in the original literature review reported results of two-pollutant models for $NO_2$ and PM mass, the majority using measurements of $PM_{2.5}$, and one large study using $PM_{10}$. Another reported results from a three-pollutant model. The reported associations of $NO_2$ concentrations with mortality were reduced somewhat by adjustment for PM and sometimes lost statistical significance.

For each study, we compared the single-pollutant coefficients for $NO_2$ and PM with the combined mutually adjusted coefficients reported from the same study. The combined adjusted coefficients were similar to, or slightly larger than, the single-pollutant association reported with either pollutant alone. This suggests that use of one or other of the single pollutant model results, alone, would underestimate the total effect of the air pollution mixture to some degree, but that summing effects predicted on the basis of both unadjusted coefficients would substantially over-estimate the effects of a pollutant mixture. The confidence intervals around the reported coefficients suggest some uncertainty regarding this conclusion.

Insufficient studies were available to examine multi-pollutant model results for $NO_2$ adjusted for other traffic pollutants such as primary combustion particles, particle number concentration, carbon monoxide or polycyclic aromatic hydrocarbons (PAHs). (Correlations between $NO_2$ and these pollutants are likely to be very high: this would have made any results from multi-pollutant models difficult to interpret, had they been available). There was also insufficient evidence to assess possible confounding of $NO_2$ associations by ozone and noise. However, we note that ozone can be negatively correlated with $NO_2$ implying that adjustment for ozone might increase the estimated $NO_2$ coefficient.

Having investigated the associations reported in epidemiological studies, and noted the challenges in separating the effects of different pollutants, the Committee then considered the issue of causality.

## Two-pollutant models and causality

We noted in our March 2015 statement that it would be sensible to regard $NO_2$ as causing some of the health effect found to be associated with it in epidemiological studies. However, this overall conclusion was not outcome specific. The work on this report was not resourced to consider all of the evidence relating to causality of long-term exposure to $NO_2$ and all-cause mortality but we have considered the epidemiological evidence on this outcome in the general population in detail. The range of opinions within the Committee on the implications of this new evidence for the causality argument is given below.

With regard to an association between $NO_2$, itself, and mortality one strand of opinion views the epidemiological evidence as providing only weak and insufficient support for the assertion that such an association is causal in nature and thus does not support quantification other than in some limited form (see Chapter 10). This view is based on the following:

a The observed association between mortality and long-term exposure to $NO_2$ (whether or not explained by $NO_2$ itself) has several features which weaken confidence in the relationship and in particular whether it is transferable. This view was based on the small effect size (interpreted as making chance more likely and the possibility of a confounding factor or factors playing a part less easy to discard), unexplained heterogeneity, the possible presence of small

study bias (acknowledging possible alternative explanations) and a strong possibility of confounding due to socioeconomic and lifestyle factors.

b In terms of the role of $NO_2$ itself in explaining this association, the close correlation with other pollutants was emphasised. Multi-pollutant model results were not considered informative in this respect, partly because of difficulties in interpreting results from multi-pollutant models where these exist, but also because such models are unavailable for many of the co-pollutants from the same sources as $NO_2$, especially those related to road traffic.

c The stronger causal basis for effects of short-term exposure was noted. In particular, a role for $NO_2$ itself in relation to respiratory effects was considered biologically plausible at higher ambient concentrations in studies of short-term exposure, but there is far less toxicological evidence about long-term exposures. The studies on the American Cancer Study cohort[4] showed that the association of all-cause mortality with $PM_{2.5}$ (perhaps acting as a marker for the air pollution mixture) was largely explained by cardiovascular mortality. The toxicological evidence for a causal association between $NO_2$ and cardiovascular mortality is weak. The fact that the size of the association with all-cause mortality for long-term exposure was only three times higher than in time-series studies, a less clear difference than for $PM_{2.5}$, suggested that if $NO_2$ itself has a role in the associations found in studies of long-term exposure, this may reflect the aggregate effects from short-term exposures rather than additional effects of long-term exposure to $NO_2$ itself.

A second strand of opinion, held by the majority of the Committee, accepts that there are some weaknesses in the case for causal inference eg unexplained heterogeneity, but does not go as far as regarding it as insufficient to support the likelihood that long-term exposure to $NO_2$ contributes to an increased mortality risk. This is based on the following:

a Although the effect size after meta-analysis of studies conducted in the general population (all ages) was small, effect sizes were larger in specific age groups and also in susceptible sub-groups. Larger positive and significant associations were also found for the majority of cohort studies which examined cardiovascular and respiratory mortality. These findings reduce the likelihood that the reported associations arose by chance. For all-cause mortality in the general population, heterogeneity was regarded as a plausible explanation for the apparent small study bias, and detailed sensitivity analyses within the studies with only indirect control for individual life-style factors suggested that failure to adjust for these factors did not have a major impact on the estimated coefficients.

b There was agreement that the association between long-term average concentrations of $NO_2$ and mortality over-estimates the effect of $NO_2$ itself because of the likely confounding by other pollutants. This was not, however, considered to rule out a contribution from $NO_2$. Some account was taken of multi-pollutant model results in studies with lower correlations between $NO_2$

[4] For example HEI (2000)

and $PM_{2.5}$ as being suggestive of an association with $NO_2$ independent of $PM_{2.5}$ at least, if not of other traffic pollutants. The strengthening evidence linking $NO_2$ with respiratory effects was noted. We also noted that a large cohort study in England[5] had found larger associations of air pollutants with mortality from respiratory than cardiovascular causes.

It is clear from the above that the associations of long-term average concentrations of $NO_2$ with mortality derived from epidemiological studies employing single-pollutant models actually represent the effects of a mixture of closely correlated pollutants, of which $NO_2$ is one component and PM another (insofar as it is correlated with $NO_2$). Adjusting the $NO_2$ coefficient for PM excludes (as far as possible given current evidence) effects associated with $PM_{2.5}$ concentrations, but not the effects of other traffic pollutants not closely correlated with $PM_{2.5}$ concentrations. Members agreed that there are many problems with interpretation of multi-pollutant model results that should be considered. However, the extent to which these problems apply is unknown, and Members differed in their views of their importance and whether such adjusted coefficients could be used in quantification.

This report has not considered $PM_{2.5}$ in detail, but some of the concerns we raise regarding the interpretation of $NO_2$ associations also apply to those for $PM_{2.5}$ (and other pollutants). So, the $PM_{2.5}$ single pollutant coefficient may represent effects of pollutants with which it is closely correlated (eg $NO_2$), although the evidence for causality of PM is stronger than for $NO_2$ in several respects. The interpretation of a $PM_{2.5}$ coefficient adjusted for $NO_2$ has similar challenges as the $PM_{2.5}$- adjusted $NO_2$ coefficient with views on usability differing among Members.

Because of these difficulties with allocation of the mortality effect to different pollutants, the uncertainties associated with the application of the coefficients in quantification will depend on whether the aim is to assess the effects of reductions in concentrations of $NO_2$ itself, the effects of reductions in $NO_2$ as well as of other co-varying pollutants, or to estimate the burden of the air pollution mixture as a whole. Consequently, we considered these separately.

## Threshold and cut offs

The available evidence does not suggest that a threshold for effects exists at the population level. However, as only some of the studies have included formal tests for this, the possibility of a threshold cannot be ruled out. It was considered possible that any level of annual average concentration of $NO_2$ would imply additional risk to at least some of the population, whether from $NO_2$ itself, assuming it has an effect, or from co-varying pollutants. Recent studies have shown associations of mortality with annual average $NO_2$, at concentrations lower than previous studies had shown, and there is now evidence of associations in cohorts in which the range of outdoor levels reaches as low as 5 $\mu g/m^3$ annual average $NO_2$ concentration.

There were differences of opinion regarding the application of reported concentration-response functions outside the range of studied concentrations. Some Members felt that quantification to zero was a reasonable extrapolation, and necessary when attempting to estimate mortality burden. Other Members felt that an extrapolation to zero was not justified. All Members agreed that extrapolation to zero involved additional uncertainty, compared to

[5] Carey et al. (2013)

estimation at higher concentrations where associations had been shown. We decided to quantify using both approaches and to be as open as possible about the assumptions involved in each.

## Quantification of Effects

In our 2009 report, our view regarding associations reported in the literature linking long-term exposure to particulate air pollution, represented by $PM_{2.5}$, and effects on mortality was that they:

*'almost certainly represent causal relationships in respect of the air pollution mixture of which $PM_{2.5}$ forms part, and are highly likely to be causal in terms of particulate air pollution specifically. In saying this we note that there is a small possibility that some or all of the reported associations represent the effects of some as yet unidentified confounding factor or factors.'(COMEAP, 2009a).*

There are now many more studies reporting associations of mortality with long-term exposure to $NO_2$, providing some evidence that mortality effects attributed to $PM_{2.5}$ are, in part, due to other correlated pollutants, possibly including $NO_2$. Similarly, and as described earlier, it is acknowledged that associations of $NO_2$ with mortality likely represent any effect of $NO_2$ and also of closely correlated pollutants, including $PM_{2.5}$. This complexity poses considerable challenges when considering how to quantify and interpret estimates of mortality effects based on reported associations with $NO_2$.

There was agreement across the Committee that neither the full size of the single pollutant coefficient nor the full size of an adjusted coefficient accurately represented the effect of the specific pollutant $NO_2$ alone. There was also acknowledgement of the potential problems related to interpretation of multi-pollutant model results. There were, however, strongly divergent opinions as to what to recommend for quantification in the face of the recognised uncertainty.

It was noted that the two (related but not identical) processes of (i) forming a view on the hazard of the pollutant and (ii) making recommendations for quantification, place different demands on the evidence base. It is thus possible to consider it sensible to regard $NO_2$ as causing some of the health effect found to be associated with it in epidemiological studies, as we did in our March 2015 statement, while at the same time judging that there is insufficient good quality evidence to make firm recommendations with regard to quantification. It is also possible to support recommendations for quantification while at the same time judging that there is insufficient good quality evidence to have a clear view about the causality of a specific pollutant within a mixture.

Some aspects of the epidemiological evidence that we reviewed weakened the case for a causal link between long-term exposure to $NO_2$ and all-cause mortality. We do not consider all of the reported association to be causally related to $NO_2$. We have not systematically reviewed all aspects of causality with regard to long-term exposure to $NO_2$, but the majority of the Committee believes there is a case for an $NO_2$ contribution of unknown size, based mainly on evidence of effects on the respiratory system. We have attempted to reflect the available evidence, and the uncertainty, appropriately in our recommendations.

## Difference of view

In the course of our work a number of points of disagreement arose between Members of the Committee. These points were discussed at length but some proved to be impossible to resolve. Nonetheless, there was agreement on many points.

The areas which caused disagreement were those relating to:

1) the causality of $NO_2$ associations with mortality;

2) the interpretation of results from multi-pollutant models in cohort studies; and

3) the calculation of the burden imposed on health by long-term exposure to nitrogen dioxide and by pollution mixtures well represented by nitrogen dioxide.

The following recommendations reflect the view of the majority of the Committee. Professors H Ross Anderson and Robert Maynard, and Dr Richard Atkinson, dissociate themselves from the following recommendations (and the views that led to these recommendations) other than

a the recommendation for a method of assessing the health benefits of interventions that reduce all traffic-related pollutants and

b the recommendation not to attempt a calculation of mortality burden attributable to $NO_2$ alone.

Their reasons for dissent are presented immediately after the following recommendations, and explained more fully in Chapter 10.

## Recommendations for quantification and estimates of effects

### Recommendation for a method of assessing the health benefits of interventions that primarily target emissions of oxides of nitrogen ($NO_x$)

While not a unanimous decision (some Members disagreed fundamentally), we recommend quantification of the health benefits of interventions that primarily target emissions of oxides of nitrogen ($NO_x$) by (i) basing a coefficient on the summary estimate from our meta-analysis of the single pollutant models, and (ii) as far as practicable adapting this unadjusted coefficient to reflect the effect of $NO_2$ alone.

This adaptation was considered in two stages. First, the coefficient was reduced to allow for the effects of PM mass in the light of the results of the two pollutant models. (It is highly likely that there is an overlap between the associations for $NO_2$ and $PM_{2.5}$, although there are considerable uncertainties in estimating the size of this overlap.). The majority of the Committee supported reducing the unadjusted coefficient by around 20% to allow for the effects more closely associated with $PM_{2.5}$ concentrations. The figure of 20% was arrived at by detailed but informal assessment of the multi-pollutant results from 4 cohorts considered less subject to bias, eg without strong correlation between $NO_2$ and PM.

An $NO_2$ coefficient adjusted for $PM_{2.5}$ reflects the effect of $NO_2$ and also, to some extent, other pollutants with which it is closely correlated (for example, ultra-fine particles, black carbon, volatile organic compounds etc.). It excludes (as far as possible given current evidence) effects associated with $PM_{2.5}$ concentrations. Given the lack of good evidence for causality, the

extent to which this effect is likely to be causally related to $NO_2$ is unclear. It is unlikely to be zero, but also unlikely to be 100%. Consequently, estimating the effects of $NO_2$ itself, by using an adjusted coefficient, would set an upper limit for the mortality benefits of reducing $NO_2$ alone.

Was it possible to be more specific about the role of $NO_2$ alone? Given the uncertainties and lack of direct evidence, any estimate would necessarily be more speculative even than that provided after adjustment for PM. Nevertheless, discussion by the full Committee led to a majority view, based on wider qualitative evidence, that it was plausible that 30-70% of the $NO_2$ coefficient adjusted for PM was representative of the likely effect of $NO_2$ itself, as opposed to other closely correlated pollutants.

Combining both the adjustment for PM and the further adjustment for other co-varying pollutants, a majority of the Committee agreed that it was plausible that the effects on mortality attributable to $NO_2$ itself lay within the range of 25-55% of the unadjusted coefficient; and that, with suitable strong caveats, this could be used as a guide for policy assessment. This gives a reduced coefficient within the range of 1.006 to 1.013 per 10 $\mu g/m^3$ of $NO_2$ for estimating the effects attributable to $NO_2$ alone.

Several strands of evidence were used in coming to this view, including: coefficients from four studies that had reported coefficients from both single- and multi-pollutant models and in which concentrations of $NO_2$ were not highly correlated with those of PM; time-series evidence; and evidence from toxicological and chamber studies (which provides stronger evidence for a causal link between $NO_2$ and respiratory effects than cardiovascular effects). Nonetheless, there is considerable uncertainty regarding the suggested range of 25-55%. Furthermore, it does not take account of additional uncertainties reflected in the confidence interval around the unadjusted coefficient (1.023 with a 95% confidence interval of 1.008 to 1.037).

We accept that such a recommendation involves a compromise between capitalising on the strength of the single pollutant model evidence base and on the findings of the studies that employed two pollutant models, whilst acknowledging the limitations of the evidence. We think this is inevitable given the methodological difficulties in interpreting the current evidence.

Additionally, to include an assessment of the benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions, we recommend use of the unadjusted coefficient for $PM_{2.5}$ of 1.06 (95% CI: 1.04-1.08) per 10 $\mu g/m^3$ annual average $PM_{2.5}$ (derived from a meta-analysis of single pollutant studies, Hoek et al., 2013).

## Indicative results from applying the recommended method: Possible mortality benefits of reducing $NO_2$ concentrations

Using the reduced coefficient, and aware of the strong uncertainties underlying it, we estimated the mortality effects over 106 years from 2013, including effects on those born after 2013, of a 1 $\mu g/m^3$ reduction in $NO_2$ in 2013 and sustained subsequently.

For a 1 $\mu g/m^3$ reduction in $NO_2$, about 420,000 to 903,000 life years could be saved in the UK over the next 106 years, associated with an increase in life expectancy (at birth) of around 2 to 5 days. We emphasise that these are indicative results.

The full mortality benefits of reducing $NO_x$ (without reducing other pollutant emissions) include also the mortality benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions. We have not tried to assess these in the present illustrative exercise. If we had done so, overall estimated benefits would have been greater.

We re-emphasise that while a majority of the Committee considered that calculations such as these are useful, provided that the caveats and uncertainties are communicated clearly, a minority thought that they should not be done, partly because they were not confident that the caveats and uncertainties would be respected.

## Recommendation for a method of assessing the health benefits of interventions that reduce traffic-related pollutants

The Committee agreed that application of coefficients from epidemiological studies for $NO_2$ in policy assessment can be done with greater confidence for some measures than others (COMEAP, 2015a). Their use when assessing the benefits of measures that are specific to $NO_x/NO_2$ reduction (see previous Sections) will involve a much higher level of uncertainty than application to measures that reduce traffic more generally (i.e. also reducing other pollutants and noise). The reason is that the former requires estimation of a coefficient for $NO_2$ alone, and that involves informed speculation, whereas the latter involves using coefficients from actual studies – for the effects of a mixture there is no need to try to separate out an effect of $NO_2$ alone.

To assess the health benefits of interventions that reduce a mixture of traffic-related pollutants it is recommended that the unadjusted $NO_2$ coefficient (1.023 (95% CI: 1.008, 1.037 per 10 $\mu g/m^3$ annual average $NO_2$) is used, taking $NO_2$ as a marker for the mixture, to calculate the benefits of changes in the mixture.

These measures will also reduce PM concentrations, so the majority of the Committee considered that an alternative calculation of benefits associated with this reduction, using the unadjusted $PM_{2.5}$ coefficient 1.06 (95%CI: 1.04-1.08) per 10 $\mu g/m^3$ annual average $PM_{2.5}$, as a marker for the mixture can also be done. The available evidence suggests that combined estimates, derived using coefficients for $NO_2$ and $PM_{2.5}$ where each is adjusted for the effects of the other, would be either similar to or only a little higher than estimates using unadjusted single-pollutant coefficients for either $PM_{2.5}$ or $NO_2$ alone. As either of the calculations using unadjusted coefficients is likely to underestimate the full benefits of interventions to some extent (because neither marker captures the full effect of the mixture), the majority view was that the higher of the two values calculated from these two approaches for a specific intervention can be used as the value likely to under estimate the predicted benefits the least. These two estimations should not be added together, as this would over-estimate the predicted benefits.

The Committee agreed, additionally, to include an assessment of the benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions. We recommend use of the unadjusted coefficient for $PM_{2.5}$ of 1.06 (95% CI: 1.04-1.08) per 10 μg/m$^3$ annual average $PM_{2.5}$ (derived from a meta-analysis of single pollutant studies, Hoek et al., 2013).

## Results from applying the recommended method: Mortality benefits of reducing traffic-related pollutants, using a calculation based on reductions in $NO_2$ concentrations

For a reduction in all traffic-related pollutants, consistent with a 1 μg/m$^3$ reduction of $NO_2$, about 1.6 million life years could be saved in the UK over the next 106 years, associated with an increase in life expectancy of around 8 days. We think this is a good estimate of the effect of the reduction in the mixture if $NO_2$ is used as a marker of the mixture. (When considering specific policies in particular locations, it would be possible to make an alternative estimate of the benefits of reducing the mixture on the basis of reductions in $PM_{2.5}$ concentrations, as recommended above, and use the higher of the two values in policy analysis).

Our calculations do not include assessment of the mortality benefits associated with reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions. We recommend that this should be included in policy analysis.

## Recommendation of a method for assessing the mortality burden due to long-term average concentrations of $NO_2$

The Committee decided not to recommend a method or to attempt a calculation of mortality burden attributable to $NO_2$ alone. Neither the unadjusted single pollutant summary estimate nor an adjusted coefficient should be used to reflect the burden of $NO_2$ itself on the UK population. For the reasons explained above, neither allows estimation of the mortality effect attributable to $NO_2$ exposure alone; application of these coefficients would lead to *an upper limit* on the mortality burden. Methods to further adjust the coefficient, so that it applies to $NO_2$ alone, are speculative and there is a potential to mislead, if the limitations of the methods and results were ignored. This is particularly important for burden estimates, as these are used in communication with the public more than impact estimates are.

## Recommendation for a method of assessing the mortality burden of air pollution in the UK based on long-term average concentrations of $NO_2$ and $PM_{2.5}$

COMEAP's current estimate of the mortality burden of air pollution in the UK using a coefficient based on $PM_{2.5}$ (COMEAP, 2010) is an effect equivalent to nearly 29,000 deaths and an associated loss of 340,000 life years across the population in a single year. Given the correlation between pollutants, this estimate may include effects of other air pollutants, as well as PM. Nonetheless, the overall burden of air pollution in the UK may be greater than this, as a coefficient linking mortality with $PM_{2.5}$ may fail to capture the full mortality effects of the mixture as a whole. The methodology of the present report allows quantification using either $PM_{2.5}$ or $NO_2$ as the primary indicator of the mixture, and using unadjusted coefficients (in order to capture, as fully as possible, the effect of the mixture as a whole via single-pollutant analyses.) The size of the overlap between results derived from associations with $NO_2$ and $PM_{2.5}$ is unknown, but we consider it to be substantial. The results of single-pollutant estimates in $PM_{2.5}$ and in $NO_2$ should therefore *not* be added together – doing so would lead to over-estimation of the effects of the mixture. Instead, the higher of the two estimates can be used, as this is likely to under-estimate the burden the least.

The majority of the Committee supported a third approach that combines paired reductions of the summary coefficients from single pollutant models for both $NO_2$ and $PM_{2.5}$ to produce mutually adjusted coefficients. Mutual adjustment could be based on the coefficients derived from any of several cohorts; at this time, we consider that four are usable for this purpose. For each study, the percentage reduction in $NO_2$ coefficient on adjustment for PM is applied to the unadjusted summary $NO_2$ coefficient. Similarly, the percentage reduction in $PM_{2.5}$ coefficient on adjustment for $NO_2$ is applied to the unadjusted summary $PM_{2.5}$ coefficient. The estimated burdens obtained using these mutually adjusted summary coefficients are then summed to give an estimated burden of the air pollution mixture. Estimates obtained in this way can be compared with those derived using unadjusted coefficients for $NO_2$ and $PM_{2.5}$ as indicators of the mixture.

Given the variety of possible methods, we therefore recommend that the mortality burden should be presented as a range to reflect the uncertainty. Using this approach, the range of central estimates of the mortality burden of long-term exposure to the air pollution mixture in 2013 in the UK was an effect equivalent to 28,000 to 36,000 deaths at typical ages, associated with a loss of 328,000 – 416,000 life years, when effects down to zero concentration were included. When cut-offs for quantification were implemented, the estimate was an effect equivalent to 16,000 – 19,000 deaths and an associated loss of 181,000 – 224,000 life years. Each of the individual results also has uncertainty associated with it, but we have not been able to quantify that uncertainty.

The results from the individual calculations are consistent with the qualitative conclusion of the COMEAP's interim advice of December 2015 (COMEAP 2015a), that using both $PM_{2.5}$ and $NO_2$ together to estimate the mortality burden of air pollution in the UK, and using appropriately adjusted coefficients to account for the overlap between the two pollutants, would lead to mortality estimates that were somewhat higher than those estimated by COMEAP (2010), but not greatly so. The extent to which $PM_{2.5}$, $NO_2$, or other pollutants with which they are correlated contribute to the overall mortality burden of the air pollution mixture is not clear.

## View of the dissenting group: Statement of disagreement with some of the views and recommendations above

R W Atkinson, H R Anderson, R L Maynard

The authors of the dissenting view outlined in Chapter 10 have been asked to provide a statement outlining their areas of disagreement with the conclusions reached by the majority of Members of COMEAP. Here we summarise our views.

Our disagreement with the majority view concerns the following issues

a Causality

b The decision to estimate the burden of mortality and the decision to present a burden estimate which extrapolates down to zero concentration of $NO_2$

c The use and interpretation of two-pollutant models

d The inadequate consideration of uncertainties, including those indicated by the heterogeneity within the evidence

In more detail:

a In our view there is insufficient evidence to infer a causal association between long-term average ambient concentrations of $NO_2$ and risk of death

b We regard the results of two-pollutant models as too uncertain for use in differentiating associations between long-term average ambient concentrations of $NO_2$ and PM and the risk of death

c We do not agree with the proposed method for arriving at an estimate of the association between $NO_2$ and mortality separate from particle mass concentrations and pollutants derived from the same sources as $NO_2$

d We regard the evidence for a causal effect of exposure to long-term average ambient concentrations of $NO_2$ on the risk of death as too weak and imprecise to be used as a basis for a calculation of the burden imposed on public health in the UK by long-term average ambient concentrations of $NO_2$

e We think it very likely that basing mortality burden calculations on long-term average ambient concentrations of $NO_2$ will, despite listing caveats, mislead the public into believing that exposure to long-term average ambient concentrations of $NO_2$ is causally associated with an increased risk of death.

f While we disagree with the calculation of mortality burden estimates, we very much disagree with estimating the burden down to concentrations lower than those contributing to the original risk estimates, i.e. extrapolating beyond the data. Further, we disagree with presenting two estimates (cut off and zero threshold) and inviting the reader to choose

g We recognise that statistically significant associations between long-term average concentrations of $NO_2$ and risk of death have been reported. In our view these associations are best regarded as representing the associations between a mixture of pollutants of which $NO_2$ is a member and risk of death

h Single pollutant models using $NO_2$ as an indicator of the ambient mixture have been examined using meta-analytical techniques and have yielded a summary coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ increment in long-term average ambient $NO_2$ concentration. In our view this coefficient could be used in impact calculations to assess the marginal benefits of measures to abate levels of pollution mixtures represented by $NO_2$

i The current evidence base indicates a high level of heterogeneity between the $NO_2$ coefficients reported in individual studies, all but one of which is based on an overseas population. This makes extrapolation to UK cities, which, in

turn may also vary in the composition of the pollution mixture, subject to uncertainty. Hence, the size and precision of any summary estimate should be interpreted with caution

## Research recommendations

In order to reduce some of the uncertainties associated with our knowledge of the effects of long-term exposure to $NO_2$ upon health, the Committee recommends a number of different strands of research:

a Studies to reduce some of the uncertainties associated with understanding and estimating the effects of long-term exposure to $NO_2$ upon health: toxicological studies, epidemiological studies and developing understanding of errors in exposure assessment

b Studies to improve quantification of the effects associated with exposure to air pollution mixtures: development of multi-pollutant approaches and statistical methods

c Investigation of reasons for substantial between-study variability in the HRs

Details of the types of studies that would be appropriate are provided in Chapter 11.

# Contents

**The working papers listed below are available from the COMEAP website[6]:**

**Working Paper 1** Systematic review and meta-analysis of cohort studies of $NO_2$ and all-cause mortality
Richard W Atkinson and Barbara K Butland

**Working Paper 2** A viewpoint on using adjusted coefficients for $NO_2$ and $PM_{2.5}$
J Fintan Hurley

**Working Paper 3** Exploratory burden calculations of mixtures of $PM_{2.5}$ and $NO_2$
Heather A Walton and Dimitris Evangelopoulos

**Working Paper 4** Sensitivity analyses on spatial scale and population-weighted mean concentrations of $NO_2$ in London
Heather A Walton, David Dajnak, John R Stedman

[6] https://www.gov.uk/government/groups/committee-on-the-medical-effects-of-air-pollutants-comeap

# Chapter 1
# Introduction

## 1.1 Background

The Committee on the Medical Effects of Air Pollutants (COMEAP) was asked by the Department for Environment, Food and Rural Affairs (Defra) in May 2015 how to undertake quantification of the mortality benefits of reducing long-term ambient concentrations of $NO_2$. This was to assist Defra with 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. The aim of this report is to consider how, and under what circumstances, the association between long-term average concentrations of $NO_2$ and mortality can be used in quantification and how the results of these calculations should be interpreted.

Daily (short-term) and/or annual average (long-term) ambient outdoor concentrations of $NO_2$ have been reported to be associated with adverse effects including hospital admissions for various diagnoses; decrements in lung function; changes in lung function growth; respiratory symptoms; asthma prevalence and incidence; cancer incidence; effects on birth outcomes and mortality (WHO, 2006, US EPA, 2015). The World Health Organization's (WHO) Review of Evidence on Health Aspects of Air Pollution – REVIHAAP project (WHO, 2013a) noted that, since the publication of the 2005 global update of the WHO air quality guidelines (WHO, 2006), there is now stronger evidence associating health effects with outdoor concentrations of $NO_2$. WHO concluded that the evidence, including that from epidemiological studies reporting the associations of $NO_2$ having corrected for the association of fine particulate matter ($PM_{2.5}$) and from mechanistic studies, is suggestive of a causal relationship, particularly for respiratory outcomes. However, WHO also noted that it is hard to judge the independent effects of $NO_2$ in studies of long-term exposure, as correlations of concentrations of $NO_2$ with other pollutants are often high.

The REVIHAAP project concluded that the European cohort studies show associations between $NO_2$ and both all-cause/non-accidental and cause specific mortality, which may be similar to, if not larger than, those for $PM_{2.5}$. Multi-pollutant models have provided support for an effect associated with $NO_2$ independent of that associated with particle mass metrics. However, studies which looked at correlations between $NO_2$ and other pollutants reported moderate to high correlations; in European studies, the correlation coefficient between pollutants can be greater than 0.80. This makes it difficult to identify to what extent the adverse effects are associated with $NO_2$ or with other pollutants, such as metrics of particulate mass. Nonetheless, there was supporting evidence which led REVIHAAP to conclude that at least part of the association between $NO_2$ and effects on health, as observed by epidemiological studies, was likely to be caused by $NO_2$.

After consideration of the authoritative reviews by WHO and also by the US Environmental Protection Agency (WHO, 2013a, US EPA, 2015), and additional evidence, the Committee published a statement in March 2015 (COMEAP, 2015b), on the evidence for effects of $NO_2$ on health, which concluded that:

a 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.

b 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.

The Statement also concluded that the associations between $NO_2$ and health effects observed in a substantial number of both short- and long-term exposure epidemiological studies should not be wholly attributed to other correlated pollutants such as PM. Although the statement did not draw conclusions on specific health outcomes, in general the plausibility of a causal role of $NO_2$ was supported by toxicological studies (COMEAP, 2015b). This judgement was in line with recent reviews by the US EPA and WHO. This shift in understanding has strengthened the case for policies to abate $NO_2$, regardless of whether or not concentrations in the UK exceed EU limit values.

In accordance with Government practice, policy development for pollution abatement is required to consider the costs and benefits of various strategies. For policies to abate $NO_x$ emissions, the relationship between long-term average concentrations of $NO_2$ and mortality had the potential, if quantification were recommended, to have a substantial influence if included in cost-benefit analyses. Assessors from government departments as well as feedback from Public Health England (PHE)'s Air Pollution and Public Health Advisory Group and other stakeholders identified estimates of mortality associated with long-term average concentrations of $NO_2$ as a priority for the Committee's consideration.

## 1.2 Approach

A critical requirement for modelling the benefits of efforts to reduce emissions of pollutants is a concentration-response function (CRF) that describes the relationship between ambient concentrations of those pollutants and health effects. Identifying a CRF for use in quantification of effects involves hazard assessment and a series of related questions and analyses which are addressed in order to estimate impacts in the population. COMEAP's role in the cost-benefit analysis process is to recommend CRFs and to explain their appropriate use and interpretation when applied. It is also tasked with estimating the health impacts (benefits) of illustrative reductions in pollution concentrations and the burden imposed on public health by current concentrations.

The first task was to identify potentially relevant studies of mortality in relation to long-term exposure to $NO_2$ in populations sufficiently similar in socio-demographic characteristics to the target population (UK). Further refinement required consideration of whether single or multi-pollutant models were to be used and whether the CRF was likely to be linear over all concentrations.

Having selected studies that fulfilled these criteria, there was a choice between using a coefficient from a single study deemed most suitable or summarising the selected studies in a meta-analysis if they were sufficiently similar in design. Systematic review and meta-analysis draws on the full evidence base, using statistical approaches to derive a summary estimate for use as the CRF. Meta-analysis offers the additional benefits of increasing the precision of any estimate and exploring any heterogeneity amongst the studies, as well as identifying the possibility of small study bias. Underlying these procedures are efforts to ensure that bias is not introduced by not including all the relevant evidence, or by post-hoc selection of evidence or analytic results.

The Committee agreed that it was preferable to derive a CRF from the full evidence base using meta-analytical techniques, rather than recommend a coefficient selected from a single study. It was noted that whether a coefficient based on single- or two-pollutant models was most appropriate might depend upon the context of the assessment. This is discussed later in the report.

To begin this work, the Committee discussed issues relevant to quantification of the associations of mortality with long-term average concentrations of $NO_2$ at its November 2014 (COMEAP/2014/02) and March 2015 meetings. At the COMEAP meeting in March 2015, Members discussed the paper COMEAP/2015/03, which invited them to consider the evidence associating long-term average concentrations of $NO_2$ with increased mortality risk, and to give their views on causality. Views were also requested on whether, and under what circumstances, this pollutant-outcome pair should be used in cost-benefit analyses of measures intended to reduce ambient air pollution, or to quantify the mortality burden attributable to ambient air pollution. There was also further discussion by the full Committee at the June 2015 meeting (paper COMEAP/2015/05). Discussion included consideration of the recommendations made by the WHO Health Risks of Air Pollution In Europe (HRAPIE) project. These were that quantification of the association between annual average concentrations of $NO_2$ and all-cause mortality could be included, as well as effects of $PM_{2.5}$. However, the HRAPIE authors noted that there was uncertainty about the effects being independent of other pollutants so this should be calculated as part of an "extended" set of impacts (i.e. it is categorised as B*)[1]. They suggested that the effects of $NO_2$ might be overestimated by up to 30% (WHO, 2013b).

At the March 2015 meeting, the Committee agreed that whether associations between $NO_2$ and health endpoints had to be regarded as causal before quantification could be considered appropriate depended upon the purpose of the quantification. If quantification was intended to evaluate a policy which solely targeted $NO_2$ concentrations, then the associations with $NO_2$ would need to be considered causal for this to be appropriate. If, on the other hand, $NO_2$ was regarded as being a surrogate for the effects of other co-emitted pollutants, or noise, then quantification on the basis of associations of effects with $NO_2$ concentrations would be acceptable, for example, to estimate the benefits of a measure to limit traffic.

[1] The HRAPIE project's recommendations for quantification were classified into two categories, depending upon the availability of data to reliably quantify effects. Pollutant-outcome pairs in Group B were those for which there was more uncertainty. Those marked with an asterisk (*) contributed to the total effects of the extended set (Group B*) of effects

It was suggested that, at its broadest level, $NO_2$ could be regarded as a marker of combustion of a fossil fuel. This distinguished it from PM, some of which arises from non-combustion sources. However this should not be taken to mean that reducing combustion, regardless of type/source, would necessarily confer the benefits predicted by the coefficients for associations with $NO_2$. For example, controlling space heating may not produce the same benefits as controlling traffic, because the relationship of $NO_2$ with co-pollutants would be different within the two mixtures. Therefore, the scientific question "Is it causal?" is different from the question "Can it be used for quantification?" More detailed discussion of the potential uses for a coefficient for the association of long-term average concentrations of $NO_2$ and mortality is included in Chapter 7.

A Committee working group was set up in June 2015 to expand on COMEAP's discussions. Its aims were: to identify relevant studies and carry out a meta-analysis to identify a CRF for quantification and undertake quantification, if possible. A report would then be prepared for consideration by the Committee. The terms of reference and the Membership of the working group can be found in Appendices 1 and 3 respectively.

COMEAP and its working group discussed this topic on many occasions in coming to the views and recommendations in this report. While Members were generally in agreement on the evidence and the uncertainties in interpretation, for many of the issues discussed in the report there was a strong divergence of opinion as to what to recommend in the face of the recognised uncertainty. The report seeks to express the full range of opinions of the Committee, noting where views have full Committee agreement or were supported by only some, or the majority, of the Members.

## 1.3 Objectives

The objectives of the working group for this report were to:

a. Undertake a systematic review of cohort studies that have reported associations of long-term average concentrations of $NO_2$ with all-cause mortality and, from these, to derive a summary concentration-response coefficient

b. Consider how, and under what circumstances, the association of long-term average concentrations of $NO_2$ with mortality should be used in health impact assessment studies, cost-benefit analyses of measures intended to reduce ambient air pollution, and to quantify the mortality burden attributable to $NO_2$

c. Quantify the association of long-term average concentrations of $NO_2$ with all-cause mortality, considering the following questions:

    a. What would be the public health benefit of a 1$\mu g/m^3$ reduction of annual mean $NO_2$ concentration?

    b. What is the mortality burden to public health in the UK from the effects of long-term exposure to average concentrations of $NO_2$?

d. Comment on the associated uncertainty of any estimates of effects and benefits.

## 1.4 Outcomes

The group made rapid progress initially in agreeing the coefficient for $NO_2$ derived from single pollutant models (Chapter 2). However, the subsequent consideration of the derivation of a coefficient adjusted for the effects of other pollutants which are correlated with $NO_2$ proved far more controversial. The issues which needed to be considered are described in Chapter 3. There was a range of views within both the $NO_2$ working group and the full Committee as to the extent to which the health effects can be causally attributed to $NO_2$, and the propriety of deriving a coefficient for the effects of $NO_2$ alone, and its use in calculations of the mortality burden. It was not possible to reach a consensus view by discussion, and hence the viewpoints of those who felt it possible, with appropriate caveats, to derive a coefficient for $NO_2$ itself and also to conduct burden calculations, and of those who felt that these actions were inappropriate, appear separately in the report. Chapters 4 (on estimating a coefficient for effects of $NO_2$) and 5 (on approaches to burden calculations) represent the views of the majority of the Committee. The subsequent Chapters 6 to 8 consider the issues involved in the use of the coefficients, and Chapter 9 reports the results of their use in impact and burden calculations. The views of the minority of Members who disagree with the approaches outlined in Chapters 4 and 5 are explained in Chapter 10 and its Annexes. Summaries of the views of both the majority and dissenting group are provided in Chapter 12. An overview of the issues which proved controversial is given in Chapter 13, and Chapter 11 suggests future research to help address some of the uncertainties encountered. Further information on the working methods of the Committee appears in the Working Papers which are available on the COMEAP website[1].

This is the first time in the lifetime of COMEAP (over 20 years) that it has not proved possible to reach a consensus acceptable to the entire Committee. The lack of consensus in this case is a reflection of the complexity of the issues considered, the weaknesses of the evidence base and the differing views of Members on the level of proof needed to make statements, even if qualified with caveats. We hence present a comprehensive overview of the issues which we considered, and the range of views expressed.

Key conclusions and recommendations are summarised in Chapter 12. Professors H Ross Anderson and Robert Maynard, and Dr Richard Atkinson, dissociate themselves from several of the conclusions and many of the recommendations for quantification; their reasons for this are also summarised in Chapter 12 and explained in more detail in Chapter 10.

A number of working papers were developed by Members of the $NO_2$ Working Group, and other experts, to support discussion of various aspects of the work and to develop approaches to quantification. These are listed below, and are available from the COMEAP website[1]:

**Working Paper 1** Systematic review and meta-analysis of cohort studies of $NO_2$ and all-cause mortality
Richard W Atkinson and Barbara K Butland

[1] Working papers referred to in this report are available from the COMEAP website: https://www.gov.uk/government/groups/committee-on-the-medical-effects-of-air-pollutants-comeap

**Working Paper 2** A viewpoint on using adjusted coefficients for $NO_2$ and $PM_{2.5}$
J Fintan Hurley

**Working Paper 3** Exploratory burden calculations of mixtures of $PM_{2.5}$ and $NO_2$
Heather A Walton and Dimitris Evangelopoulos

**Working Paper 4** Sensitivity analyses on spatial scale and population-weighted mean concentrations of $NO_2$ in London
Heather A Walton, David Dajnak, John R Stedman

# Chapter 2
# Deriving a summary estimate for $NO_2$ and all-cause mortality from single pollutant models

## 2.1 COMEAP's Interim Recommendation

Defra requested an interim recommendation by the end of July 2015. This was to assist with the development of an air quality plan, which was published for consultation on 12th September 2015 and the finalised plan was published in December 2015.

In July 2015, the working group considered two published meta-analyses reviewing cohort studies of associations with long-term exposure to $NO_2$ and mortality indexed to 2013 (Hoek et al., 2013, Faustini et al., 2014) as well as evidence from the WHO projects REVIHAAP and HRAPIE (WHO, 2013a,b). The working group made an interim recommendation for a concentration response coefficient of 1.025 (1.02-1.04) per 10 $\mu g/m^3$ $NO_2$. A letter sent informing Mr Rory Stewart, then the Parliamentary Under Secretary for Defra, of this recommendation was later published as a COMEAP interim recommendation in December 2015 (COMEAP, 2015a).

The working group decided to undertake their own systematic review and meta-analysis to derive a coefficient for use to quantify the association of long-term average concentrations of $NO_2$ and mortality to incorporate newly published studies, particularly recent evidence from a large English cohort.

## 2.2 Systematic review

Dr Richard Atkinson and Ms Barbara Butland, St George's, University of London, undertook a systematic review and meta-analysis of cohort studies of $NO_2$ and all-cause mortality. The methods used, inclusion and exclusion criteria and results are included in Working Paper 1. An overview of the approach and a summary of the results are provided here.

Three search strings 1) "cohort" & "$NO_2$" & "mortality"; 2) "cohort" & "air pollution" & "mortality"; and 3) "long-term" & "$NO_2$" & "mortality" were applied to Ovid Medline without Revisions for the period 1996 to October Week 1 2015 and to EMBASE for the period 1996 to 2015 Week 41 to identify publications reporting results for cohort studies of $NO_2$ and

mortality.[1] These searches were supplemented by citation searches in 6 review articles (Brunekreef, 2007, Faustini et al., 2014, Hamra et al., 2015, Hoek et al., 2013, Latza et al., 2009, Atkinson et al., 2016).

The searches returned 996 records. After removal of duplicates and application of the *a priori* inclusion/exclusion criteria (See Working Paper 1 for details), 28 articles analysing 21 cohorts (including the ESCAPE consortium of individual cohorts as one meta-analytical result) reported results for $NO_2$ and all-cause mortality.

To ensure that only one result from each cohort was included, studies were also excluded if the cohort was included in the ESCAPE meta-analysis, or if the same cohorts had been analysed in other, more recent, publications included in this review. Therefore, only one result from each cohort studied was selected for quantitative analysis.

As the aim of our review was to derive a summary hazard ratio (HR) considered to be representative of risk in the general population, studies of cohorts comprising sub-groups defined by pre-existing disease and selected age ranges were excluded. Sub-group analysis was suggestive of increased summary HRs in subjects with pre-existing disease compared to general population samples and in cohorts that selected participants based upon relatively small age ranges compared to broader age ranges – see Working Paper 1 for details.

The study by Bentayeb et al. (2015) does not report any age restriction on cohort members at recruitment. The study was therefore classified as 'adult' rather than 'restricted' in age range and included in the meta-analysis. Subsequent investigation conducted in July 2017 identified a paper related to Bentayeb et al. which indicated the age range of cohort participants was restricted to ages 35-50. The coding for Bentayeb et al. (2015) was changed therefore to reflect this new information and the meta-analysis repeated. Details are given in Working Paper 1. As the coding correction came too late to be reflected in subsequent calculations and, as the change in the random-effects summary HRs was very small, the results from the original analyses of 11, rather than 10, cohorts were retained throughout the report

[1] Results of studies published after these dates have not been included in our review

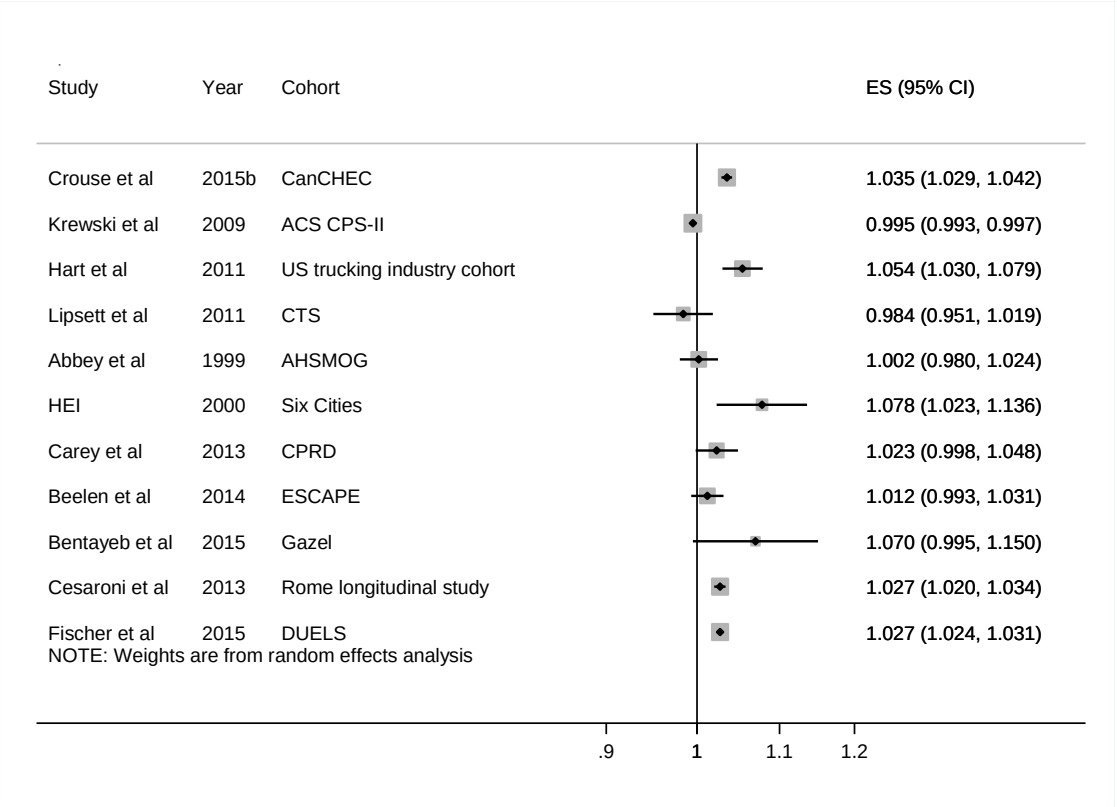


**Figure 2.1 HRs (95% CI) per 10 µg/m³ for cohort studies reporting associations between $NO_2$ and all-cause mortality**

## 2.3 Meta-analysis

### 2.3.1 Results

Eleven cohorts formed the basis of our original meta-analysis (Figure 2.1): (Abbey et al., 1999, Beelen et al., 2014 (the ESCAPE consortium of 22 individual cohorts), Bentayeb et al., 2015, Carey et al., 2013, Cesaroni et al., 2013, Crouse et al., 2015b, Fischer et al., 2015, Hart et al., 2011, HEI, 2000, Krewski et al., 2009, Lipsett et al., 2011).

Meta-analysis of the 11 studies gave a fixed-effects summary HR of 1.010, (95% CI: 1.009, 1.012) per 10 µg/m³ increment in $NO_2$. The corresponding random-effects summary HR was 1.023 (95% CI: 1.008, 1.037) per 10 µg/m³. There was substantial heterogeneity between study estimates, $I^2$=97%. The exclusion of Bentayeb et al. (2015) did not materially alter the random-effects summary estimate [1.021 (95% CI: 1.006, 1.036) per 10µg/m³ based upon 10 studies].

### 2.3.2 Adjustment for individual confounders

Of the 11 studies originally selected for meta-analysis, 4 did not control for individual level smoking and body mass index (BMI), instead adjustment was undertaken at an ecological level or indirectly. To assess the potential impact of the omission of this we stratified the meta-analyses by level of covariate adjustment – i.e. those controlling for smoking and BMI at the

individual level and those that did not. The corresponding HRs differed substantially; 1.011 (95% CI: 0.995, 1.027) vs 1.031 (95%CI: 1.025, 1.037) per 10 μg/m$^3$ respectively. The exclusion of Bentayeb et al. (2015) did not materially alter this finding [Working Paper 1].

Both Cesaroni et al. (2013) and Fisher et al. (2015) note this limitation of their studies. However, the Cesaroni study also presented results from a smaller subset (7845) for which individual smoking measures were available and noted that adjustment for smoking did not alter associations between $NO_2$ and mortality. The authors also adjusted for smoking related comorbidities. Fisher et al. conducted a sensitivity analysis adjusted for regional age-standardised smoking-attributable mortality and noted an attenuation of the association from 1.03 (95% CI: 1.02, 1.03) to 1.02 (95% CI: 1.02, 1.03). A sensitivity analysis using the English cohort (Carey et al., 2013) found that additional adjustment for individual level smoking status and BMI after earlier adjustment for a small area marker of socio economic status attenuated the HRs by a further 15% (personal communication). The sub-groups stratified by level of covariate adjustment could vary by chance, given the small number of studies in each subgroup. Nonetheless, it remains possible that studies which are unable to control for individual confounders may be overstating the size of the association between long-term concentrations of $NO_2$ and all-cause mortality.

The Committee decided to include all the studies rather than restrict the meta-analysis to studies which controlled for individual confounders, because the total number of studies with relevant information is small and the limited evidence from within-study analyses available suggests that any over-estimation of HRs is not great. The Committee recognise that there may be some residual confounding and associated over-estimation of HRs.

### 2.3.3 Small study bias analysis

Small study bias includes publication bias - the publication or non-publication of research findings, depending on the nature and direction of the results (Higgins and Green, 2011). The presence of small study bias in air pollution epidemiology has been noted (Anderson et al., 2005). It can arise from a number of stages in the process of publication of research findings. These include analyst decisions in model selection and the reporting of null results, decisions by study investigators to submit results for peer review and decisions by journal editors to publish study findings.

The likelihood of small study bias in the studies included in our meta-analysis was explored using the Begg test, the Egger test and the Trim & Fill procedure (Begg and Mazumdar, 1994, Egger et al., 1997, Duval and Tweedie, 2000). Neither the Begg nor Egger tests were statistically significant, whereas the Trim and Fill procedure identified some asymmetry suggesting that the imputation of additional results to achieve symmetry was warranted. The degree of adjustment to the summary estimate varied under the different model specifications available within the Trim and Fill technique.

There may be other reasons apart from small study bias for an asymmetrical funnel plot, and the presence or absence of symmetry does not prove the absence or presence of small study bias. It can also be due to heterogeneity between studies, differences in study methodology,

exposure misclassification[1] or chance  There was substantial heterogeneity between the study estimates, $I^2$=97% so the interpretation of the results from the Trim and Fill procedure requires further investigation.

We therefore do not recommend adjustment for small study bias until further understanding of the causes of heterogeneity is available but note the possibility that the unadjusted HR may be subject to some bias as a result (an overestimation of the summary estimate).

### 2.3.4 Summary

We have concluded that there is epidemiological evidence from cohort studies that shows an association between long-term (annual) average concentrations of $NO_2$ and an increase in all-cause mortality.

Meta-analyses of coefficients from single pollutant models from 11 studies (after exclusion of studies on specific age groups) gave a random-effects summary hazard ratio of 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ increment in $NO_2$.

There is substantial heterogeneity between the 11 coefficients selected for meta-analysis. Higher coefficients were obtained from studies with weaker control for individual level confounding factors (although the number of studies available for this analysis was small) and there is a possibility of small study bias. This heterogeneity needs fuller investigation.

The summary coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ $NO_2$ has not been adjusted for $PM_{2.5}$ or $PM_{10}$ or other pollutants. It reflects the combination of: (i) any causal association of $NO_2$, (ii) a component of the effect on mortality of any other air pollutants (including PM) and environmental hazards (for example, noise) with which $NO_2$ is correlated, and (iii) any effect of residual confounding or small study bias.

It is unlikely that most or all of this statistical association represents a causal effect of $NO_2$. The following chapter discusses causality of the association of mortality with long-term average concentrations of $NO_2$ and the independence of the association from PM mass and other pollutants.

[1] Exposure misclassification (measurement error) is explained in Section 3.2.3.1

# Chapter 3
# Issues relevant to the estimation of a coefficient for effect of $NO_2$ alone

## 3.1 The effect of $NO_2$

We have derived a coefficient from a meta-analysis of the results of epidemiological studies that used single pollutant models to investigate the relationship between long-term average concentrations of $NO_2$ and mortality. Such a coefficient does not reflect the effects of $NO_2$ alone: it reflects any effect of $NO_2$ and also, to some extent, the effects of other pollutants with which $NO_2$ is correlated.

Assessing to what extent the association between long-term concentrations of $NO_2$ and mortality may be causal requires consideration of whether:

a the association can be considered causal in terms of effects of a pollution mixture

b it is reasonable to consider that $NO_2$ makes some contribution to the association

c it is reasonable to consider that the entire association can be explained by effects of $NO_2$ itself

COMEAP considered causality for the health effects of $NO_2$ in general for the March 2015 statement (COMEAP, 2015b), relying mainly on assessments by other organisations. Some discussions of certain aspects of the evidence with regard to long-term exposure and mortality have taken place in the process of preparing this report. Evaluations by both REVIHAAP (WHO, 2013a) and the US EPA (US EPA, 2016) were based on literature published up to about 2013. Generally, it is agreed that there is more mechanistic evidence supporting a causal role for particles than for $NO_2$. However, it is worth noting that there is considerable mismatch between the number of research publications on PM compared with those on $NO_2$. Figure 3.1 shows cumulative numbers of papers published on PubMed on "(nitrogen dioxide or $NO_2$)" or "(particulate matter or $PM_{10}$ or $PM_{2.5}$ or black smoke or sulphate or nitrate or secondary particles)" and health. In some ways, a research focus on PM is reasonable, given the evidence on adverse effects of PM. However, it has to be considered that the relative lack of mechanistic evidence for effects of $NO_2$ could be as much about not investigating as about actual evidence for the absence of an effect.

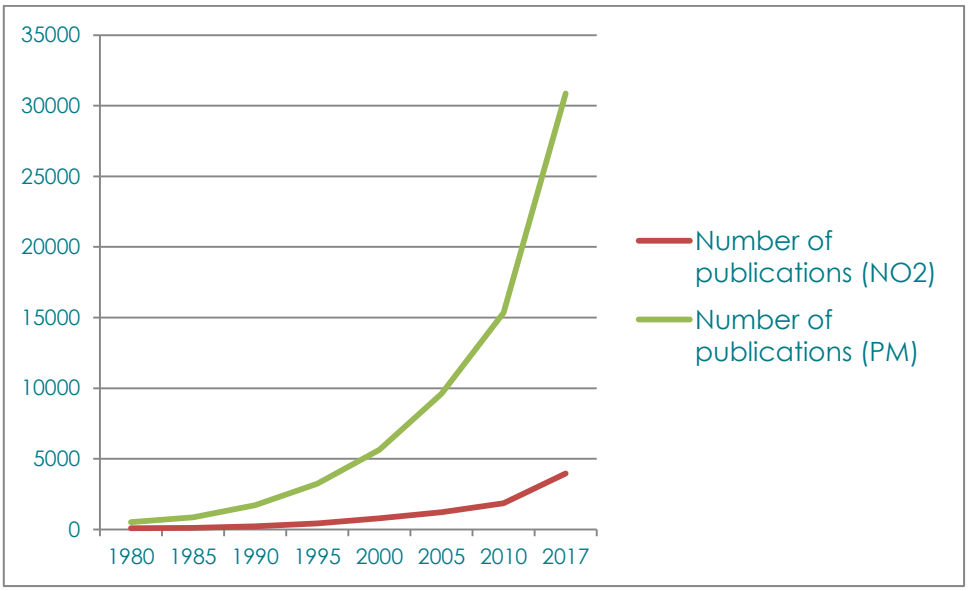


**Figure 3.1 Comparison of cumulative number of publications on PM and $NO_2$**

The following sections consider the main lines of evidence for causality and $NO_2$, which are based on time-series and cohort epidemiological studies, and from animal and human toxicological studies.

### 3.1.1 Evidence from time-series studies of $NO_2$ and mortality

Ecological time-series studies conducted in different parts of the world, including Europe, have identified positive associations between daily variations in ambient concentrations of $NO_2$ and daily mortality from all causes as well as from cardiovascular and respiratory diseases (Anderson et al., 2007, US EPA, 2016, Mills et al., 2015, WHO, 2013a, WHO, 2006). The studies published up to May 2011 were subjected to systematic review and meta-analysis (Mills et al., 2015). Based on 31 (of 84) single- and multi-city studies selected for meta-analysis, the random-effects estimate for all-cause mortality in the all age group was 0.71% (95% CI 0.43, 1.00) per 10 $\mu g/m^3$ increase in 24 hour average $NO_2$. Results for deaths from all cardiovascular and all respiratory diseases were 0.88% (0.63, 1.13) and 1.09% (0.75, 1.42), respectively. Similarly, positive associations with maximum 1 hour average concentrations of the pollutant were observed. For both averaging times, evidence of high heterogeneity between geographical region-specific estimates of $NO_2$ and mortality was identified and unexplained. With the exception of deaths from all respiratory causes, little evidence of small study bias was found for 24 hour $NO_2$ estimates.

The degree of sensitivity of the risk estimates for associations between daily average concentrations of $NO_2$ and mortality to control for the effects of particulate air pollution was also examined by Mills and colleagues (Mills et al., 2016) using the subset of the time-series studies that reported both single- and two-pollutant model estimates of $NO_2$ adjusted for metrics of PM. The majority of the studies used $PM_{10}$ to control for the effects of particulate air pollution. A 10 $\mu g/m^3$ increase in 24 hour $NO_2$ was associated with a 0.92% (0.58, 1. 72) increase in the risk of death from all causes in all ages. This was attenuated somewhat to 0.85% (0.52, 1.18) following control for $PM_{10}$. Control for $PM_{2.5}$ and $PM_{10\text{-}2.5}$ led to increases in the

estimates for $NO_2$ and all-cause mortality: from 0.53% (0.42, 0.64) to 0.57% (0.24, 0.89) after adjustment for $PM_{2.5}$; from 0.62% (0.19, 1.06) to 0.73% (0.28, 1.18) after adjustment for $PM_{10-2.5}$. Robustness of the association between 24 hour average concentrations of $NO_2$ and all-cause mortality to control for PM was observed across the range of temporal correlations between $NO_2$ and PM. No clear relationship could be observed between the reported correlations and changes in the size of $NO_2$-all-cause mortality study estimates after adjustment for PM.

There are a number of difficulties in interpreting multi-pollutant models, particularly if concentrations of pollutants are highly correlated and/or if exposure to one pollutant is less well represented by measurements or modelled estimates of ambient concentrations than another (see section 3.2.3.1). Nonetheless, the large number of time-series studies and the robustness of the $NO_2$ estimates to adjustment for PM across the range of correlations provides some confidence in these conclusions.

Estimates for daily PM and mortality, reported in the time-series studies providing two-pollutant model results for $NO_2$ adjusted for PM, were also reviewed by Mills and colleagues (Mills et al., 2016). These appeared to be sensitive to adjustment for $NO_2$. Meta-analysis yielded a 0.51% (0.29, 0.74) estimate for all-cause mortality per 10 $\mu g/m^3$ increase in 24 hour $PM_{10}$ which was reduced to 0.18% (-0.11, 0.47) after control for 24 hour $NO_2$. The estimate for $PM_{2.5}$ (0.74% (0.34, 1.14)) was less attenuated by control for $NO_2$, though this lost statistical significance (0.54% (-0.25, 1.34).

Similarly, effects estimates linking $NO_2$ with cause-specific (respiratory or cardiovascular) mortality were also robust to adjustment for PM, with greater attenuation seen when coefficients for PM were adjusted for $NO_2$.

Mills et al. (2016) provide evidence of $NO_2$-associations with mortality which remain after control for PM mass. However, the limited data with control for primary combustion particles did not permit the authors to draw conclusions about potential confounding of the $NO_2$ - mortality associations by this component of PM. The issue of potential confounding by traffic-related pollutants therefore remains and requires further investigation.

The US EPA (2016) and (WHO, 2013a) also considered the issue of whether the associations between daily $NO_2$ and mortality reflected effects of exposure to the pollutant itself or to a pollutant mixture / constituent with which $NO_2$ is correlated (US EPA, 2016, WHO, 2013a). Both the US EPA and WHO identified consistent epidemiological evidence of associations between daily $NO_2$ and all-cause mortality which persisted after control for PM-mass (mainly $PM_{10}$) and other co-pollutants, but also noted the lack of studies controlling for traffic-related pollutants.

### 3.1.2 Evidence from toxicological studies investigating the effects of $NO_2$

COMEAP last considered the toxicological evidence in human volunteers and animal studies for long-term exposure to $NO_2$ in 2009 when it looked at the effects of $NO_2$ on respiratory morbidity in children. At that time the Committee felt that the studied concentrations were above ambient levels and that it was difficult to relate the toxicological endpoints with the health effects examined in the epidemiological studies (COMEAP, 2009b).

### *3.1.2.1 Chamber studies of controlled human exposures to $NO_2$*

WHO's REVIHAAP project (WHO, 2013a) acknowledged that chamber studies of controlled human exposures to $NO_2$ have often failed to clearly demonstrate effects at concentrations which occur in ambient air, and to show a clear dose-response. This has contributed to questioning of the plausibility of $NO_2$ being the causal agent of adverse health effects found to be associated with it in environmental epidemiological studies. The REVIHAAP authors noted that, nonetheless, there is evidence of small effects on inflammation and increased airway hyper-responsiveness at $NO_2$ concentration ranges that are not far from those that occur at roadsides or in traffic for multiple hours. It may be that the higher concentrations in these micro-environments induce health effects which are reflected in associations reported in time-series epidemiological studies (as the daily variability at background sites also reflects the daily variability at hot spots.) The REVIHAAP authors also commented that sub-groups of responders were identified in studies of airway hyper-responsiveness and that chamber studies may underestimate the responses of sensitive sub-groups within the population. Their view was that the presence of more sensitive subgroups in the population, together with the higher concentrations at microenvironments, could explain some of the apparent mismatch between human chamber studies and the population-based epidemiology.

In its Integrated Science Assessment, the US EPA (2016) also reports evidence of increased inflammatory responses to allergen challenge in asthmatics and notes that the results of chamber studies indicate that airway responsiveness of individuals with asthma is increased by brief exposure to $NO_2$ at concentrations which are not much higher than peak ambient concentrations.

The US EPA evaluation includes consideration of a review and meta-analysis (Brown, 2015) of chamber studies in which airway responsiveness to a range of inhaled agents (for example, histamine, methacholine, carbachol and allergen) was measured before and after exposures to $NO_2$ in individuals with asthma. The studies were heterogeneous in terms of agent used to provoke an airway response, lung function measure used to assess responsiveness and in dose and duration of $NO_2$ exposure. Overall they suggest that about 70% of people with asthma will become more sensitive to provoking agents following exposure to $NO_2$ at rest. Using information from a subset of 5 studies (72 participants) with relevant data, one quarter of people with asthma would experience a 'clinically relevant' increase in airway responsiveness at exposures between 100 and 500 ppb (188-940 $\mu g/m^3$). Of note, there was no evidence of greater effects in studies that tested higher exposures to $NO_2$. Brown (2015) suggested that this was due to between-study differences and this is supported within the small number of studies that evaluated effects of exposures at rest to increasing $NO_2$ concentrations. Also of note, in this meta-analysis, there was no statistically significant increase in mean response to inhaled allergen after exposure to $NO_2$ when considered across those that did and did not respond.

The US EPA (2016) found little direct evidence from studies of controlled human exposures of effects of $NO_2$ on lung function or respiratory symptoms in asthmatics, or of effects in those with chronic obstructive pulmonary disease (COPD). Evidence of effects in healthy individuals is also limited, with no effects found on respiratory symptoms or lung function, though there is some evidence of airway responsiveness and pulmonary inflammation (US EPA, 2016). Little evidence is available from chamber studies to suggest whether or not there are direct effects of $NO_2$ on the cardiovascular system (US EPA, 2016, WHO, 2013a).

Evidence for the effects of $NO_2$ in human subjects comes from the RAPTES project (Risk of Airborne Particulates: a hybrid Toxicological-Epidemiological Study). In this project, young adult volunteer subjects were exposed for five hours with intermittent exercise in a range of polluted environments while air quality for a wide range of particle components and gases was constantly measured. The effects of exposure were evaluated through a range of tests. These included biomarkers for acute nasal airway inflammation (Steenhof et al., 2013), effects on lung function (Strak et al., 2012), effects on biomarkers in blood (Strak et al., 2013a, Strak et al., 2013b) and effects on circulating white blood cell counts (Steenhof et al., 2014). Statistically significant associations of some effects were found with a number of components or metrics of airborne particulate matter, but the most consistent association throughout all of the effects measured was with short-term exposure to $NO_2$, which showed associations, robust to adjustment for PM metrics, with both respiratory effects (reductions in lung function) and an indicator of cardiovascular risk (thrombin generation) though not with some other acute vascular blood markers (for example, C-reactive protein and fibrinogen). A range of other traffic-generated pollutants including elemental carbon and particle number count were also monitored but showed few consistent associations.

Nonetheless, other studies on human volunteers have suggested that particulate pollution, rather than $NO_2$, is responsible for the reported cardiovascular effects of pollution mixtures. For example, REVIHAAP cites a series of studies by Langrish and co-workers. Langrish et al. (2010, cited in WHO, 2013a) found that exposure of healthy volunteers to 4ppm $NO_2$ for 1 hour did not cause vascular dysfunction (vascular vasomotor or fibrinolytic function). This result contrasted with the group's previous findings using diesel exhaust containing high concentrations of $NO_2$ (Mills et al., 2007, cited in WHO, 2013a). The group subsequently exposed volunteers to diesel exhaust either with or without abatement by a particle trap. Reductions in particle number and mass concentration by the trap were associated with reduced adverse cardiovascular outcomes (vascular and prothrombic effects) (Lucking et al., 2011, cited in WHO, 2013a). This was interpreted as strongly supporting the view that particles, and not $NO_2$, were driving the previously reported cardiovascular effects, especially as $NO_2$ concentrations increased almost five-fold with use of the particle trap.

The evidence examining the possible mechanisms by which air pollutants might affect cardiovascular health, including other studies investigating effects of $NO_2$, has recently been examined in another report by COMEAP (COMEAP, 2018, in press). The report notes that, compared with the literature on particulate matter, there have been few studies examining the potential adverse effects of gaseous pollutants on cardiovascular morbidity. It concludes that the available studies had reported inconsistent findings and did not allow any firm conclusions to be reached.

### *3.1.2.2 Evidence from toxicological studies investigating the effect of $NO_2$*

Toxicological research investigating the effects of $NO_2$ in experimental animal studies have studied endpoints including oxidative stress, inflammation, susceptibility to infection, changes in lung structure, non-specific airway hyper-responsiveness and response to allergen challenge. Sub chronic and chronic exposures (weeks to months) to low levels of $NO_2$ have been shown to have effects, including alterations to lung metabolism, structure and function, inflammation and increased susceptibility to pulmonary infections (Jarvis et al., 2010). The REVIHAAP authors note that some of these effects have been seen at concentrations as low as 0.04 ppm (75 $\mu g/m^3$) up to 0.64 ppm (1200 $\mu g/m^3$)(WHO, 2013a).

The US EPA noted that while there was inconclusive toxicological evidence, there was some biological plausibility for $NO_2$-induced impaired host defence. Some studies demonstrated effects on potential mechanistic events underlying susceptibility to infection. Studies in experimental animals exposed to $NO_2$ for several weeks found nasal eosinophilia and enhanced mast cell responses (US EPA, 2016).

Emphysema-like changes (destruction of alveolar walls and airspace enlargement), features characteristic of human COPD (increased mucus production and progressive airway obstruction), generation of an atopic immune response and airway hyper-responsiveness have been reported in experimental animal studies only at concentrations of $NO_2$ (15 040 – 47 000 $\mu g/m^3$) much greater than ambient concentrations (Jarvis et al., 2010). A study in dogs reported human type emphysema after exposure for 5.5 years to concentrations of $NO_2$ lower than this (0.64ppm, 1 200 $\mu g/m^3$)[1] (Hyde et al., 1978, cited in WHO, 2013a). As this was the lowest concentration tested, it is not clear whether effects would have been observed after exposure to lower concentrations.

A cancer bioassay of exhaust emissions from a modern diesel engine with only low levels of PM emissions, undertaken as part of the Advanced Collaborative Emissions Study (ACES), showed no carcinogenic effects, although lung toxicity consistent with long-term exposure to high doses of $NO_2$ was observed (McDonald et al, 2015). The authors noted that if $NO_2$ was, in part, acting as a marker for other emissions then the cancer effect seen in epidemiological studies could be due to polycyclic aromatic hydrocarbons or metals (Greenbaum et al., 2013). The WHO REVIHAAP project found that in vitro and in vivo genotoxicity tests such as DNA fragmentation and micronucleus assays revealed no or weak evidence of effects (WHO, 2013a). The US EPA identified toxicological studies in tumour-prone rodents or with co-exposure with a known carcinogen, which showed that co-exposure to ambient-relevant $NO_2$ exposures can increase lung tumour incidence but noted no direct carcinogenic effects from $NO_2$ (US EPA, 2016).

Microenvironments of higher concentrations of $NO_2$ exist particularly near busy roads. Exposure to $NO_2$ that is similar to the profile expected for humans may provide more relevant toxicological information. The effects of a low baseline exposure to $NO_2$ with short peaks may be consistent with that experienced in an urban area, increased peak exposures at rush hour for instance. While annual average concentrations of $NO_2$ in the UK (Figure 8.1) are much lower than the concentrations discussed in this section on toxicological evidence, certain microenvironment concentrations can approach the concentrations mentioned.

### 3.1.3 Summary of time-series and toxicological evidence

There is evidence from time-series studies of associations between all-cause mortality and hourly and daily $NO_2$ concentrations. These remain robust to adjustment for PM mass. There are few studies that have controlled for other traffic-related pollutants, so confounding by ultrafine particles, or by other pollutants which are not routinely measured, cannot be ruled out.

[1] Animals were also exposed to NO (25 ppm) at the same time. The effect was thought to be due to $NO_2$, as there was less effect on co-exposure to higher concentrations of NO (REVIHAAP, WHO 2013a).

Animal studies and studies on human volunteers provide some support for the view that short-term exposure to $NO_2$ can cause respiratory effects. This does not mean that effects are necessarily large or affect all individuals. Available studies only explore effects down to the high end of concentrations experienced by some people in some microenvironments. There are few toxicological studies on the cardiovascular effects of $NO_2$, and those available provide at best weak evidence for long-term exposure to $NO_2$ having a causal role in cardiovascular effects.

### 3.1.4 Causality of the associations observed in cohort studies

REVIHAAP concluded that "As there is consistent short-term epidemiological evidence and some mechanistic support for causality, particularly for respiratory outcomes, it is reasonable to infer that $NO_2$ has some direct effects". Its conclusion about cohort studies of long-term exposure was more guarded. Having noted the complications caused by correlated pollutants, it concluded: "Despite this, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations are suggestive of a causal relationship" (WHO, 2013a).

For long-term exposure and respiratory effects, the US EPA considered that the $NO_2$ associations were 'likely to be causal'. This was mainly based on studies of $NO_2$ and asthma development. Although the epidemiological studies did not examine two-pollutant models – the correlations were regarded as too close – the biological plausibility was regarded as strong enough to support the conclusion. REVIHAAP commented that associations with deficits in lung function growth in single-pollutant models noted in the WHO 2005 Global Update of the air quality guidelines had been confirmed even in cities with low concentrations, and there is now evidence for an effect independent of $PM_{10}$ and $PM_{2.5}$ in multipollutant models, at least in a city (Mexico city, (Rojas-Martinez et al., 2007)) with a range of $NO_2$ concentrations at the upper end of the concentration range in Europe. They also highlighted the study of bronchitic symptoms in asthmatics by McConnell et al. (2003) (later recommending this for use in quantification (WHO, 2013b) in Group B). We have earlier (COMEAP, 2015b) noted the evidence showing associations between long-term exposure to $NO_2$ and respiratory mortality, children's respiratory symptoms and lung function, while also noting the close correlation with other pollutants.

For long-term exposure and total mortality the US EPA (US EPA, 2016) considered the evidence 'suggestive but not sufficient to infer a causal relationship'. (The same conclusion was reached for cardiovascular effects.) It was noted that epidemiologic associations were observed in large cohorts in diverse locations followed for long durations up to 26 years. However, it was noted that cardiovascular disease was the leading cause of death and even on the respiratory side, COPD and respiratory infections were important causes of respiratory mortality but asthma was not. In contrast, the mechanistic evidence on $NO_2$ was strongest for asthma. (The animal study evidence on emphysema and respiratory infections was not mentioned in this context).

REVIHAAP (WHO, 2013a) noted that, as with the short-term effects, in the studies of long-term exposure and mortality, $NO_2$ may represent other constituents. They considered that despite this, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence of associations in time-series studies are suggestive of a causal relationship. REVIHAAP's view was that it is much harder to judge the independent effects of $NO_2$ in the long-term studies because the correlations between concentrations of $NO_2$ and other pollutants

are often high. The view was influenced by other long-term exposure studies and lung function and bronchitic symptoms in asthmatics, which included multi-pollutant models suggesting a separate effect of $NO_2$ from some other pollutants (correlations with other pollutants were not always high). Studies on asthma prevalence were also discussed, although the very close correlations with other pollutants in those studies were noted. REVIHAAP also cross-references the table on animal evidence in discussing its conclusion on long-term effects.

It is acknowledged that more research has been undertaken on PM than $NO_2$, meaning that the epidemiological and toxicological evidence to support a role for PM is greater, particularly for cardiovascular outcomes. In addition, there are well-accepted plausible mechanisms of action by which PM is thought to exert adverse effects. Nonetheless, plausible mechanisms for effects of $NO_2$ can also be proposed. The experimental studies on PM used concentrated ambient particles and so, like those on $NO_2$, are not of exposures at ambient concentrations. It is suggested that it is unlikely to be solely one pollutant or the other that causes all the observed effect, but that there is stronger evidence to support causality of PM. More research on $NO_2$ is needed.

## 3.2 Confounding by other pollutants

We have derived a coefficient from a meta-analysis of the results of epidemiological studies that used single pollutant models to investigate the relationship between long-term average concentrations of $NO_2$ and mortality. As discussed in section 3.1, such a coefficient cannot be said to reflect the effects of $NO_2$ alone. It reflects any effect of $NO_2$ and also, to some extent, the effect of other pollutants with which $NO_2$ is correlated. These include $PM_{2.5}$, other fractions of PM, and other components of the air pollution mixture. Thus, such a coefficient is likely to overestimate the effects of $NO_2$ alone.

We do not know the extent of the over-estimation. In principle, the effect of $NO_2$ itself could lie anywhere between 0% and 100% of the effect estimated using the unadjusted coefficient derived in Chapter 2. Where it does lie depends on the causal role of $NO_2$ relative to other components of the air pollution mixture that are correlated with it, but the available evidence and methods do not allow us to come to a quantitative view on this at this stage. The following observations are made:

a The REVIHAAP assessment as summarised above, and COMEAP's own statement of 2015 (COMEAP, 2015a), which supported some causal effect of $NO_2$ itself, underpinned most of the work of the $NO_2$ working group and later Committee discussions.

b However, some Members of the Committee (see "Views of the Dissenting Group" in Chapter 10) are unconvinced that $NO_2$ itself has a causal role in the relationships linking $NO_2$ concentrations with mortality in cohort studies, other than as possibly expressing an aggregate effect of short-term exposure.

c For $NO_2$, the estimated coefficient from time series studies (0.7%, 95% CI 0.43-1.00 per 10 $\mu g/m^3$ increase in 24 hour average $NO_2$, Mills et al., 2015) is closer to that estimated from cohort studies (2.3%) than is the case for $PM_{2.5}$ (1.04%, 95% CI 0.53-1.56 per 10 $\mu g/m^3$ increase in 24 hour average $PM_{2.5}$ (Atkinson et al., 2015) compared with 6% per 10 $\mu g/m^3$ increase in annual average $PM_{2.5}$ (COMEAP 2009a, Hoek et al., 2013)).

d While all available coefficients for $NO_2$ reflect, to some extent, an effect of other pollutants with which $NO_2$ is correlated, use of the unadjusted coefficient includes $PM_{2.5}$ as one of those correlated pollutants.

The extent to which the unadjusted coefficient for $NO_2$ from cohort studies reflects a causal effect of $NO_2$ itself is unknown. However, the majority of Members consider it is unlikely to be close to 0%. Factors taken into account by Members in coming to this view include that

a The evidence from time-series studies indicates an association of short-term exposure to $NO_2$ with mortality, and there is some evidence to suggest causality for these associations. Associations reported in cohort studies likely reflect effects of short-term exposures to some extent.

b The evidence for respiratory effects of $NO_2$

They also consider it to be unlikely to be 100%, because of confounding.

In the following sections, we discuss to what extent associations with PM mass, ozone and noise may affect the reported association of long-term average concentrations of $NO_2$ with all-cause mortality. We were not able to discuss how the associations were affected by other traffic pollutants such as ultrafine particles, black carbon, carbon monoxide or others because there is insufficient evidence available.

### 3.2.1 Possible confounding by ozone

Chemical interactions between oxides of nitrogen and ozone are important. Most $NO_2$ is not directly emitted, but is formed in the atmosphere from oxidation of directly emitted nitric oxide by ozone (equation 1)

$$NO + O_3 \rightarrow NO_2 + O_2 \quad (1)$$

This commonly leads to a negative correlation of $NO_2$ and ozone concentrations. In summer conditions, however, photolysis of $NO_2$ and subsequent chemical reactions can lead to enhanced formation of ozone, and positive correlations may be seen, particularly away from urban centres.

Negative correlations of $NO_2$ and ozone are very frequently observed in urban areas. If both pollutants are harmful, this may tend to obscure the detection of effects of both pollutants in epidemiological studies, as effects of one gas will be greatest when concentrations, and hence effects, of the other are least. Jerrett et al. (2013) argued that it is important to have both ozone and $NO_2$ in regression models that attempt to predict the health effects of either pollutant. Their estimated hazard ratios for $NO_2$ for a Californian cohort were strengthened by inclusion of ozone in their model, but the vast majority of studies have taken no account of possible confounding by ozone.

Of the studies included in the $NO_2$ meta-analysis of the single-pollutant coefficients, five did not report correlation coefficients for ozone in their analyses (Beelen et al., 2014, Cesaroni et al., 2013, Crouse et al., 2015b, Fischer et al., 2015, Hart et al., 2011). One of the studies included ozone and $NO_2$ in their analysis but did not report the correlation between the pollutants (Krewski et al., 2009).

In the studies that investigated the correlations, Bentayeb et al. (2015) and Carey et al. (2013) reported a negative correlation between ozone and $NO_2$ whereas the Lipsett study reported that $NO_2$ was positively correlated with ozone with a coefficient of 0.52 (supplementary data, Lipsett 2011). HEI (2000, Appendix G) reported Pearson correlation coefficients of around 11%. Abbey et al. also reported a positive correlation of 0.36 when ozone (mean concentration, 26.1 ppb (51.2 μg/m3)) was compared to the mean concentration of $NO_2$, 36.8 ppb (69.2 $\mu g/m_3$) [1] , and a correlation of 0.4 when $NO_2$ was compared to ozone concentrations above 100 ppb (196 $\mu g/m_3$) (Abbey et al., 1999).

Due to the different correlations reported in the studies included in the meta-analysis it is difficult to indicate how the summary estimate could be affected by ozone. Crouse et al. (2015a) report results from three-pollutant modelling of $NO_2$, $PM_{2.5}$ and ozone; results from this study are used later (Chapter 4) when considering available coefficients from multi-pollutant models.

When $NO_x$ emissions are reduced, ozone concentrations can increase (close to source) due to reduced removal of ozone by reaction with NO. We discussed whether the adverse health effects associated with this increase in ozone concentrations should be included in an assessment of the impacts of reducing $NO_x$ emissions. We noted that, as ozone is often negatively correlated with $NO_2$, $NO_2$ coefficients from models that do not include ozone may underestimate the effect associated with $NO_2$. Therefore, as our recommendation for the assessment of the benefits of $NO_2$ reduction will not use a $NO_2$ coefficient derived from an ozone-adjusted model, it is likely that the health benefits of interventions could be underestimated. To a certain extent, this underestimation will be offset by the omission of the counteracting adverse health impacts of increases in ozone concentrations, although there is no guarantee that the underestimation and the omission will be of similar size. Also, a further complication would be the additional requirement for ozone modelling, which would require knowledge of how much $NO_2$ is primary (emitted as $NO_2$) and how much is secondary (formed in the atmosphere by reactions). This area requires considerably more thought and investigation.

### 3.2.2 Possible confounding by noise

Question C1 of the REVIHAAP report addressed the health effects of proximity to roads and indicated that noise was a confounder in studies of the effects of air pollutants emitted by traffic. However, it was noted that associations remain after adjustment for noise, and the REVIHAAP authors concluded that the epidemiological studies show effects of air pollution that cannot be explained by noise (WHO, 2013a).

Nonetheless, noise could be a confounder in studies on $NO_2$, if appropriate adjustment is not undertaken. Two of the 11 studies included in the meta-analysis acknowledged that noise could be a confounder (Krewski et al., 2009, HEI, 2000) but none of the studies adjusted for noise, so it is not possible for us to quantify the likely size of the confounding effect by noise. We note that the size of this confounding effect might be important when considering quantification, as it is possible that estimates of effects associated with $NO_2$ that are not

[1] Conversion factor of 1ppb= 1.96 $\mu g/m^3$ assuming 25ºC and 1013mb atmospheric pressure).

adjusted for noise may over-estimate the effects associated with $NO_2$ and/or traffic-related pollutants to some extent.

### 3.2.3 Independence from associations with PM mass

We know that the annual average concentrations of $NO_2$ are correlated with those of particles and that, therefore, associations with $NO_2$ likely reflect some effect of particles. The problem is made more difficult by the possibility that levels of $NO_2$ might affect the response to particles and, perhaps, vice versa (i.e. an interaction between the pollutants). Furthermore, concentrations of $NO_2$ may well be more closely correlated with concentrations of sub-fractions of $PM_{2.5}$ than with $PM_{2.5}$ alone. Another consideration is that the extent of exposure misclassification may differ between $NO_2$ and $PM_{2.5}$ or sub-fractions of $PM_{2.5}$ (see section 3.2.3.1 below).

Given this correlation, single pollutant models based on $NO_2$ will over-estimate the associations with $NO_2$ because they will, to some extent, reflect the effects of PM mass. Similarly, single-pollutant models based on PM will over-estimate the associations with PM as they are likely, to some extent, to reflect the effects of $NO_2$ or other closely correlated pollutants.

#### *3.2.3.1 Two pollutant models*

Two-pollutant models use statistical techniques to try to separate the effects of different pollutants. In a two-pollutant model, the relationship between the health effect and the pollutant of interest (for example, $NO_2$) is estimated with the influence of the other pollutant (for example, $PM_{2.5}$) held constant.

##### *Two-pollutant model – challenges in interpretation*

Assessment of $NO_2$ and PM simultaneously in a two-pollutant model is not straightforward. Each pollutant will have different amounts of exposure misclassification. Exposure misclassification in this context refers to differences between the exposure metrics used in the epidemiological study and the 'true' exposures of the population at risk. This includes differences between the 'true' concentrations and the measurements and/or modelled values used when estimating risks, and differences between concentrations and personal exposures. There is often correlation between pollutant concentrations, and the extent to which exposures are misclassified (for each pollutant) can also be correlated; relationships are often complex (Bateson et al., 2007; Kim et al., 2007; Dionisio et al., 2014; Butland et al., 2013).

Of particular relevance is the 'transfer of effect' which may occur when two pollutants are highly correlated and where one is measured or modelled with more error than the other. In certain situations, some of the effect of the pollutant measured with more error may be 'transferred' to the other, leading to biased estimates of the effects of both pollutants (Zidek et al., 1996; Fung and Krewski, 1999; Zeger et al., 2000). For a transfer of effect to be large there would need to be strong correlations between the exposures ($NO_2$ and PM) and/or the magnitude of any exposure misclassification (measurement errors). From our current knowledge we believe that transfer of effect may well occur but without detailed knowledge of the correlations between the exposures ($NO_2$ and PM) or the mechanisms for any associated exposure misclassification, it is not clear in which direction this might occur nor are we able to estimate the extent of such a transference.

The statistical issues can be summarised as:

a Lack of interaction term. Where models do not include an interaction term (between $NO_2$ and PM) there is an implicit assumption that the effect of $NO_2$ (and thus the size of the coefficient) does not vary when concentrations of PM are low or high, and vice versa. It is unclear as to whether this is a tenable assumption in the studies considered here: the relevant studies did not report results of any tests for interaction.

b Multi-collinearity. High correlation between pollutants (arising due to common sources and meteorological conditions), can lead to unstable parameter estimation. This problem can be reduced by focusing on studies where correlation (between PM and $NO_2$) is not high.

c Transfer of effect: Differing levels of misclassification when estimating exposures to pollutants, together with high correlation between the pollutants and/or the magnitude of any misclassification in exposures, can lead to effects apparently being 'transferred' from one pollutant to another. We know from simulation studies that the effects of pollutants for which estimated exposures represents actual exposures less well, even if the relationship is causal, may 'transfer' to a pollutant for which the estimated exposures more accurately represents actual exposure, even if the relationship with the latter pollutant isn't causal.

d Overlapping confidence intervals. The confidence intervals for $NO_2$ (adjusted for PM) overlap substantially with those (unadjusted) from the single pollutant models meaning that there is no information on whether any change in HRs on adjustment is statistically significant. One interpretation of this would be that adjustment for PM has no effect on the $NO_2$ coefficient, however none of the Committee proposed this interpretation.

These issues need to be borne in mind when reading the descriptions of the two-pollutant model results in the section below.

It should be noted that the use of adjusted coefficients *per se* should not necessarily be a cause for concern when quantifying the health effects associated with a particular risk factor. Whether arising from time series studies, panel studies or cohort studies, all the coefficients that are used in quantifying the effects of air pollution will have been adjusted for potential confounding factors. In cohort studies for example, the risks of (increases in) air pollution will be have been estimated allowing for both characteristics of the individuals within the study (eg age, gender, ethnicity, smoking habit, occupation) and of the locations (eg cities) in which they reside.

In the discussion in this report, 'adjusted coefficients' refers not to adjustment for this broad variety of potential confounding variables but to the specific cases where PM and $NO_2$ are both included in the analysis (eg a multi-variable regression model) when estimating risks. In this case, the coefficient for PM will be 'adjusted' for $NO_2$, and *vice versa*. Using adjusted coefficients in this setting can lead to specific issues including those related to the high correlations that are often encountered between pollutants (relative to those that might be expected with other potential confounders, eg lifestyle characteristics).

Within the Committee as a whole, there was no disagreement on the principle of using 'adjusted coefficients' (in terms of those arising from analyses that included both PM and $NO_2$), conditional on there being sufficient confidence in those coefficients. However, there was disagreement about the extent to which the adjusted coefficients that are available could be considered to be informative and suitable for use in quantifying health effects, given the methodological issues outlined above.

### *Two-pollutant model results*

For this report we considered the studies identified in the systematic review that had also reported results from two pollutant models for $NO_2$ and PM mass, to explore the extent to which the $NO_2$ association is reduced in two-pollutant models. This includes studies identified in the review but not necessarily included in the single pollutant meta-analysis. Details of the studies are presented in Working Papers 2 and 3.

Of these studies, only six reported results for all-cause mortality from both single- and two-pollutant models (Cesaroni et al., 2013, Carey et al., 2013, Beelen et al., 2014, Fischer et al., 2015, HEI 2000 and Jerrett et al., 2013). The HRs from the single- and two-pollutant models for $NO_2$ and PM mass, in the cohorts reporting both, are shown in Table 3.1. Five of the studies used $PM_{2.5}$ as the particle metric and one used $PM_{10}$ (Fischer et al., 2015). None of the cohorts assessed the independence of $NO_2$ from traffic-related particles (ultrafine, elemental carbon etc.). One of the studies from the review of single pollutant models for $NO_2$ reported on a subset of a large cohort (Crouse et al., 2015b). Another paper by the same authors reports results for the whole cohort for three-pollutant models including $NO_2$, $PM_{2.5}$ and $O_3$ (Crouse et al., 2015a) and this is also included in the table and informed our discussions.

Correlations between the $NO_2$ and $PM_{2.5}$ exposure metrics (Table 3.1) were very high in two studies; with correlation coefficients of 0.79 in the Cesaroni et al. (2013) and 0.85 in the Carey et al. (2013) studies. Correlation was less high in three studies (0.2-0.7, Beelen et al., 2014, 0.55, Jerrett et al., 2013, 0.40 Crouse et al., 2015a) and weak in one -0.08 (HEI, 2000). In the Fischer study, which used $PM_{10}$ rather than $PM_{2.5}$, the correlation with $NO_2$ was 0.58 (Fischer et al., 2015).

To address the problem of confounding by correlated pollutants, two pollutant models can be used to derive coefficients for $NO_2$ which are adjusted for the effects of PM mass and vice versa. In principle such models should provide a better estimate of the effects associated with the pollutants individually, than single pollutant models. However, as discussed above, problems can arise with two-pollutant models in some situations, especially (but not only) if the correlations between pollutants are very high.

Generally, the adjusted coefficients (i.e. the $NO_2$ coefficients adjusted for PM, and the PM coefficients adjusted for $NO_2$) reported in these studies are lower than the unadjusted ones. This is what would be expected with positively correlated co-pollutants. The extent of change following adjustment is summarised in Table 3.1, for $NO_2$ and for PM respectively, in the two columns identified as "%". It shows that the pattern of reduction varied between studies and between pollutants.

For the four cohorts with moderate correlation, both the $NO_2$ and PM adjusted coefficients were moderately reduced. Apart from Beelen et al. (2014) the percentage reduction of the PM coefficient on adjustment for $NO_2$ was more marked than that of the $NO_2$ coefficient after

adjustment for PM. In the two high-correlation cohorts, mutual adjustment left one coefficient more-or-less unchanged while practically removing any evidence of association with the other pollutant – and the studies differed in terms of which pollutant was unchanged. While not proven to be occurring, marked effect transfer (as described in section 3.2.3.1) is more likely when the pollutants are highly correlated.

Results from the ACS cohort (HEI et al., 2000), where the crude correlation between annual average $NO_2$ and $PM_{2.5}$ was very low and almost zero, were perhaps the most surprising. In single-pollutant models there was a clear and statistically significant association between $PM_{2.5}$ and all-cause mortality, but the single-pollutant coefficient for $NO_2$ was negative and statistically significant (see Figure 3.2). It is clear that something unusual is happening in this analysis, which may be due to residual confounders. It may be relevant that this is the only study of the six with an exposure metric based only on averaging monitoring site concentrations within a city and comparing cities. Using two-pollutant modelling accentuated this unusual result, with the coefficient for $PM_{2.5}$ (adjusted for $NO_2$) now higher, whereas the coefficient for $NO_2$, adjusted for $PM_{2.5}$, was more clearly negative. These unusual results were however not reproduced in a later of the series of papers from the ACS study (Turner et al., 2015), which was published too late for inclusion in the present analysis.

One approach to determining whether there are independent associations with the two pollutants is to combine the hazard ratios per interquartile range from each of the two-pollutant models ($NO_2$ adjusted for $PM_{2.5}$ and $PM_{2.5}$ adjusted for $NO_2$) within each study. Because analysis is on the log scale, and the individual HRs are estimated per inter-quartile range of the relevant pollutant in that study, combining the HRs across pollutants indicates the size of effect of the mixture as a whole. Particularly if effect transfer is occurring, the estimated effect of the mixture as a whole is likely to be more accurate than that estimated for the individual components. If this total is greater than either single pollutant model result alone, it suggests that there is not complete overlap between single-pollutant associations with the pollutants. Table 3.1 and Figure 3.2 shows the sum of the HRs for the mutually adjusted coefficients (ie $NO_2$ adjusted for PM and PM adjusted for $NO_2$).

In the first four studies of Table 3.1 the combined HRs were similar to the larger of the $NO_2$ or PM single pollutant HRs, though whether the $NO_2$ or PM single-pollutant coefficient was larger varied by study. In a fifth study, Jerrett et al. (2013), the combined $NO_2$ and $PM_{2.5}$ HR was larger than both single pollutant model HRs and in another (the HEI study with unusual results) the combined HR lay between the two single pollutant HRs. The aggregate results are not presented for the final, seventh, cohort because this reported coefficients from multi-, rather than two-, pollutant models. The combined HRs provide more stable and reliable estimates of the associations between exposure to the two correlated pollutants and all-cause mortality (notwithstanding the lack of interaction terms) than do the single-pollutant estimates.

The uncertainty in the interpretation of the multi-pollutant models should be borne in mind but these studies suggest the need to take into account the likely overlap of effects represented by coefficients for the association of mortality with long-term average concentrations of $NO_2$ and PM that are derived from single-pollutant models. This is needed to avoid over-estimation of effects associated with $NO_2$ concentrations and the pollutant mixture as a whole. Also, as noted earlier, there is overlap of $NO_2$ with other, unmeasured, pollutants which cannot be adjusted for because they are unmeasured.

**Table 3.1 Hazard ratios (HRs) from single and two/multi pollutant models for $NO_2$ and $PM_{2.5}/PM_{10}$ (HRs are expressed per IQR[1])**

| Study | Cohort | Correlation $NO_2/PM_{2.5}$ exposure metrics | $NO_2$ IQR (µg/m³) | $NO_2$ | $NO_2$ adjusted for $PM_{2.5}$/ $PM_{10}$ | %[2] | $PM_{2.5}$/ $PM_{10}$ IQR (µg/m³) | $PM_{2.5}$/ $PM_{10}$ | $PM_{2.5}$/ $PM_{10}$ Adjusted for $NO_2$ | %[2] | Combined $NO_2$ adj/ PM adj HR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cesaroni et al. (2013) | Rome | 0.79 | 10.7 | 1.029 (1.022, 1.036) | 1.026 (1.015, 1.037) | 10 | 5.7 | 1.023 (1.016, 1.031) | 1.004 (0.994, 1.015) | 82 | 1.030 |
| Carey et al. (2013)[3] | CPRD | 0.85 | 10.7 | 1.022 (0.995, 1.049) | 1.001 0.959, 1.044) | 95 | 1.9 | 1.023 (1.000, 1.046) | 1.023 (0.989, 1.060) | 0 | 1.024 |
| Beelen et al. (2014)[4] | ESCAPE | 0.2-<0.7 | 10.0 | 1.015 (0.993, 1.036) | 1.007 (0.967, 1.049) | 53 | 5.0 | 1.070 (1.016, 1.127) | 1.060 (0.977, 1.150) | 14 | 1.067 |
| Fischer et al. (2015)[5] | DUELS | 0.58 | 10.0 | 1.027 (1.023, 1.030) | 1.019 (1.015,1.023) | 29 | 2.4 | 1.019 (1.016, 1.022) | 1.010 (1.007, 1.013) | 46 | 1.029 |
| HEI (2000)[6] | ACS CPS II | -0.08 | 81.4 | 0.95 (0.89, 1.01) | 0.90 (0.84, 0.96) | 105 | 24.5 | 1.15 (1.05, 1.25) | 1.22 (1.11, 1.33) | -42 | 1.09 |
| Jerrett et al. (2013) | ACS CPS II | 0.55 | 7.7 | 1.031 (1.008, 1.056) | 1.025 (0.997, 1.054) | 19 | 5.3 | 1.032 (1.002, 1.062) | 1.015 (0.980, 1.050) | 53 | 1.040 |
| Crouse et al. (2015a)[7] | CanCHEC | 0.40 | 15.2 | 1.052 (1.045,1.059) | 1.045 (1.037, 1.052) | 13 | 5 | 1.035 (1.013,1.049) | 1.011 (1.003,1.020) | 68 | |

1 Except for Crouse et al. (2015a), which used per mean minus 5th percentile rather than IQR, and Beelen et al. (2014), which used per 10 µg/m³ $NO_2$ and 5 µg/m³ $PM_{2.5}$

2. The percentage reduction in HR after adjustment for the other pollutant

3. $PM_{2.5}$ results –personal communication

4. Based on 14 cohorts in which correlation between $NO_2$ and $PM_{2.5}$ was less than 0.7 (figures to 3 decimal places provided by personal communication)

5 $PM_{10}$

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

7 $NO_2$ adjusted for $PM_{2.5}$ and $O_3$. $PM_{2.5}$ adjusted for $NO_2$ and $O_3$ .

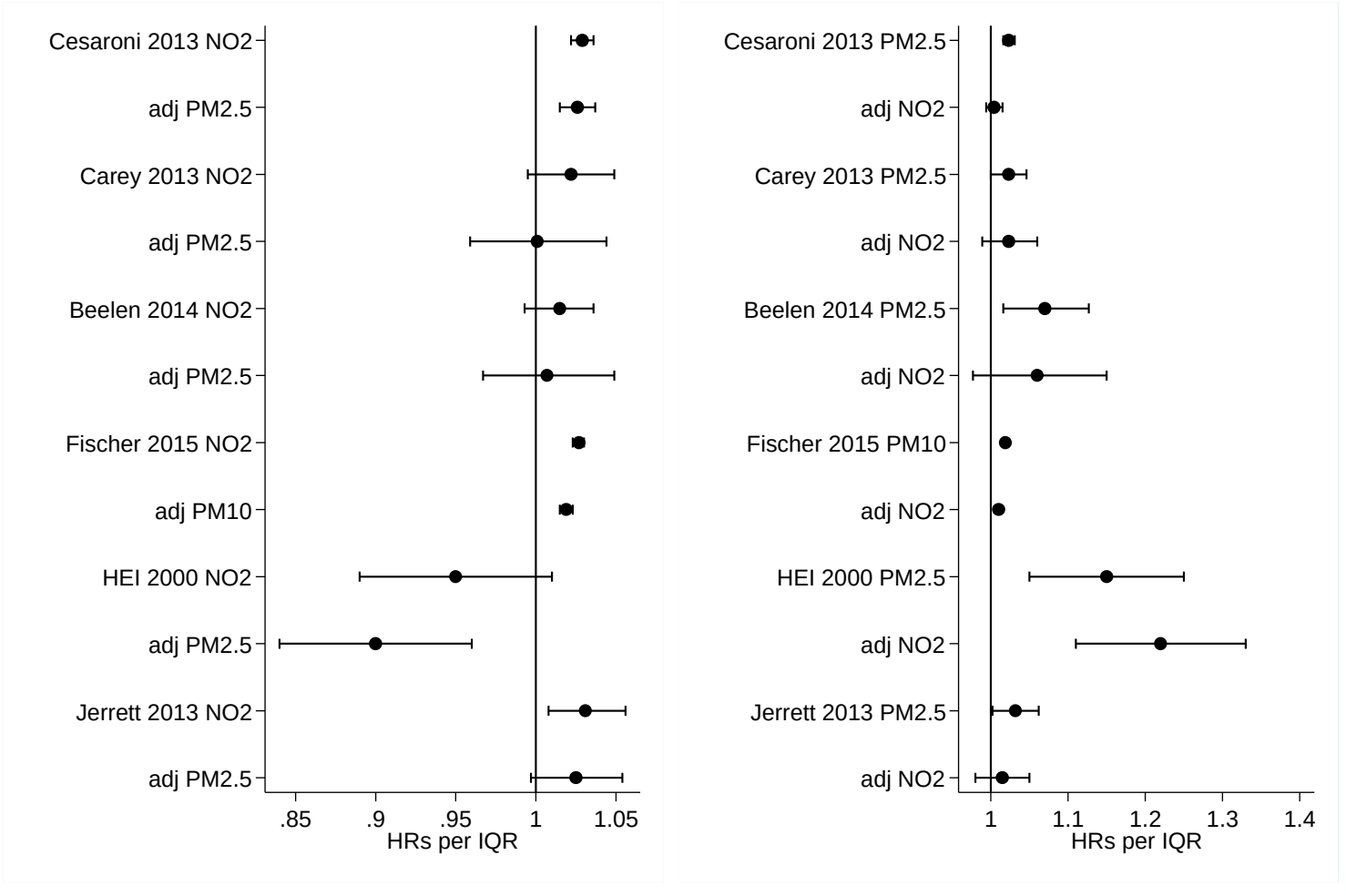


**Figure 3.2: Hazard ratios from single and two pollutant models for $NO_2$ and $PM_{2.5}$ or $PM_{10}$ (HRs are expressed per IQR). A: $NO_2$ coefficients from each study unadjusted and adjusted for PM and B: PM coefficients unadjusted and adjusted for $NO_2$**

Across the six studies, the combination of the adjusted coefficients is in general a little, but only a little, higher than the greater of the two estimated unadjusted coefficients. However, whether the 'greater of the two unadjusted coefficients' relates to unadjusted $NO_2$ or unadjusted PM varied by study.

## 3.3 Summary

In the few studies which report coefficients from both single- and two-pollutant models, the associations of mortality with $NO_2$ concentrations are fairly robust to adjustment for effects associated with PM concentrations. Although coefficients were reduced by adjustment for PM, associations remained and statistical significance was often retained.

Available two-pollutant models for $NO_2$ and PM suggested there is likely to be some association with long-term average concentrations of $NO_2$ that is independent of the association with PM mass and vice versa

Few studies have examined possible confounding by ozone or noise or other pollutants. We note that the correlation between $NO_2$ and ozone can be negative, implying that adjustment for ozone might increase the estimated $NO_2$ coefficient.

A possible interpretation of an unadjusted coefficient for $NO_2$ is that it reflects any causal effect of $NO_2$ and also, to some extent, the effects of other pollutants with which $NO_2$ is correlated. These include $PM_{2.5}$, other fractions of PM, and other components of the air pollution mixture (eg ultrafine particles, Black Carbon, Volatile Organic Compounds etc.).

A coefficient for $NO_2$ adjusted for $PM_{2.5}$ is likely to reflect any effect of $NO_2$ and also, to some extent, other pollutants with which $NO_2$ is closely correlated but it would exclude (as far as possible) effects associated with $PM_{2.5}$ concentrations and other components of the air pollution mixture that are more closely correlated with $PM_{2.5}$ concentrations than with $NO_2$ concentrations. Nonetheless, the possibility of residual confounding, effect transfer etc. need to be borne in mind when interpreting adjusted coefficients.

Using a single pollutant coefficient for $NO_2$ and a single-pollutant coefficient for $PM_{2.5}$ and adding the results, would overestimate the combined effects associated with the two pollutants

As noted in our interim statement (COMEAP, 2015a): "….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."

There are some difficulties in interpreting the results of the coefficients reported from two-pollutant models. When the correlation between the pollutants is high, results from two-pollutant models may be subject to biases that arise from exposure misclassification, meaning that associations may, to some extent, be ascribed to the wrong pollutant (effect transfer). Our conclusions from two-pollutant models have been based on studies with correlations less than 0.7.

A related difficulty is the uncertainty in transferring, for use in the UK, the results of cohort studies in particular locations, with specific correlation structures between $NO_2$, $PM_{2.5}$, other pollutants and other non-pollutant explanatory variables, to other contexts with presumably different pollution mixtures and also a different mixture of non-pollution factors. These difficulties of transferability are exacerbated if quantification involves estimating effects on mortality at pollutant concentrations outside the range of those studied in the original underlying cohorts.

While the full Committee recognised the importance of these considerations, both in determining a coefficient for the effects of $NO_2$ alone, and in quantification of the public health impact of $NO_2$, it was divided as to the validity of approaches to resolution of the problems posed.

Nonetheless, the results of two-pollutant models suggest that there are effects on mortality associated with long-term average concentrations of $NO_2$ which may be independent from the associations of mortality with PM mass. This view is strengthened by consistent epidemiological evidence in time-series studies of positive associations between daily concentrations of $NO_2$ and mortality, which are generally robust after control for PM-mass (mainly $PM_{10}$) although it is relevant to note that there is a lack of control for other traffic-related pollutants (Mills et al., 2015, US EPA, 2016, WHO, 2013a). WHO (2013a) noted that evidence from epidemiological studies of populations living near busy roads, where effects that vary with distance from the road cannot be explained by varying $PM_{2.5}$ concentrations, also strengthen this view.

The majority of the Committee therefore thought it appropriate to proceed further and consider how to summarise the possible extent of overestimation, in single pollutant models, of the effect associated with $NO_2$. These considerations drew on the four informative cohort studies which reported coefficients from two- or multi-pollutant models and in which concentrations of $NO_2$ and PM were not highly correlated (correlation $< 0.7$).

# Chapter 4
# Estimating a coefficient for effects of $NO_2$

## 4.1 Previous approaches to adjusting the $NO_2$ coefficient for PM

The HRAPIE authors suggested that, because of the correlation between $NO_2$ and PM, the effects of $NO_2$ might be overestimated by approximately a third of the true value, if coefficients from single-pollutant models were used to quantify the association between long-term average concentrations of $NO_2$ and health outcomes (WHO, 2013b). This was based on a comparison of coefficients from single- and two-pollutant models in a small number of studies, in which the maximum reduction in the association for $NO_2$ on adjustment for $PM_{2.5}$ was 33%.

Based on this, in our interim statement we advised that, when included in an assessment which also includes assessment of health impacts on the basis of $PM_{2.5}$, a reduction of the recommended coefficient by up to 33% is proposed to take account of possible overestimation due to double counting of effects associated with PM (COMEAP, 2015a). We explained that we were discussing possible methods to refine the approach to account for overestimation of the reported associations with $NO_2$. Methods considered are discussed below.

## 4.2 Meta-analyses of the single and two pollutant model derived coefficients

One approach could be to recommend a coefficient derived from a meta-analysis of two pollutant models instead of using the summary estimate from the meta-analysis of the results of studies using single-pollutant models. However, the statistical uncertainties described in section 3.2.3.1 were noted. In addition, there were only 6 studies with two-pollutant models (fewer than those using single pollutant models) and only 4 informative studies reporting results from two- or multi-pollutant models in which correlation between concentrations of $NO_2$ and PM was not high.

In the presence of more detailed information on the covariance of the coefficients from the two-pollutant models for each study, it would be possible to put bounds of uncertainty around the coefficients, rather than regarding them as point estimates, and to consider the extent of any overlap. However, the information required to do this was not available and, in addition, there are big differences in the power of the studies which needs careful consideration with regard to meta-analysis.

These factors suggest it would be unwise to rely solely on the two-pollutant model evidence and that it would be preferable to utilise the information from the single-pollutant studies as fully as possible. This will require a methodology for adjusting the coefficient associated with the effects of PM concentrations from the single-pollutant meta-analysis.

One possible approach considered was to undertake separate meta-analyses of the single- and two-pollutant coefficients from the chosen studies, and to calculate the ratio of the resulting summary estimates, weighted appropriately to reflect the uncertainty in the coefficients from individual studies. However, there were reservations about the appropriateness of applying the results of meta-analyses in this way, due to the implicit assumption that the coefficients (for single- and multi-pollutant models) arising from each study are independent, and the lack of a clear approach to allow an estimate of uncertainty associated with the ratio to be obtained.

Alternatively, the estimated reduction could be based on the ratios of coefficients from the single- and two-pollutant models within each study. This approach would avoid aggregating adjusted coefficients, but it is not clear how the individual ratios should be combined to derive an overall percentage reduction factor and associated measure of uncertainty. Indeed, while there are well-established methods for meta-analysis of single-pollutant coefficients, we do not know of any established template for this kind of adjustment for use with the two-pollutant models.

For these and other reasons, eg the statistical issues discussed in Section 3.2.3 the Committee does not advise using a coefficient derived using formal methods, such as from a meta-analysis of two pollutant models. These statistical issues also lead to uncertainties in using information from two pollutant models more generally. Even among the majority, there were differences of opinion as to whether these uncertainties are likely to be substantial.

## 4.3 Percentage reduction from an individual study

The Committee discussed using a % reduction from a particular study as a means of adjusting the single-pollutant coefficient for the effects associated with PM concentrations. COMEAP (2009a) had based its risk coefficient for mortality and long-term exposure to $PM_{2.5}$ on the results of Pope et al. (2002), despite results also being available from other cohorts. The study considered was Fischer et al. (2015) which had a dominant influence on a limited earlier attempt at meta-analysis of % reduction across six of the seven studies of Table 3.1 (though this attempted meta-analysis was of questionable validity – see above). However, and in contrast to Pope et al. (2002), there are significant methodological limitations to Fischer et al. (2015). (eg $PM_{10}$ was used rather than $PM_{2.5}$; limited adjustment was made for confounding factors).

Approaches that would take into account more than just one of the % reductions from the two-pollutant studies were then considered. Carrying out a meta-analysis of the % reductions derived from the two-pollutant studies was ruled out based on the discussion above. A reduction could perhaps be derived from an informal 'typical' percentage reduction in hazard ratio from the two pollutant model studies in which correlation between PM and $NO_2$ concentrations was not too high. This would need to recognise that this would only be an approximation.

The Committee deliberated over the confidence which could be placed on this approach. The statistical issue of how reliably, with what degree of uncertainty, the effect of the mixture can be partitioned into (i) something associated with PM mass but uncorrelated with $NO_2$ (PM coefficient adjusted for $NO_2$) and (ii) something associated with $NO_2$ but uncorrelated with PM mass ($NO_2$ coefficient adjusted for PM) is challenging.

## 4.4 Expert judgement approach

The Committee agreed that, even if the coefficient was adjusted to allow for double counting of the effects more closely associated with concentrations of $PM_{2.5}$, further adjustment would be needed to attempt to account for confounding by other correlated pollutants in order to express quantitatively the role of $NO_2$ itself. It was not possible to derive this numerically, in a formal way. Indeed, this may never be possible to do directly from epidemiological studies, given the close correlations between $NO_2$ and other traffic-related pollutants and the lack of studies of the effects of these other pollutants.

The Committee considered that the only way to do this was to use expert judgement inferring possible values indirectly from other evidence. Even this was difficult, given the sparsity of available toxicological evidence on $NO_2$. The different and uncertain nature of the derivation of these suggested values compared with, say, the meta-analysis used to derive the single pollutant summary estimate should be acknowledged and noted when the coefficients approximated in this way are used.

We therefore decided to recommend use of the summary estimate from a meta-analysis of coefficients from single pollutant models but used expert judgement to reduce this coefficient to account for confounding by both PM mass (in the light of the results of the two pollutant models) and for the possible effects of other pollutants which correlate more strongly with $NO_2$ than PM. The majority view of the Committee is to recommend use of 25-55% of the unadjusted coefficient 1.023 per 10 $\mu g/m^3$ annual average $NO_2$. This yields reduced coefficients of 1.006 per 10 $\mu g/m^3$ annual average $NO_2$ and 1.013 per 10 $\mu g/m^3$ annual average $NO_2$ respectively.

This percentage was derived by reducing the unadjusted coefficient by 20% to adjust for effects associated with $PM_{2.5}$ concentrations, based upon the results of multi-pollutant models. We considered this to be an informal representative value, obtained by considering the distribution of values of % reduction in, and other characteristics of, the studies listed in Table 5.1.[13] This is not ideal as the studies varied in size, giving some more power than others, but as we were in any case moving to a much more approximate approach, given the uncertainties, and formal meta-analysis was not possible, it was considered acceptable to take this simpler approach. The range should be considered as well as the average, in transmitting information into policy analysis. In the judgement of Committee Members, 30-70% of this adjusted coefficient could

[13] At the time of our discussions, the single- and two-pollutant coefficients reported by Beelen et al. (2014) from the 14 cohorts in which correlation was <0.7 were only available to us to 2 decimal places as published: unadjusted HR 1.01 (0.99-1.04) per 10 $\mu g/m^3$ annual average $NO_2$; HR adjusted for $PM_{2.5}$ 1.01 (0.97-1.05). Tables 3.1 and 5.1 include these coefficients reported to 3 decimal places (subsequently kindly provided to us by the study authors). These indicate a larger reduction on adjustment for $PM_{2.5}$ than is suggested by the published coefficients.

be suggested as being be caused by $NO_2$ itself, rather than other correlated (eg co-emitted) pollutants. This reflects the fact that, even after adjusting for PM, a coefficient may represent effects caused by other correlated (eg co-emitted) pollutants as well as $NO_2$ itself. The lower bound is to take into account possibilities such as $NO_2$ affecting respiratory, but not cardiovascular, mortality (respiratory deaths are less common) and the aggregate of short-term effects suggested by the time-series evidence. The upper bound took into account factors such as the possibility that adjustment for $PM_{2.5}$ adjusted well for primary PM from traffic. (This would not always be the case depending on actual correlations between $NO_2$ and PM components for particular study designs and locations).

It was noted that this range for the reduced coefficient would not take into account other uncertainties, such as those reflected in the confidence interval around the unadjusted coefficient (1.023 per 10 μg/m$^3$ annual average $NO_2$ with a 95% confidence interval of 1.008 to 1.037).

## 4.5 Summary

We wished to adjust the summary single-pollutant coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ annual average $NO_2$ for effects associated with other pollutants. However, there are no validated statistical approaches for adjusting a summary effects estimate obtained by meta-analysis of unadjusted single-pollutant coefficients.

The view of the majority of the Committee is, therefore, that application of expert judgement is currently the best available approach for deriving a coefficient linking mortality with long-term exposure to $NO_2$ and, despite its limitations, is good enough to be used for quantification provided the uncertainties are noted.

Consequently, we have applied the judgement of Committee Members to reduce the summary coefficient obtained from meta-analysis of coefficients from single-pollutant models to derive a coefficient intended to represent mortality associated with long-term exposure to $NO_2$ itself. We recommend use of 25-55% (mid-point of range 40%) of the unadjusted coefficient 1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ annual average $NO_2$.

Several strands of evidence were used in coming to this view, including

a coefficients from four studies that had reported coefficients from both single- and multi-pollutant models and in which concentrations of $NO_2$ were not highly correlated with those of PM

b time-series evidence

c evidence from toxicological and chamber studies, which provides stronger evidence for a causal link between $NO_2$ and respiratory effects than cardiovascular effects

Nonetheless, there is considerable uncertainty regarding the suggested range of 25-55%.

This reduced coefficient may be used for assessing the benefits of reductions in concentrations of $NO_2$ itself, without corresponding reductions in concentrations of other traffic-related pollutants.

The majority of Committee Members, including all signatories of the Dissenting View, did not support the use of the reduced $NO_2$ coefficient (25-55% of the unadjusted coefficient) to generate an estimate of the burden of mortality attributable to current exposure to $NO_2$ itself.

Because burden estimates are intended to convey the size of the effect of air pollution on public health, an estimate of the overall effect of the air pollution mixture was considered sufficient.

Approaches for estimating the burden of the air pollution mixture on the basis of associations of mortality with long-term average concentrations of PM and $NO_2$ are discussed in the next chapter.

# Chapter 5
# Approaches to burden calculations

## 5.1 Introduction

Neither the unadjusted single pollutant summary estimate nor an adjusted coefficient can be used with confidence to reflect the mortality burden on the UK population due to exposure to $NO_2$. While, in theory, the recommendation for impact calculations could be used to give equivalent results for the burden attributable to $NO_2$ itself, we consider it more appropriate to provide burden results only for the air pollution mixture as a whole. Burden calculations are generally used to highlight the size of the overall problem. This avoids the need to apportion the burden between $NO_2$ and $PM_{2.5}$, which we do not think is possible to do reliably.

Nonetheless, the majority of Members considered it important to explore the implications for burden calculations of some possible alternatives to previous calculations based only $PM_{2.5}$, to see what difference it would make, if

a either the single pollutant estimate for $NO_2$ was used to represent the mixture or

b if the results of two-pollutant models were used to adjust the summary effects estimate obtained from meta-analysis of coefficients from single-pollutant models.

The approaches adopted are described in this chapter and further explored in Working Paper 3.

## 5.2 Approach to using two-pollutant models

We have used the relatively small number of cohort studies which report results from two-pollutant models to inform our estimate. Table 3.1 identifies six cohorts with such two-pollutant models and summarises their results. It also contains adjusted coefficients available from a 7th cohort study, which are based on a three-pollutant model (i.e. with simultaneous inclusion of and adjustment for ozone as well as $NO_2$ and $PM_{2.5}$).

### 5.2.1 Studies included for estimating adjusted coefficients

It was agreed that the adjusted coefficients from Cesaroni et al. (2013) and Carey et al. (2013) were, in practice, uninformative because of the very high correlation between $NO_2$ and $PM_{2.5}$ (see earlier) and so were excluded, whereas (from the viewpoint of correlation between $NO_2$

and PM), the other four studies which reported results of two-pollutant models seemed likely to be subject to a lesser degree of bias[14].

We also excluded the unusual results from HEI (2000). We note that a more recent study based on the same American Cancer Society (ACS) cohort had become available (Turner et al., 2015). This newer study gave results that were much more in line with other studies with regard to associations with $NO_2$. We did not however use Turner et al. (2015) instead of HEI (2000) as it had been published after the cut-off date for our literature review.

As well as including Beelen et al. (2014) and Jerrett et al. (2013), we decided to continue to use Fischer et al. (2015) despite its limitations (eg use of $PM_{10}$ rather than $PM_{2.5}$), because the number of available studies was small, the authors had done good work with the available data, and the study itself was a very large one.

Finally, we included results from a fourth study (Crouse et al., 2015a). The adjusted coefficients it reported were based on a three-pollutant model (i.e. with ozone also) and not simply a two-pollutant one. With so few studies available, we decided to include it: while different from the other (two-pollutant) studies, it certainly meets the need of providing coefficients adjusted for other pollutants, and it had been published before the cut-off date for the review.

The four studies used to inform our approach to estimating the mortality burden attributable to the air pollution mixture are summarised in Table 5.1.

These studies represent the available evidence base of coefficients linking mortality with $NO_2$ and adjusted for PM published before 5 October 2015, because they are derived from a literature search of publications that was comprehensive in its search for cohort studies of mortality and $NO_2$ published before that date. It is likely that any cohort providing both $PM_{2.5}$ coefficients adjusted for $NO_2$ and $NO_2$ coefficients adjusted for PM, is likely to have been identified in the initial literature search for cohorts linking mortality with annual average $NO_2$.

[14] Correlation between pollutants is not the only aspect that can lead to bias, although it is an important one. The variance in the measurement errors and the correlation between the measurement errors for each pollutant also affect the degree of bias. We had no information on these aspects.

**Table 5.1: Hazard ratios[1] from single and two pollutant models for four cohorts used for quantification**

| Study | Cohort | Correlation $NO_2/PM_{2.5}$ exposure metrics | $NO_2$ IQR ($\mu g/m^3$) | $NO_2$ | $NO_2$ adjusted $PM_{2.5}$/ $PM_{10}$ | %[2] | $PM_{2.5}$/ $PM_{10}$ IQR ($\mu g/m^3$) | $PM_{2.5}$/ $PM_{10}$ | $PM_{2.5}$/ $PM_{10}$ adjusted $NO_2$ | %[2] |
|---|---|---|---|---|---|---|---|---|---|---|
| Beelen et al. (2014)[3] | ESCAPE | 0.2-<0.7 | 10.0 | 1.015 (0.993, 1.036) | 1.007 (0.967, 1.049) | 53 | 5.0 | 1.070 (1.016, 1.127) | 1.060 (0.977, 1.150) | 14 |
| Fischer et al. (2015)[4] | DUELS | 0.58[4] | 10.0 | 1.027 (1.023, 1.030) | 1.019 (1.015,1.023) | 29 | 2.4 | 1.019 (1.016, 1.022) | 1.010 (1.007, 1.013) | 46 |
| Jerrett et al. (2013) | ACS CPS II | 0.55 | 7.7 | 1.031 (1.008, 1.056) | 1.025 (0.997, 1.054) | 19 | 5.3 | 1.032 (1.002, 1.062) | 1.015 (0.980, 1.050) | 53 |
| Crouse et al. (2015a)[5] | CanCHEC | 0.40 | 15.2 | 1.052 (1.045, 1.059) | 1.045 (1.037, 1.052) | 13 | 5 | 1.035 (1.013, 1.049) | 1.011 (1.003, 1.020) | 68 |

1 HRs expressed per IQR (Fischer et al., 2015, Jerrett et al.,, 2013), mean minus 5th percentile (Crouse et al., 2015a) or 10 $\mu g/m^3$ $NO_2$ and 5 $\mu g/m^3$ $PM_{2.5}$ (Beelen et al., 2014)

2. The percentage reduction in HR after adjustment for the other pollutant

3 Based on 14 cohorts in which correlation between $NO_2$ and $PM_{2.5}$ was less than 0.7. HRs provided to 3dp by the authors in December 2017

4. $PM_{10}$

5 $NO_2$ adjusted for $PM_{2.5}$ and $O_3$. $PM_{2.5}$ adjusted for $NO_2$ and $O_3$

## 5.3 Options for developing adjusted coefficients for use in burden calculations

### 5.3.1 Overview

As well as burden estimates developed using summary estimates from meta-analyses of single-pollutant coefficients, the majority of the Committee supported exploration of the use of mutual adjustment of coefficients using information from individual studies.

Two main options were considered for developing an adjusted coefficient using data from any of the four studies above. One was to use the adjusted coefficients from that study directly, i.e. use directly the mutually adjusted coefficients in Table 5.1, with associated CIs. The other was to take, for each of $NO_2$ and PM, the % by which the single-pollutant coefficient was reduced on mutual adjustment, and to apply that % reduction to the relevant summary estimate from the meta-analysis of unadjusted single-pollutant coefficients.

These two approaches have different strengths and weaknesses, in respect of representativeness and/or transferability, and of providing estimates of uncertainty.

### 5.3.2 Representativeness and/or transferability

There are always issues about the transferability to the UK of relationships from where primary studies were carried out. Using the second approach, i.e. transferring only % reduction (or, equivalently, % 'retained'), limits the extent to which the particularities of any of the four studies determine the value of the final adjusted coefficient. This is because the only study characteristic which we transfer is an estimate of the effect of adjustment, expressed as % reduction in the coefficient due to adjustment; the underlying size of the effect from the particular two-pollutant study is not used, except insofar as it contributes to the meta-analysis of the unadjusted coefficient. That meta-analysis is based on a much greater and much more representative body of evidence about the underlying size of the association than can be provided by any of the four studies of Table 5.1; and so from this viewpoint the second strategy is preferable.

It should be noted that the % reductions themselves are subject to transferability issues. This is because the correlation between pollutants and the magnitude of misclassifications in exposures are likely to vary by location and these affect the degree of bias in the multi-pollutant models, which in turn affects the % reduction. This may be countered to some extent by using several studies but we cannot be sure, as we do not know at present how these aspects vary in the different locations. These aspects also need to be understood in the area where the concentration-response functions would be applied. These are areas for further work.

### 5.3.3 Uncertainty estimates / confidence intervals

Direct use of the adjusted coefficients from a particular study gives not only a pair of adjusted coefficients, but also an associated pair of CIs. We did not have a means of deriving a valid CI for an adjusted coefficient derived using the second approach, i.e. by applying a % reduction to an unadjusted coefficient.

Development work, reported in Working Paper 3 led to a discussion of inferences about the possible range of CIs for this. This required assumptions to be made about a range of covariances, because this information is not available, and the approach also does not work well when unadjusted coefficients are not statistically significant, as was the case for Beelen et al. (2014).

### 5.3.4 Option selected

We opted for the second strategy, of transferring % reductions only, on the grounds that it was preferable to maintain a more representative estimate, albeit without information on the CI, than it was to base the entire quantification on a single study, even though we would then have had valid estimates of associated CIs.

### 5.3.5 Using pairs of percentage reduction from the same study

We considered whether it would be best to use a pair of average percentage reductions to amend the unadjusted summary coefficient, or a pair of values of % reduction from any one particular study. We noted that the particularities of the correlation structure in any one study affect simultaneously the adjustment of $NO_2$ for PM and the adjustment of PM for $NO_2$. Therefore, adjustment using a pair of coefficients, or a pair of values of % reduction, from the same study, preserves something of that mutual dependence which may be lost if average values across the four studies were used. In addition, using an average loses potentially useful information about the extent to which applying a pair of % reductions from each of four studies does, or does not, give similar results. Therefore, applying paired reductions from each study was our preferred approach. The percentage reductions, and adjusted summary coefficients, used in the calculations are presented in Table 5.2.

It should be noted that applying these paired % reductions from individual studies to different concentration ranges than those in the original studies, may not fully retain the principle that the total is likely to be more accurate than use of the individual adjusted coefficients. If one adjusted coefficient for eg $PM_{2.5}$ is over-estimated due to effect transfer, and is applied in a situation where the concentration range is much larger than in the original study, then that over-estimation will be exaggerated relative to the under-estimation in the other adjusted coefficient (in this example, for $NO_2$) assuming the concentration range for $NO_2$ is similar to that in the original study. Further work is needed to explore this point. Application of these paired reductions requires an assumption that the adjusted coefficients, and therefore the % reductions, are not too badly affected by bias.

**Table 5.2 Various illustrative coefficients for use in approximate burden calculations**

| **Indicator Pollutant** | **Unadjusted coefficient from meta-analysis** ($NO_2$ this report; $PM_{2.5}$ COMEAP, 2010 and Hoek et al., 2013). Robustly established | **Various options for adjusted coefficients** ($NO_2$ adjusted for $PM_{2.5}$ and *vice versa* (derived as paired $NO_2$ and $PM_{2.5}$ % reductions from unadjusted to adjusted coefficients from each study). Derivation of confidence intervals for ratios for correlated variables was not possible so CIs not given | | | |
|---|---|---|---|---|---|
| | | Jerrett et al., (2013) | Fischer et al. (2015) ($PM_{10}$) | Beelen et al. (2014) | Crouse et al. (2015) (with $O_3$) |
| % reduction on adjusting $NO_2$ single pollutant coefficient for $PM_{2.5}$ | n/a | 19% | 29% | 53% | 13% |
| $NO_2$ single pollutant model summary estimate (middle columns - summary estimate reduced by the relevant % reductions from each study) | 1.023 (1.008, 1.037) | 1.019 | 1.016 | 1.011 | 1.020 |
| % reduction on adjusting $PM_{2.5}$ single pollutant coefficient for $NO_2$ | n/a | 53% | 46% | 14% | 68% |
| $PM_{2.5}$ single pollutant model summary estimate (with % reduction applied – far columns) | 1.06 (1.04, 1.08) Also 1.01,1.12 | 1.029 | 1.033 | 1.053 | 1.019 |

## 5.4 Summary

Whilst recognising the uncertainties involved, we decided it was appropriate to attempt to estimate the burden of mortality in the UK attributable to the air pollution mixture, on the basis of associations reported with PM and $NO_2$.

We propose reporting a range of possible values of the mortality burden, derived:

a Using summary single-pollutant (i.e. unadjusted) coefficients for either $PM_{2.5}$ or $NO_2$ and also

b By four separate estimations, each undertaken using information from one of the four available multi-pollutant cohort studies with moderate correlations between annual average $NO_2$ and PM concentrations. For each study, the percentage reduction in $NO_2$ coefficient on adjustment for PM is applied to the unadjusted summary $NO_2$ coefficient used in (a) above. Similarly, the percentage reduction in $PM_{2.5}$ coefficient on adjustment for $NO_2$ is applied to the unadjusted summary $PM_{2.5}$ coefficient. The estimated burdens obtained using these mutually adjusted summary coefficients are then summed to give an estimated burden of the air pollution mixture.

# Chapter 6
# Threshold, cut-off and counterfactual for quantification

## 6.1 Concepts

While the epidemiological studies indicate associations between long-term average concentrations of $NO_2$ and mortality in locations with a wide range of $NO_2$ concentrations, it is important to consider whether these associations continue to apply at very low concentrations. We therefore need to consider whether there is evidence for a threshold. In the context of exposure to a hazard increasing the risk of health effects in the exposed, a threshold is a level of exposure below which there is no increase in risk. The concept is rooted in the well-known ability of the human body to resist or recover from small doses of otherwise toxic hazards. In practice, however, demonstrating the existence of a threshold is often difficult. Issues include the possibility that a threshold may be a function of exposure rather than concentration, where the latter is measured as an imperfect surrogate for the former; and that a human population may exhibit variation in time-frame of exposure and individual subjects' thresholds, which could perhaps be considerable.

Even if there is no evidence that a threshold of effect exists, it may be appropriate to use a concentration cut off in the calculations. We use this 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.

To estimate the burden attributable to current concentrations of pollution a theoretical baseline (reference) concentration against which the burden of existing concentrations will be compared, called a 'counterfactual' is needed. Given that the purpose of a burden estimate is to express 'the size of the problem', the implicit counterfactual is the absence of pollution, down to a threshold if one exists, or zero otherwise. A number of different approaches to selecting a counterfactual can be considered; if alternatives are used, then the differences between the question being answered and 'burden' as commonly understood, should be made explicit. These include:

a the plausible lowest level, irrespective of whether it is currently attainable in practice (for example, "natural background"). For $PM_{2.5}$, COMEAP (2010) considered this to be zero anthropogenic $PM_{2.5}$. In the case of $NO_2$, the Committee thought that all $NO_2$ is anthropogenic)

b the lowest level which could reasonably be achieved as a policy target

c the lowest level observed in epidemiological studies

d the lowest level above which there is confidence in the relationship observed in epidemiological studies

## 6.2 Assessing the evidence for a threshold of effect

Establishing the shape of the exposure-response relationship at very low concentrations is difficult because of the much greater uncertainties at the extremes of exposures within a study. WHO's Health Risks of Air Pollution In Europe - HRAPIE project (WHO, 2013b) found no evidence for a threshold at concentrations above 20 μg/m³ long-term average concentration of $NO_2$. This reflected evidence from studies by Naess et al. (2007) and Cesaroni et al. (2013). Naess found increases in the risk of deaths from all causes at 40 μg/m³, in 51-70 year olds; for the older age group (71-90 years old) the increase in risk was linear between 20-60 μg/m³, with tight confidence intervals. In the Rome study (Cesaroni et al., 2013), a linear relationship was reported. The mean concentration was 43.6 μg/m³ and a statistically significant linear concentration response function above 20 μg/m³ for natural mortality was observed (Cesaroni et al., 2013).

However, a subsequent journal article by the authors of the HRAPIE report (Heroux et al., 2015) noted that Raaschou-Nielsen et al. (2012) shows a significant, almost linear concentration–response relationship between long-term $NO_2$ concentration and mortality in a Danish cohort, throughout the observed range of $NO_2$ concentrations, which in the large majority of subjects was below 20 μg/m³ (minimum 10.5 μg/m³, median 15.1 μg/m³, and maximum 59.6 μg/m³). They also noted that the study by Naess et al. (2007) showed a steeper response below 20 μg/m³ in 71-90 year olds.

Of the studies included in our meta-analysis, Cesaroni et al. (2013), Fischer et al. (2015), Beelen et al. (2014) and Crouse et al. (2015a) included consideration of the shape of the concentration response curve for long-term concentrations of $NO_2$ and all-cause mortality. For the Dutch study, associations between $NO_2$ and non-accidental mortality did not deviate significantly from a linear relationship and the median concentration was 31 μg/m³ (Fischer et al., 2015). Beelen et al. (2014) found no significant deviations from linearity in the associations between $NO_2$ and mortality in any of the 22 constituent ESCAPE cohorts.

Tests for non-linearity for the relationship with all-cause mortality, where performed (Cesaroni et al., 2013; Fischer et al., 2015; Beelen et al., 2014) were not statistically significant. Naess et al., 2007 did not perform a test for non-linearity but the data presented suggest it is unlikely that significant non-linearity would have been found in the older age group that dominates the mortality data.

### 6.2.1 Summary

Associations were observed in studies with $NO_2$ concentrations as low as 5 μg/m³ $NO_2$. The available studies do not suggest that a threshold for effects exists at the population level. However, as only some of the studies have included formal tests for this, the possibility of a threshold cannot be ruled out.

The Committee therefore, considered whether the calculations should quantify to zero or restrict calculations to a concentration that reflects the range of concentrations reported in the studies.

## 6.3 Quantifying to zero

Levels of $NO_2$ in the environment can be very low in remote areas, for example, levels as low as 7.5 ppt (0.014 μg/m$^3$) have been measured in Australia (Sommariva et al., 2004). The current state of knowledge does not allow for a natural rather than anthropogenic (man-made) proportion of $NO_2$ to be identified (European Commission, 2011). Therefore, quantifying to zero could be one option. While this is outside the range of concentrations used in the epidemiological studies contributing to the concentration-response function, it is close to the minimum concentration in the European Study of Cohorts for Air Pollution Effects ESCAPE study (1.5 μg/m$^3$, Beelen et al., 2014).

Extrapolating down to zero (no cut-off) introduces additional uncertainties into the impact and burden estimates, as it assumes that the concentration-response relationship is linear below the concentrations studied.

Such an assumption (simple extrapolation) may under-estimate the real effect: there are a number of empirical studies that point to a steeper slope at lower levels. Crouse et al. (2015a) applied a natural spline fit for $NO_2$ and concluded it was supralinear – larger changes in risk for a unit change in concentration at low concentrations compared with higher values. If this is the case, marginal changes in exposure in areas of low pollution will translate into larger marginal reductions in deaths compared with equivalent marginal changes in higher areas of pollution. Similarly, in a study on traffic pollution and mortality (all- cause and cause-specific) in London (Halonen et al., 2016), the analysis found that the relationship was non-linear (although it did not indicate a threshold), which necessitated a piecewise regression approach. This yielded higher associations in the lowest (25.8 to 33 μg/m$^3$) of four categories of exposure and in some cases negative associations in the higher exposure categories. These results might reflect a lack of adequate control for confounding rather than the true effects but it suggests that extrapolating using a linear relationship may under-estimate impacts at low concentrations compared to the 'true' (though strictly unknown) relationship.

As there is limited information as to the nature of the exposure response below the range of data in the various studies, an extrapolation to zero would be based on an untested assumption of linearity rather than empirical evidence and this extrapolation is subject to additional uncertainty.

## 6.4 Restricting calculations to concentrations within the studied range

An alternative scenario would be to use a cut off that reflects the studied range of concentrations over which a linear concentration-response relationship was observed. For example, WHO's Health Risks of Air Pollution In Europe - HRAPIE project (WHO, 2013b) recommended a cut-off for quantification of 20 μg/m$^3$ when using a concentration response function for mortality associated with long-term exposure to $NO_2$. However, the HRAPIE authors later considerations of additional studies which included populations exposed to lower

concentrations, led to a conclusion that calculating impacts only above 20 μg/m$^3$ may be too conservative (Heroux et al., 2015).

We considered a range of options for how to define the 'range of data' including the use of the lowest concentration reported in the studies, the 5$^{th}$ percentile, the minimum concentrations weighted by study size and the10$^{th}$ percentiles. These options are discussed below.

One approach could be to use the lowest concentration reported in the studies included in our meta-analysis to derive the coefficient. A minimum concentration of around 1.5 μg/m$^3$ was reported for three cohorts (Swedish, North Italian and Austrian) in the ESCAPE study (Beelen et al., 2014). We did not choose this option as it did not reflect the range of minimum concentrations in the other studies.

The approach followed by the Global Burden of Disease project for $PM_{2.5}$ was to use a counterfactual bounded by the minimum value and 5$^{th}$ percentile of the concentrations in the largest cohort study used to derive the coefficient (Burnett et al., 2014, Lim et al., 2013). If we used a similar approach, then the Dutch cohort study is the largest[15] cohort study included in the meta-analysis, with over 7 million subjects (Fischer et al., 2015). It reported a minimum concentration of 11 μg/m$^3$ and the 5$^{th}$ percentile was 19 μg/m$^3$.

As other studies in the meta-analysis also contribute to the pooled estimate, it seems unreasonable to leave these out entirely. The minima and 5$^{th}$ percentiles given in or estimated from the studies in the meta-analysis are presented in Table 6.1.

The lowest minimum, 5$^{th}$ percentile and 10$^{th}$ percentile concentrations within the cohorts in the ESCAPE study and the average of the minima weighted by the weights in the ESCAPE meta-analysis (5.2 μg/m$^3$) are all at or below 5 μg/m$^3$, as is the minimum in Carey et al. (2013), and the minima and 5$^{th}$ percentiles in Abbey et al. (1999), Bentayeb et al. (2015) and Crouse et al. (2015).

So, a cut-off of 5 μg/m$^3$ is within the range of concentrations used in epidemiological studies. On the other hand, studies with minima above 5 μg/m$^3$ have greater weight in the meta-analysis. Nonetheless, the combined weight of the studies quoted above was 52.4% for the studies with minima below 5 μg/m$^3$ and 24.2% for the studies with 5$^{th}$ percentiles below 5 μg/m$^3$, all of which showed positive associations, although one only marginally so (Abbey et al., 1999).

[15] While Fischer et al. (2015) had the largest number of subjects; the ACS study (Krewski et al., 2009) had a marginally larger weight in the meta-analysis (Figure.2, Working Paper1). The 5$^{th}$ percentile for this study was 24.7 μg/m$^3$ (calculated from Appendix G, HEI 2000).

**Table 6.1 Minima and 5th percentiles of studies included in the meta-analysis and used to derive a cut-off**

| Study ranked by increasing 5th percentile | Source of 5th percentile | Minimum (µg/m³) | 5th percentile (µg/m³) | Weight in meta-analysis) |
|---|---|---|---|---|
| Crouse et al. (2015b) | Derived from footnote to Table 2 of the paper | 0 | 0.8 | 11.82 |
| Bentayeb et al. (2015) | Estimated from Figure 3 of the paper | < 2.5 | 2.5 | 2.97 |
| Abbey et al. (1999) | Estimated from other percentiles | 0 | 3 | 9.43 |
| Hart et al. (2011) | Estimated from Figure 2B of (Hart et al., 2009) | 0 | 7.52 | 9.18 |
| Beelen et al. (2014) | Estimated from Figure 1 and weighted according to meta-analysis weights in Figure 2B of the paper | 5.2 | 10.7 | 10.02 |
| Carey et al. (2013) | Carey, personal communication | 4.5 | 10.95 | 8.96 |
| HEI (2000) | Calculated from only 6 points, minimum concentration above reference was 19.9 | Reference 11.5 | 13.6 | 4.63 |
| Lipsett et al. (2011) | Estimated from other percentiles | 9.4 | 15 | 7.12 |
| Fischer et al. (2015) | From the paper | <19 | 19 | 12.02 |
| Krewski et al. (2009) | Calculated from Appendix G of Krewski et al., 2000. | 14.57 | 24.74 | 12.05 |
| Cesaroni et al. (2013) | Cesaroni, personal communication | 13 | 27.5 | 11.79 |

If one considers the concentrations and proportion of the population exposed to $NO_2$ in the UK, the lowest annual average modelled $NO_2$ on a 1 km by 1 km grid square in 2013 is 1.6 µg/m³. The proportion of the population and the percentage of land area for cut offs of 5, 10 and 15 µg/m³ $NO_2$ were calculated. This showed that 48% of the land area and 4% of the population are equal to or below 5 µg/m³, 76% of the land area and 18% of the population are equal to or below 10 µg/m³ and 93% of the land area and 43% of the population are equal to or below 15 µg/m³. (See Figures 8.2 and 8.3 in Chapter 8).

## 6.5 Committee approach for cut off

Members held divergent views on which of the two approaches outlined above should be used and it was not possible to come to a consensus view. As with the calculations for $PM_{2.5}$ in COMEAP 2010, the Committee therefore agreed that calculations using both approaches

would be undertaken when quantifying effects of mortality from long-term average concentrations of $NO_2$:

a Not using a cut off (0 $\mu g/m^3$) and assuming a linear dose-response relationship continues below the range of studied concentrations

b Using a cut-off of 5 $\mu g/m^3$. (In practice, this means subtracting a value of 5 from the 1 km x 1 km grid concentrations. For example, for a 1 km x 1 km grid concentration of 30 $\mu g/m^3$, a concentration of 25 $\mu g/m^3$ would be used and any 1 km x 1 km grid below 5 $\mu g/m^3$ set to zero.)

Using a cut-off for quantification, based on the lower end of concentrations in studies in which associations have been shown, estimates the portion of the predicted benefits of interventions (or, if appropriate, burden) in which there is greatest confidence, because no extrapolation beyond the range of data is involved. As associations were observed in cohort studies with concentrations of $NO_2$ as low as 5 $\mu g/m^3$ annual average, we consider this to be an appropriate cut-off.

Further extrapolation down to zero estimates the additional benefit (or effect) that is likely under the assumption that the same concentration-response relationship holds below concentrations that have currently been studied. Without such extrapolation any benefit (or effect) below 5 $\mu g/m^3$ annual average $NO_2$ remains unquantified.

We recommend quantifying to both zero and to 5 $\mu g/m^3$ annual average $NO_2$

# Chapter 7
# Interpretation and Application of coefficients

## 7.1 Interpretation of coefficients

It is important to consider the context of an assessment when determining how $NO_2$ coefficients might be applied in quantification. The REVIHAAP authors noted that relevant considerations would include (1) whether the primary purpose is to estimate the burden of current air pollution or to predict the health impacts of a change, (2) whether emissions of traffic-related pollutants other than $NO_2$ will also be affected by the planned measures, (3) the spatial scale of the assessment and (4) what other pollutants are included in the assessment (WHO, 2013a). There is also a need to consider whether it is possible to estimate the combined effect of long-term average concentrations of $NO_2$ and PM on mortality. Table 7.1 describes the types of coefficients that might be used to represent associations between long-term average concentrations of $PM_{2.5}$ and $NO_2$ and mortality, and their possible interpretations. Nonetheless, the possibility of residual confounding, effect transfer etc need to be borne in mind when interpreting adjusted coefficients.

**Table 7.1: Types of coefficients that might be used to represent associations between long-term average concentrations of $PM_{2.5}$ and $NO_2$ and mortality**

| Coefficient | Possible interpretation |
|---|---|
| Unadjusted coefficient for $PM_{2.5}$ | Reflects the effect of $PM_{2.5}$ and also, to some extent, the effect of other pollutants with which $PM_{2.5}$ is correlated. These include other fractions of PM, $NO_2$, and other components of the air pollution mixture. |
| Unadjusted coefficient for $NO_2$ | Reflects any causal effect of $NO_2$ and also, to some extent, the effects of other pollutants with which $NO_2$ is correlated. These include $PM_{2.5}$, other fractions of PM, and other components of the air pollution mixture (eg ultrafine particles, Black Carbon, Volatile Organic Compounds etc.). |
| Coefficient for $PM_{2.5}$ adjusted for $NO_2$ | Reflects the effect of $PM_{2.5}$ and also, to some extent, the effects of other pollutants with which $PM_{2.5}$ is most closely correlated but excludes (as far as possible) effects associated with $NO_2$, and other components of the air pollution mixture which are more closely correlated with $NO_2$ concentrations than with $PM_{2.5}$ concentrations. Given the good evidence and plausibility of causality, it is reasonable to regard the majority of this effect as likely to be causally related to $PM_{2.5}$. |

| | |
|---|---|
| Coefficient for $NO_2$ adjusted for $PM_{2.5}$ | Reflects any effect of $NO_2$ and also, to some extent, other pollutants with which $NO_2$ is closely correlated but excludes (as far as possible) effects associated with $PM_{2.5}$ concentrations and other components of the air pollution mixture that are more closely correlated with $PM_{2.5}$ concentrations than with $NO_2$ concentrations. Given the weaker evidence for plausibility and causality, the extent to which this effect is likely to be causally related to $NO_2$ is unclear. It is unlikely to be zero, but also unlikely to be 100%. |

## 7.2 Quantification of effects of $NO_2$ alone

In Chapter 2 we concluded that the $NO_2$ coefficient derived from meta-analysis of single-pollutant models cannot be interpreted as indicating only, and perhaps not even mainly, causal effects of $NO_2$ alone. It almost certainly, at least in part, reflects an effect of particles and perhaps other pollutants/factors. We therefore recommend that calculations using this coefficient should NOT be interpreted as representing solely the effects of $NO_2$.

We have therefore (Chapter 4) used an expert judgement approach to recommend a reduced coefficient which we think is likely to represent effects caused by exposure to $NO_2$ itself. The reductions made to this coefficient are intended to take into account, as far as possible, confounding by both $PM_{2.5}$ and other potentially causal pollutants which are spatially correlated with $NO_2$. This reduced coefficient is more appropriate for assessing the benefits of reductions in concentrations of $NO_2$ itself, without corresponding reductions in concentrations of other traffic-related pollutants. It is needed to assess the likely benefits of policies and interventions that will reduce emissions of nitrogen oxides ($NO_x$) without proportionately reducing emissions of other traffic- or combustion-related pollutants.

In the following sections we consider approaches for impact assessments of interventions which primarily target emissions of $NO_x$ and then our view on calculating a mortality burden due to long-term average concentrations of $NO_2$ itself.

### 7.2.1 Impact calculations to assess the health benefits of interventions that primarily target emissions of $NO_x$

Some pollution reduction measures (for example, use of selective catalytic reduction of traffic emissions) are specific to $NO_x/NO_2$ reduction and are expected to have little or no impact on the emissions of other traffic-related pollutants. Use of a $NO_2$ coefficient derived from epidemiological studies to assess the benefits of these types of measures will involve a high level of uncertainty, as neither an unadjusted nor adjusted coefficient can be interpreted as representing solely the effect of $NO_2$.

#### *7.2.1.1 Coefficient for $NO_2$ alone*

We have decided to recommend use of the summary estimate from a meta-analysis from the single pollutant models but we have used expert judgement to reduce this coefficient to account for confounding by both PM mass (in the light of the results of two pollutant models) and for the possible effects of other pollutants which correlate more strongly with $NO_2$ than PM.

A majority view of the Committee was that approximately 25-55% of the unadjusted summary coefficient derived from the meta-analysis of single pollutant models (1.023 per 10 μg/m$^3$ $NO_2$) could be regarded as causally related to $NO_2$. This gives a range of between 1.006 per 10 μg/m$^3$ and 1.013 per 10 μg/m$^3$. This takes into account that, even after adjusting for PM, a coefficient may represent effects caused by other correlated – eg co-emitted – pollutants as well as $NO_2$ itself .

The lower bound is to take into account possibilities such as:

a $NO_2$ affecting respiratory, but not cardiovascular, mortality (respiratory deaths are less common)

b The associations reported in cohort studies representing the aggregate of the effects of short-term exposure suggested by the time-series evidence. Associations reported in cohort studies likely reflect effects of short-term exposures to some extent [16]

The upper bound took into account factors such as the possibility that adjustment for $PM_{2.5}$ adjusted well for primary PM from traffic. (This would not always be the case depending on actual correlations between $NO_2$ and PM components for particular study designs and locations).

It was noted that this is a range of "central" estimates. It would not take into account other uncertainties, such as those reflected in the confidence interval around the unadjusted coefficient (1.023 per 10 μg/m$^3$ $NO_2$ with a 95% confidence interval of 1.008 to 1.037).

Adding estimates of the mortality benefits of interventions obtained using either the unadjusted or reduced coefficients for $NO_2$ recommended in this report to assessments based on an unadjusted concentration-response function for $PM_{2.5}$ will lead to an over-estimate of potential benefits.

### *7.2.1.2 Including assessment of nitrates*

One effect of reducing $NO_x$ emissions is a consequent reduction in nitrate particles. This needs to be taken into account in the analyses of the overall benefits of $NO_x$ reduction. One way to do this is to include nitrate effects as a separate component, to be added to the effect of reducing $NO_2$ concentrations. Because the reduction in nitrate concentrations occurs some distance from the source of $NO_x$ emissions, it would not be represented by the $NO_2$ coefficient. The mortality impact of reductions in nitrate concentrations, as a result of reductions in $NO_x$ emissions, can be assessed using a coefficient for $PM_{2.5}$, together with the current understanding (COMEAP 2015b) that the various components of $PM_{2.5}$ should be quantified using the same overall $PM_{2.5}$ coefficient (unless the component is being used as a marker of the particulate mixture as a whole, which is not the case here).

The question that arises is should an unadjusted or adjusted coefficient be used for $PM_{2.5}$ in the context of nitrate reductions? There was limited discussion of the personal preferences of

[16] We do not recommend quantification of mortality associated with both long- and short-term exposures in the same assessment, as the associations in cohort studies likely reflect the effects of short-term exposures to some extent (COMEAP, 2010)

working group Members about this. The group proposed use of an unadjusted coefficient, because (i) the Committee had not carried out the work needed to recommend an adjusted coefficient for $PM_{2.5}$ and (ii) it was noted that the impact from nitrate in the Defra calculations for the $NO_2$ air quality plans is not large and so the choice had little practical consequence. (It could however be important for other policies.)

As the present work on $NO_2$ did not extend to making a fundamental evaluation of an unadjusted coefficient for $PM_{2.5}$, two options were considered. One was using COMEAP's current recommendation for an unadjusted PM coefficient of 1.06 (95% CI: 1.02–1.11, including the wider plausibility interval of 1.01 and 1.15, as recommended in COMEAP, 2009a). However, it was agreed that the Hoek et al. (2013) meta-analysis, which gave the same central estimate of 1.06 but with a smaller 95% CI (1.04-1.08) should be used. This has the advantages of being based on not just the ACS study, but on 11 cohorts including the ACS, and of being recommended by WHO (2013b) for quantification EU-wide.

Therefore we recommend inclusion of an assessment of the benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions. We recommend use of the unadjusted coefficient for $PM_{2.5}$ of 1.06 (95%CI:1.04-1.08) per 10 $\mu g/m^3$ annual average $PM_{2.5}$ (derived from a meta-analysis of single pollutant studies, Hoek et al., 2013).

*Nitrates: Summary*

One consequence of reducing $NO_x$ emissions is a reduction in nitrate particles. Because this effect occurs some distance from the source of the $NO_x$ emissions, nitrate concentrations would not be expected to be correlated with those of $NO_2$. Therefore, the health effects of nitrate particles arising from $NO_x$ emissions would not be represented by the associations with $NO_2$ concentrations reported from epidemiological studies.

The mortality benefits arising from reductions in nitrate concentrations can therefore be included as a separate component in health impact assessments, to be added to the predicted benefits associated with reductions in $NO_2$ concentrations calculated using either the unadjusted or reduced coefficient.

### 7.2.2 Burden calculations to assess the effect of mortality due to long-term exposure to $NO_2$

Neither the unadjusted single pollutant summary estimate nor an adjusted coefficient can be used with confidence to reflect the mortality burden on the UK population due to $NO_2$ itself. While, in theory, the above recommendation for impact calculations could be used to give equivalent results for burden, we consider it more appropriate to provide burden results only for the air pollution mixture as a whole. Burden calculations are generally used to highlight the size of the overall problem. This avoids the need to apportion the burden between $NO_2$ and $PM_{2.5}$ exactly, which we do not think is possible to do reliably.

## 7.3 Impact calculations on the basis of $NO_2$ being a marker for traffic-related pollutants

The majority of the Committee thought that quantification of the mortality impacts of a pollution mixture might be performed on the basis that $NO_2$ is a marker for a mixture of

pollutants; for example, this could be for a pollution mixture including $PM_{2.5}$ (where PM measurements are not available) or for reduction of a mixture of traffic-related air pollutants the composition of which will not be changed much by a proposed traffic measure.

The REVIHAAP authors considered that the uncertainty of using a coefficient for $NO_2$ as a marker for traffic was less than for evaluations of the effects of $NO_2$ itself (WHO, 2013a). Regarding $NO_2$ as a marker for a pollutant mixture means that the question of whether or not $NO_2$ alone has a causal role in the associated effects is less important than when quantifying the impact of a measure that reduces $NO_2$ only – so long as the relationship of $NO_2$ with the causal agent(s) is sufficiently similar to that in the epidemiological studies from which the coefficient used in the quantification was derived. The REVIHAAP report also suggests that this approach would be appropriate for predicting the health impacts of measures that affect traffic volume (that remove or reduce traffic), such as pedestrianisation, which do not change the composition of the emissions or the vehicle fleet (WHO, 2013a).

Some interventions, such as replacing Euro 3/III vehicles by Euro 6/VI, would not only reduce $NO_x$ emissions but would also reduce emissions of a number of other potentially causal pollutants/metrics (eg volatile organic compounds, aldehydes, organic compounds bound to primary PM). These types of interventions, as well as those that would reduce or remove traffic, would have beneficial effects on co-pollutants.

To estimate the effect on mortality of reductions of the whole pollution mixture we recommend that the unadjusted $NO_2$ coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ annual average $NO_2$ is used. These measures will also reduce PM concentrations, so an alternative calculation of benefits associated with this reduction, using the unadjusted $PM_{2.5}$ coefficient 1.06 (95%CI: 1.04-1.08) per 10 $\mu g/m^3$ annual average $PM_{2.5}$, can also be done.

As either of these calculations is likely to underestimate the likely benefits of interventions, the higher of the two values calculated from these two approaches can be used as the better prediction of the benefits.

Using a single pollutant coefficient for $NO_2$ and a single-pollutant coefficient for $PM_{2.5}$, and adding the results, would overestimate the combined effects associated with the two pollutants.

An assessment of the benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions using the unadjusted coefficient 1.06 (95%CI:1.04-1.08) per 10 $\mu g/m^3$ annual average $PM_{2.5}$ (derived from a meta-analysis of single pollutant studies, Hoek et al., 2013) may additionally be used (see section 7.2.1.2 above).

## 7.4 Estimating the mortality burden of air pollution in the UK, using long-term average concentrations of $NO_2$ and PM

Another need is to estimate what the combined effect associated with concentrations of the two pollutants might be, as an estimate of the mortality burden of air pollution in the UK. Our interim statement on $NO_2$ (COMEAP 2015b) noted that "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".

The results of the individual two pollutant models, as presented in Table 3.1, suggest that calculations based on $PM_{2.5}$ (or, for one study, $PM_{10}$) and $NO_2$ in combination would be greater, by a small amount, than those based on unadjusted $PM_{2.5}$ or unadjusted $NO_2$ coefficients alone. (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.)

Our current estimate of a mortality burden equivalent to 29,000 deaths and an associated 340,000 life years lost across the population (COMEAP, 2010) may represent more than just the effects of $PM_{2.5}$ but may, nonetheless, need to be increased to represent the full impact of multiple pollutants, including $NO_2$ and other correlated pollutants.

An approach to estimation of the mortality burden resulting from long-term exposure to the combined air pollution mixture was proposed, agreed and implemented. Methods are discussed in Chapter 5 and 8 and Working Paper 3. The results are reported in Chapter 9. This compares the results using the single pollutant model estimate for either $PM_{2.5}$ or $NO_2$ as a marker for the mixture, with results using pairs of percentage reductions of these coefficients, reflecting the reductions from mutual adjustment in multi- pollutant models in each of four cohort studies. The latter is the theoretically preferable approach if the multi-pollutant model results could be taken at face value. Some, even within the majority view that favoured quantification, were more sceptical of this.

The potential difficulties in interpreting coefficients from multi--pollutant models have been described in Chapter 3. Excluding studies with higher correlations between pollutants reduces the overall likelihood of bias in results from two-pollutant models. However, the extent to which this source of potential bias has the potential to materially affect conclusions will remain unclear until more is understood about the effects of correlations between pollutants and the magnitude of, and interactions between, the misclassification of exposures. Using paired reductions in coefficients from individual studies cancels out some of the biases but only applies within single studies. Applying this pairing elsewhere with different concentration ranges may exaggerate or ameliorate the bias in the results for each pollutant depending on how the ratio of concentrations for each pollutant compares with the original study.

Some Members felt that such an approach was too uncertain to be justified, and their view is expressed in Chapter 10.

We note that further work on the conceptual and methodological challenges of dealing with multi-pollutant model results, and/or other approaches to assessment of mixtures would be valuable in developing these methods in the future.

## 7.5 Summary of recommendations

### 7.5.1 Recommendation for assessing the health benefits of interventions that primarily target emissions of $NO_x$

To assess pollution reduction measures which are specific to $NO_x/NO_2$ reduction, we have decided to recommend use of the summary estimate from a meta-analysis from the single pollutant models but we have used expert judgement to reduce this coefficient to account for confounding by both PM mass (in the light of the results of the two pollutant models) and for the possible effects of other pollutants which correlate more strongly with $NO_2$ than PM. The majority view of the Committee is to recommend use of 25-55% (mid-point of range 40%) of the unadjusted coefficient 1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ annual average $NO_2$. This yields coefficients of 1.006 per 10 μg/m$^3$ annual average $NO_2$ and 1.013 per 10 μg/m$^3$ annual average $NO_2$ respectively.

As discussed in Section 4.4, this was derived by reducing the unadjusted coefficient by 20% to adjust for effects associated with $PM_{2.5}$ concentrations, based upon the results of the multi-pollutant models. Expert judgement suggests that 30-70% of this adjusted coefficient may be caused by $NO_2$ itself, rather than other correlated (eg co-emitted) pollutants.

We see this as a way of gaining the greatest capture of information based upon the strength of the single pollutant model evidence base and on the findings of studies that employed two pollutant models. We accept that such a recommendation is subject to large uncertainty: we think this is inevitable given the current state of the evidence, but nevertheless consider it reliable enough to be useful.

Additionally, to include an assessment of the benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions use the unadjusted coefficient 1.06 (95%CI:1.04-1.08) per 10 μg/m$^3$ annual average $PM_{2.5}$ (derived from a meta-analysis of single pollutant studies, Hoek et al., 2013).

### 7.5.2 Recommendation for assessing the health benefits of interventions that reduce traffic-related pollutants

To assess the health benefits of interventions that reduce traffic-related pollutants in general it is recommended that the unadjusted $NO_2$ coefficient (1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ annual average $NO_2$) is used.

These measures will also reduce PM concentrations, so an alternative calculation of benefits associated with this reduction in PM, using the unadjusted $PM_{2.5}$ coefficient 1.06 (95%CI: 1.04-1.08) per 10 μg/m$^3$ annual average $PM_{2.5}$, can also be done.

As either of these calculations is likely to underestimate the likely benefits of interventions, the higher of the two values calculated from these two approaches can be used as the value likely to underestimate the predicted benefits the least.

Additionally, to include an assessment of the benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions use the unadjusted coefficient 1.06 (95%CI:1.04-

1.08) per 10 μg/m$^3$ annual average $PM_{2.5}$ (derived from a meta-analysis of single pollutant studies, Hoek et al., 2013).

### 7.5.3 Recommendation for assessing the mortality burden due to long-term exposure to $NO_2$

Neither the unadjusted single pollutant summary estimate nor an adjusted coefficient is recommended for use to estimate the burden of $NO_2$ on the UK population.

### 7.5.4 Recommendation for assessing the mortality burden based on long-term average concentrations of $NO_2$ and $PM_{2.5}$

It is likely that our current estimate of an effect on mortality in the UK in a single year equivalent to nearly 29,000 attributable deaths at typical ages and an associated loss of life of 340,000 life years across the population may represent more than just the effects of particulate air pollution and may need to be increased as it does not account for effects that are more closely associated with long-term average concentrations of $NO_2$.

To explore the possible mortality burden attributable to the air pollution mixture on the basis of PM and $NO_2$, we recommend generating a range of burden estimates by applying percentage reductions from two-pollutant models to summary effects estimates from meta-analyses of unadjusted coefficients. These can be compared with estimates produced on the basis of unadjusted single pollutant coefficients. An approach to the estimation of the combined burden is set out in Chapter 5 and has the support of the majority of the Committee.

# Chapter 8
# Methods and inputs for quantification

## 8.1 Impact calculations

The coefficient recommended for use in an impact calculation will depend on the type of policy or intervention that is being considered. Table 8.1 outlines the coefficients used by the Committee in impact calculations that quantified the benefits expressed as an effect on mortality of a sustained reduction in annual average $NO_2$ across the UK by 1 µg/m$^3$.

**Table 8.1: Coefficients recommended for impact calculations**

| Type of calculation | Coefficients |
|---|---|
| To assess the health benefits of interventions that primarily target emissions of $NO_x$ | Use 25-55% (mid-point of range 40%) of 1.023 (95% CI: 1.008, 1.037) per 10 µg/m$^3$ annual average $NO_2$. i.e. a range of 1.006 per 10 µg/m$^3$ to 1.013 per 10 µg/m$^3$.<br>and<br>1.06 (95%CI: 1.04-1.08) per 10 µg/m$^3$ annual average $PM_{2.5}$ for an assessment of the benefits of reductions in secondary nitrate due to reduced $NO_x$ emissions. |
| To assess the health benefits of interventions that reduce traffic-related pollutants | 1.023 (95% CI: 1.008, 1.037)<br>(with or without an alternative calculation using 1.06 (95%CI:1.04-1.08) per 10 µg/m$^3$ annual average $PM_{2.5}$ and then using the higher value)<br>and<br>1.06 (95%CI: 1.04-1.08) per 10 µg/m$^3$ annual average $PM_{2.5}$ for an assessment of the benefits of reductions in secondary nitrate due to reduced $NO_x$ emissions. |

Life-table analyses for changes in mortality rates to produce life years gained and increased life expectancy were carried out using the IOMLIFET spreadsheet tool (Miller and Hurley, 2006) using 2013 life expectancy data, separately for England, Wales, Scotland and Northern Ireland. Baseline population data on deaths and life expectancies are summarised in Table 8.2. Life expectancy for the UK was calculated by weighting separate country results by relevant population size. Life years gained for the UK were calculated by summing the separate country results.

As in the 2010 report quantifying effects attributable to particulate air pollution (COMEAP, 2010), when assessing the impact of a reduction policy, the current (2013 in this case)

populations plus new births during the follow-up period were used, since people not yet born in 2013 would also benefit from sustained pollution reductions in future. The analysis did not attempt to take account of patterns of migration or changes in birth rate and it was assumed that the same number of new births occurred annually throughout the follow-up period as in 2013. The impact of pollution reduction on life expectancy has been expressed in terms of life expectancy from birth of the cohort born in 2013. This impact on life expectancy was calculated by comparing the predicted life expectancy based on 2013 mortality rates with the predicted life expectancy when mortality rates have changed with the reduction in air pollution.

For all impact calculations in this report, we assumed an immediate reduction in $NO_2$ concentrations, following the methodology from the COMEAP 2010 report. A follow-up period of 106 years was used, i.e. a period long enough to allow the current (2013) population to die out. This ensured that the full extent of mortality benefits to those alive in 2013 was reflected. A shorter follow-up period would fail to include benefits that only occur later on, even though they may be a significant contributor to the overall impact.

As for the $PM_{2.5}$ analysis in COMEAP's 2010 report, the reduced hazard rates were applied to the population from the age of 30 years.

## 8.2 Burden calculation

As noted in Chapter 5, a burden calculation for $NO_2$ alone is not recommended so has not been undertaken. Potential ways in which the overall mortality burden associated with long-term average concentrations of $NO_2$ and $PM_{2.5}$ may be estimated are discussed in detail in Chapter 5 and Working Paper 3. A number of calculations were carried out using various coefficients to provide a range for the possible overall burden on mortality.

The reductions in coefficients used are listed in Table 5.2. The two- and three- pollutant model results from Jerrett et al. (2013), Fischer et al. (2015) ($PM_{10}$ rather than $PM_{2.5}$), Beelen et al. (2014) and Crouse et al. (2015a) (with ozone) were used. The other multipollutant studies were excluded as discussed in Chapter 5.

For each study the $NO_2$ coefficient was adjusted for PM and vice versa, and the adjusted coefficient compared with the relevant single-pollutant coefficient to derive a range of paired percentage reductions. These reductions were then used to reduce the $NO_2$ single pollutant model summary estimate derived from our meta-analysis (1.023 per 10 $\mu g/m^3$) and the summary coefficient for $PM_{2.5}$ derived from the Hoek meta-analysis (1.06 per 10 $\mu g/m^3$) to provide a range of pairs of reduced summary HR per 10 $\mu g/m^3$. These are presented in Table 5.2.

The summary estimates and the pairs of reduced HRs were combined with the relevant population-weighted mean concentration for England, Wales, Scotland and Northern Ireland with or without the relevant cut-off of $NO_2$ above 5 $\mu g/m^3$ and anthropogenic $PM_{2.5}$ above 7 $\mu g/m^3$ (see Table 8.3 and Working Paper 3).

The relevant age-specific deaths recorded for 2013 were then multiplied by the attributable fraction ((scaled HR-1)/scaled HR) to give numbers of deaths attributable to pollution. These were then multiplied by the baseline expected remaining life expectancy to derive life years lost.

The results of attributable deaths and life-years lost for each paired reduction were summed. Then the results from constituent countries were summed to the UK.

## 8.3 Cut-off and counterfactual for quantification

The Committee agreed (see Chapter 6**)** that calculations using two approaches would be undertaken when quantifying effects of mortality from long-term average concentrations of $NO_2$:

a Not using a cut off (0 μg/m$^3$) and assuming a linear dose-response relationship continues below the range of studied concentrations

b Using a cut-off of 5 μg/m$^3$. i.e. subtracting value of 5 from the 1 km x 1 km grid concentrations. For example, for a 1 km x 1 km grid concentration of 30 μg/m$^3$, a concentration of 25 μg/m$^3$ was used and any 1 km x 1 km grid below 5 μg/m$^3$ set to zero.

## 8.4 Pollution estimates

### 8.4.1 Scale of modelling

Finer scale modelling of $NO_2$ is likely to lead to greater exposure contrasts and reduced misclassification of exposures as the effect of emissions from roads is subject to less spatial averaging than for coarser scale modelling. It may also indirectly represent other traffic pollutants to a greater degree than broader scale modelling. Previous discussions on $PM_{2.5}$ (COMEAP, 2010) suggested the possibility of larger coefficients in studies modelling exposure at a finer spatial scale and comparing the null result in the ACS study (Krewski et al., 2009) with later studies using Land Use Regression (LUR) models suggested this was also the case for $NO_2$. This suggested that it was important to examine the spatial scale of the studies used in the meta-analysis done for this report.

A range of scales were used in the studies investigating the association between long-term average concentrations of $NO_2$ and mortality and used in the meta-analysis of single-pollutant coefficients. Of the studies included in the meta-analysis, four used land use regression and the home address/postcode[17] (Cesaroni et al., 2013, Crouse et al., 2015b, Hart et al., 2011, Beelen et al., 2014) and another used it to develop a 100 x 100m grid (Fischer et al., 2015). Others used central monitoring station data and related it to zipcode (Krewski et al., 2009 HEI, 2000, Lipsett et al., 2011 Abbey et al., 1999). Some of these central monitors were reported to be up to 50 km away from the postcode (Abbey et al., 1999). One study used dispersion modelling at a 1 km x 1 km scale (Carey et al., 2013) and another used chemistry and emission data models to link to postcode (Bentayeb et al., 2015).

[17] This does not necessarily mean that the exposure metric is as fine as address level, as neighbouring addresses could be allocated the same value. The variables put into the LUR model may have different geographical scales and the contribution of each variable to the model may vary. This is not always clear from the papers.

Faustini et al. (2014) undertook separate meta-analyses with and without studies with potentially more accurate exposure assessment (defined as those using LUR models, dispersion models or other address level models) and did not find much difference in the meta-analytical central estimate or the degree of heterogeneity. Nonetheless, the spatial scale issue potentially remains an important consideration as illustrated by a recent study in 10 Canadian cities (Crouse et al., 2015b) that found a greater effect for within-city rather than between city exposure metrics. As the scale of modelling used in the available cohort studies is varied and not always clear, it was agreed that it would be appropriate and pragmatic to use the modelling utilised by Defra that is already available across the whole of the UK, at 1 km by 1 km scale. Sensitivity analyses comparing this with finer scale modelling available in London is described in Working Paper 4.

### 8.4.2 Modelling of $NO_2$ concentrations across the UK for 2013

Annual mean $NO_2$ concentrations have been estimated at a spatial resolution of 1 km × 1 km grid squares across the UK for 2013. Figure 8.1 shows a map of annual mean ambient $NO_2$ concentrations for 2013, with an inset showing London at a higher resolution (Defra, 2016). The Pollution Climate Mapping (PCM) model has been used to calculate these estimates. The methods used to model $NO_2$ concentrations in 2013 for the UK have been described in detail elsewhere (Defra, 2016). Figure 8.2 shows the percentage of the UK population that are resident in areas above various PCM modelled $NO_2$ concentrations in 2013. This was done at 1 km x 1 km grid resolution for the 2011 resident population on a 1 km x1 km basis. Over 96% of the population were resident in grid squares with annual mean concentrations of at least 5 $\mu g/m^3$ in 2013 and just 1% of the population are resident in grid squares with $NO_2$ above 40 $\mu g/m^3$. Figure 8.3 shows the distribution of the UK population within specific bands of $NO_2$ concentrations in 2013.

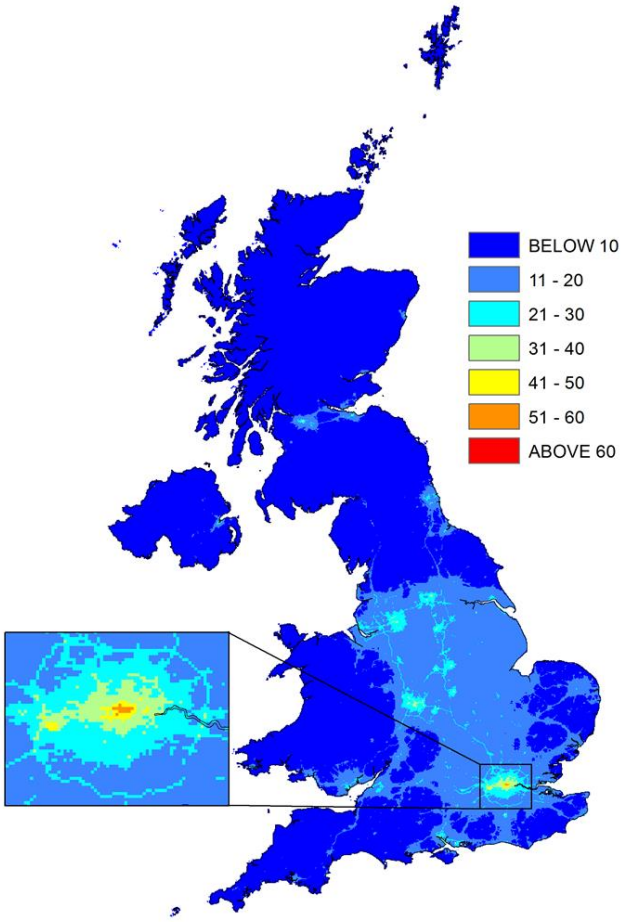


**Figure 8.1: Estimated annual mean $NO_2$ concentration in 2013 (µg/m³). The inset shows London at higher resolution.**

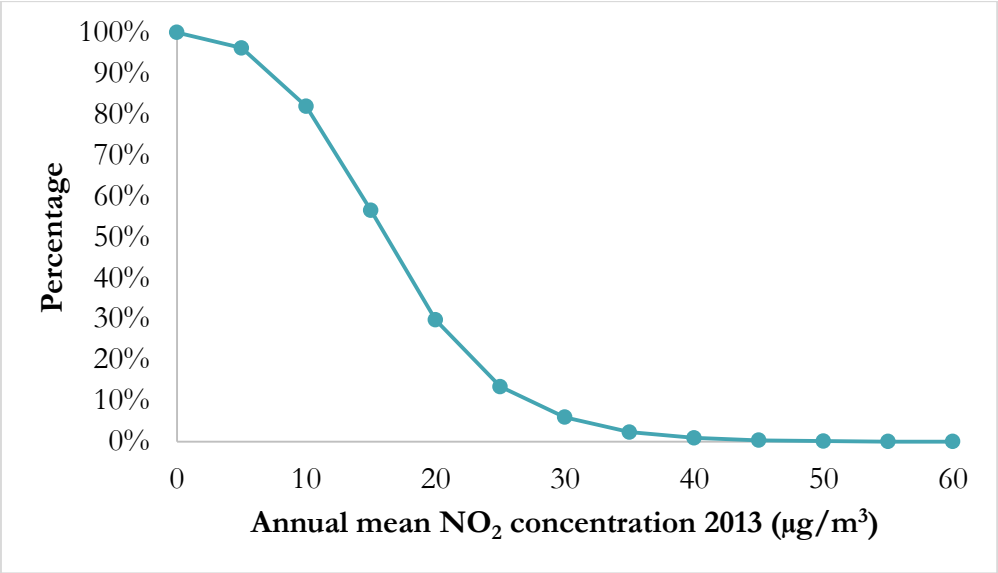


**Figure 8.2: Percentage of UK resident populations above various PCM modelled $NO_2$ concentrations in 2013 at 1 km x 1 km grid resolution for the 2011 resident population also on a 1 km x 1 km basis**

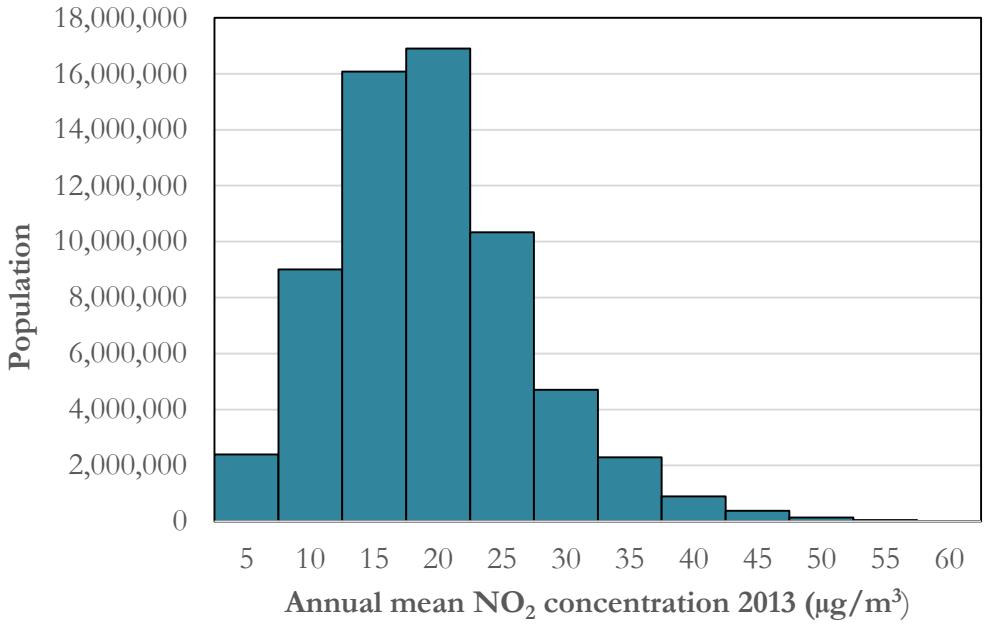


**Figure 8.3: Distribution of UK population within specific bands of concentrations of $NO_2$ in 2013**

## 8.5 Baseline population data

Baseline 2013 population data including total mid-year estimates of population, total deaths and life expectancy are presented in Table 8.2. Mid-year estimates of population for each country, and total number of deaths (minus neonatal), each by 1 year age group were supplied from the Office for National Statistics, PHE, National Records of Scotland and the Department of Finance and Personnel of Northern Ireland.

**Table 8.2: Baseline 2013 population data (population rounded to the nearest 1000)**

| Country | Total population | Population aged 30 years and over | Total deaths in the population | Life expectancy (years) | |
|---|---|---|---|---|---|
| | | | | Males | Females |
| England | 53,866,000 | 33,744,000 | 473,552 | 79.61 | 83.28 |
| Wales | 3,082,000 | 1,965,000 | 32,138 | 78.37 | 82.39 |
| Scotland | 5,328,000 | 3,440,000 | 54,700 | 77.23 | 81.27 |
| Northern Ireland | 1,830,000 | 1,102,000 | 14968 | 78.41 | 82.51 |
| UK total | 64,106,000 | 40,250,000 | 575,358 | - | - |

## 8.6 Population-weighted mean concentrations

In brief, the population-weighted mean annual mean $NO_2$ concentration was calculated by multiplying the 1 km × 1 km annual mean $NO_2$ concentration values from the PCM model for 2013 by 1 km × 1 km population statistics for all ages derived from the 2011 census. The values for all of the grid squares were summed and then divided by the total population summed across each area. Population-weighted mean $NO_2$ concentrations for a range of geographic areas are presented in Table 8.3.

Table 8.3 and Figure 8.1 indicate that $NO_2$ concentrations vary across the UK, with the highest population-weighted mean $NO_2$ in inner and outer London, reflecting local, particularly traffic, sources. Population-weighted mean $NO_2$ for Scotland, Wales and Northern Ireland tends to be lower than in England.

The concentration above 5 $\mu g/m^3$ is not a simple subtraction of 5 $\mu g/m^3$ from the total concentration, since the concentration input prior to the population-weighting is based on concentrations in individual 1 km by 1 km grid squares, and in some cases, the concentration will be below 5 $\mu g/m^3$. In the latter case, the concentration used in the burden estimate would be set to zero and the population-weighting would only be based on the population in the other 1 km by 1 km grid squares.

**Table 8.3: Population-weighted mean $NO_2$ concentration in 2013 (µg/ $m^3$)**

| Country | Population-weighted mean $NO_2$ concentration (µg/$m^3$) | |
|---|---|---|
| | **Total** | **Above 5** |
| England | 18.63 | 13.64 |
| Wales | 12.28 | 7.29 |
| Scotland | 10.92 | 6.14 |
| Northern Ireland | 8.53 | 3.76 |
| UK | 17.39 | 12.42 |

## 8.7 Cessation lag

There is likely to be some delay in the reduction of mortality risk following a reduction in pollution. Therefore, calculations of the impact of reductions in air pollution should take account of the cessation lag, which denotes the time pattern of reductions in mortality hazards following a reduction in pollution. However, there is little direct evidence about what these time patterns are likely to be.

When quantifying the mortality impacts associated with long-term exposure to $PM_{2.5}$, COMEAP (2010) used the cessation lag structure recommended by the US Environmental Protection Agency (US EPA, 2004, 2010). In this distribution, 30% of the risk reduction occurs in the first year after pollution reduction, 50% occurs across years 2–5 (i.e. 12.5% per year) and the remaining 20% of the risk reduction is distributed across years 6–20 with smoothed annual values. These three components of the distribution reflected short-term, cardiovascular and lung cancer effects, respectively.

We considered it would be reasonable to use the same distribution of risk reduction for impact assessments undertaken on the basis of coefficients linking $NO_2$ with mortality. The following paragraphs summarise some of the relevant evidence regarding epidemiological associations and likely causality of $NO_2$. These indicate that there is more uncertainty in applying this cessation lag distribution in assessments in which a reduced coefficient is used to estimate effects attributable to reductions in exposure to $NO_2$ itself, than in using it in assessments in which an unadjusted coefficient is used to estimate the effects of a reduction in a mixture of traffic-related pollutants. Nonetheless we have previously shown (COMEAP, 2010) that cost-benefit analyses are more sensitive to other assumptions such as economic discounting than to the cessation lag used.

The assumption that some of the effect occurs in the first year is consistent with an immediate reduction in respiratory exacerbations, such as those reflected in short-term associations in time-series studies between $NO_2$ and respiratory hospital admissions and emergency room visits, especially for asthma. Many studies have demonstrated that these associations are not confounded by co-pollutants, including $PM_{10}$ and common gaseous pollutants, but there is insufficient information about adjustment for ultrafine particles (WHO, 2013a).

A reduction across years 2-5 might reflect cardiovascular effects. The REVIHAAP authors noted that new evidence continues to show positive associations between short-term increases in $NO_2$ concentrations and hospital admissions and emergency room visits for cardiovascular and/or cardiac diagnoses, but there are mixed results from multi-pollutant studies. They also noted that cohort studies report associations between long-term average concentrations of $NO_2$ and cardiovascular mortality (WHO, 2013a). However, there are only a small number of chamber studies that investigate direct effects of $NO_2$ on the cardiovascular system with most, but not all, finding no evidence (WHO, 2013a; US EPA, 2016).

There is variable evidence for cancer effects: positive associations between long-term exposure to $NO_2$ and lung cancer mortality have been reported in some studies (Carey et al., 2013, Cesaroni et al., 2013, Jerrett et al., 2013, Næss et al., 2007, Brunekreef et al., 2009, Hamra et al., 2015) but others have reported no associations with lung cancer incidence (Raaschou-Nielsen et al., 2013, Brunekreef et al., 2009, Krewski et al., 2009). The toxicological evidence does not suggest that $NO_2$ is a direct carcinogen. A cancer bioassay of exhaust emissions from a modern diesel engine with only low levels of PM emissions, undertaken as part of the Advanced Collaborative Emissions Study (ACES), showed no carcinogenic effects, although lung toxicity consistent with long-term exposure to high doses of $NO_2$ was observed. The authors noted that if $NO_2$ was, in part, acting as a marker for other emissions then the cancer effect seen in epidemiology studies could be due to polycyclic aromatic hydrocarbons or metals (Greenbaum et al., 2013). The US EPA concluded that the evidence from some epidemiologic studies for lung cancer incidence and mortality combined with some toxicological evidence for lung tumour promotion is suggestive of, but not sufficient to infer, a causal relationship between long-term $NO_2$ exposure and cancer (US EPA, 2016).

In the absence of any direct evidence to indicate an alternative cessation lag to that used to quantify the mortality impacts associated with long-term exposure to $PM_{2.5}$, and the fact that $NO_2$ may act as a marker for other emissions, it was considered appropriate for impact calculations to use the same cessation lag.as that used for the COMEAP (2010) report for PM. This was applied in the impact calculations but not the burden calculations as the latter represents a 'snapshot' view and assumes that concentrations have been at similar levels over time or that effects are instantaneous. This is discussed in COMEAP (2010). The cessation lag used in impact assessments assumed the following:

a 30% of the risk reduction occurs in the first year after pollution reduction,

b 50% occurs across years 2–5 (i.e. 12.5% per year)

c the remaining 20% of the risk reduction is distributed across years 6–20 with smoothed annual values.

## 8.8 Additional analyses

### 8.8.1 Modelling of $NO_2$ concentrations across London for 2010

Concentrations of $NO_2$ vary over small spatial scales; therefore using 1 km by 1 km modelling is liable to under-estimate population exposure. Within-city variation in $NO_2$ is likely to be large because $NO_2$ arises from local sources and is known to vary over smaller areas in proximity to traffic (Gililand et al., 2005) so the finer the scale of modelling, the higher the

population-weighted exposure may be. Drs Heather Walton and David Dajnak, King's College London undertook a range of sensitivity analyses for London to provide information on the importance of spatial scale, including the uncertainty due to different methodological assumptions around the PCM regional estimate for London, as well as the uncertainty due to different methodological assumptions regarding population weighting methodology.

The methods and results are detailed in Working Paper 4. Broadly, the methods followed those in COMEAP (2010) and those for the main calculations in this report. The interim recommendations for the coefficient, counterfactuals and approach to cessation lag were used. The differences in the methods to take advantage of more detailed data available in London generally follow Walton et al. (2015). The Working Paper is intended only as an illustration of the principles of changing spatial scale rather than the absolute value of the results. Its overall conclusion is that the spatial scale of the modelling had only a minor effect upon the calculated mortality effects in the case of London.

#### *8.8.1.1 Differences between PCM modelling and LAQT modelling*

For the main calculations annual mean $NO_2$ concentrations were estimated using the PCM model at a spatial resolution of 1 km x 1 km for 2013. For London, annual mean $NO_2$ concentrations were estimated using the London Air Quality toolkit (LAQT) dispersion model at a spatial resolution of 20 m × 20 m (and scaled up to 1 km) grid squares across London for 2010. Before the difference between the scale of modelling could be explored, it was important to investigate whether the following might influence the result:

a. Difference in year for the PCM modelling (2010 vs 2013),
b. Difference in year for both modelling and population/mortality rates
c. Then calculations were done to explore the difference between PCM modelling 1 km x 1 km and LAQT modelling 20 m x 20 m.

The choice of model for $NO_2$ concentrations does have an influence on the mortality estimates. The LAQT model gave results that were about 12-14% higher than the PCM model.

The results comparing the PCM and LAQT model were compatible with an effect of modelling scale. This is expected for finer scale modelling picking up higher more local concentrations but there are also other possible explanations, and as this is only one of the differences between the models, this was hard to confirm.

The results for the alternatives of a zero and 5 μg/m$^3$ counterfactual also vary considerably. Burden results were not calculated for other counterfactuals in London but the population-weighted mean exposure concentration used in the estimates decreases proportionately as the counterfactual increases from zero to 15 μg/m$^3$ (no areas of London were below 15 μg/m$^3$).

Working up from 20 m x 20 m modelling, population-weighting by output area rather than 1 km x 1 km grid did not make a large difference, despite different underlying distributions of population and concentration by OA and 1 km x 1 km grid. Output areas identify both areas of low concentration and population in generally high concentration areas, and areas of high concentration and population in generally low concentration areas. When all areas are above the relevant cut off, this probably averages back to a similar result. Using more disaggregated inputs such as borough concentrations and mortality rates very slightly increased the difference

between population-weighting by output area and 1 km x 1 km grid but they were still very similar.

The overall conclusion is that the spatial scale of the modelling had only a minor effect upon the calculated mortality effects in the case of London.

# Chapter 9
# Quantification results

## 9.1 Results of the impact calculations

### 9.1.1 Impact calculations assessing the benefits of interventions that primarily target emissions of $NO_x$

The benefits of a sustained 1 μg/m$^3$ reduction in annual average $NO_2$ across the UK, arising from measures that primarily target emissions of $NO_x$, were estimated.

A range of the likely benefits was calculated using 25% and 55% of 1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ annual average $NO_2$ i.e. 1.006 and 1.013 per 10 μg/m$^3$. Note that the range includes only the uncertainty related to the extent that the coefficient expresses a causal effect of $NO_2$ itself; it does not incorporate uncertainty expressed by the CI around the coefficient.

The estimated range of life years gained as a result of this reduction and the impact on life expectancy are presented in Table 9.1.

We also recommend that when assessing the benefits of interventions that primarily target emissions of $NO_x$, assessment of the benefits of reductions in secondary nitrate (distant from source) due to reduced $NO_x$ emissions are derived using the unadjusted coefficient 1.06 (95%CI:1.04-1.08) per 10 μg/m$^3$ annual average $PM_{2.5}$. This has not been done for these illustrative examples because it would require details on the specific policy intervention used and modelling of secondary nitrate concentrations.

The results show that a 1 μg/m$^3$ reduction in population-weighted annual average $NO_2$ concentrations would lead to 2-5 days increase in life expectancy from birth and life years gained across the population (over a period of 106 years) in the range of 420,000-903,000. The estimated benefits would be greater if the benefits of reducing secondary nitrate were included. The estimated life years gained are similar across the countries when the impacts per 100,000 population aged 30 years and over are calculated: for each of the four countries they were estimated as within the range of 1,000-2,200 life years per 100,000 population. This shows that the full population impacts scale approximately on the basis of population size.

These predicted mortality benefits are estimated across the whole population or birth cohort; it is not possible to determine from these results how the life years gained would be distributed between individuals within the cohort (see COMEAP 2010 for a detailed discussion of the distribution across individuals). 'Life expectancy at birth' is a forward-looking index that applies

to everybody in the population at birth; it doesn't express what actually happens to each individual afterwards.

**Table 9.1: Estimated range of life years gained (rounded to the nearest 1000) over 106 years by population including new births following a reduction of 1 μg/m³ annual average in $NO_2$**

| Pollution reduction | Country | Population-weighted mean concentration (μg/m3) | Range of Life-years gained | Range of increased life expectancy (days) for the 2013 birth cohort | |
|---|---|---|---|---|---|
| | | | | Males | Females |
| 1 μg/m³ | England | 1 | 350,000 – 757,000 | 2 -5 | 2-4 |
| | Wales | 1 | 20,000 – 43,000 | 2 -5 | 2-4 |
| | Scotland | 1 | 35,000 – 76,000 | 2 -5 | 2-5 |
| | N Ireland | 1 | 12,000 – 27,000 | 2 -5 | 2-4 |
| | UK total | 1 | 420,000 – 903,000 | 2 -5 | 2-4 |

* Life years gained for the UK is calculated by summing the separate country results. Life expectancy for the UK is calculated by weighting separate country results by relevant population size.

There is no formal way of assessing the statistical uncertainty around this range of estimates. The ranges reported reflect expert opinion on the likely importance of $NO_2$ itself as a causal factor of the associations reported in epidemiological studies. It does not include other uncertainties such as are reflected in the 95% confidence interval of the summary single-pollutant coefficient obtained by meta-analysis.

### 9.1.2 Impact calculations assessing the benefits of interventions that reduce traffic-related pollutants

To calculate the impact of interventions that reduce $NO_2$ and other traffic-related pollutants, the coefficient 1.023 (95% CI: 1.008, 1.037) per 10 μg/m³ annual average $NO_2$ is recommended and was used in the illustrative calculations below.

The impacts of 1 μg/m³ reduction were estimated. The life years gained as a result of this reduction and the impact on life expectancy are presented in Table 9.2.

**Table 9.2: Estimated life years gained over 106 years by population including new births following a reduction of 1 µg/m³ annual average in $NO_2$ and also proportionate reductions in other traffic-related pollutants**

| Pollution reduction | Country | Population-weighted mean concentration (µg/m³) | Life-years gained | Increased life expectancy (days) for the 2013 birth cohort | |
|---|---|---|---|---|---|
| | | | | Males | Females |
| 1 µg/m³ | England | 1 | 1,332,000 | 8 | 8 |
| | Wales | 1 | 75,000 | 8 | 8 |
| | Scotland | 1 | 134,000 | 9 | 8 |
| | N Ireland | 1 | 47,000 | 8 | 8 |
| | UK total | 1 | 1,589,000 | 8 | 8 |

Interventions that target traffic pollution in general rather than $NO_x$ emissions alone are estimated as having a greater benefit for life expectancy and life years gained.

The results show that a 1 µg/m³ reduction would lead to a gain of around 1.6 million life-years for the UK over a period of 106 years and an increase in life expectancy for the 2013 birth cohort of 8 days. The estimated life years gained are similar across the countries when the impacts per 100,000 population aged 30 years and over are calculated (4,000 for each country).

When assessing interventions, a calculation using 1.06 (95% CI: 1.04-1.08) per 10 µg/m³ annual average $PM_{2.5}$ can also be performed and then the higher of the values from the $NO_2$ or $PM_{2.5}$ calculations can then be used to express the impact.

### *9.1.2.1 Uncertainty based on the lower and upper confidence intervals*

The statistical uncertainty around impact calculations assessing the benefits of interventions that reduce traffic-related pollutants is given by upper and lower confidence estimates (1.008 and 1.037) These suggest that the actual impacts could be between about one-third and 1½ times the central estimate.

For a fuller discussion of the concepts highlighted by impact calculations in general, refer to Chapter 5 of the 2010 $PM_{2.5}$ report (COMEAP, 2010).

## 9.2 Results of the burden calculations

As explained earlier in this report, those Members who felt that burden calculations are justified placed more confidence in the calculation of a burden due to exposure to the pollutant mixture than attempting to estimate burdens due to $NO_2$ and $PM_{2.5}$ exposures separately. Given the uncertainties it was decided that this should be presented as a range, rather than as a point estimate.

Three approaches were used to estimate the burden due to the pollutant mixture, using either an unadjusted single-pollutant coefficient for $PM_{2.5}$, an unadjusted single-pollutant coefficient for $NO_2$, or pairs of mutually adjusted coefficients for both $PM_{2.5}$ and $NO_2$. The results are summarised in Table 9.3 and were as follows:

### 9.2.1 Coefficients from single pollutant models

a Calculation from the single pollutant coefficient for $PM_{2.5}$. This indicates a mortality burden in the UK in 2013 due to the overall anthropogenic pollutant mixture equivalent to 29,000 deaths at typical ages, and an associated loss of 330,000 life years. This is very similar to COMEAP's (2010) estimate of the mortality burden in 2008. Both of these estimates are based on the assumption that the risk coefficient, based on evidence of effects above 7μg/m³ annual average $PM_{2.5}$, also applies at lower concentrations. This is consistent with the Committee's view that there is no 'safe level' of $PM_{2.5}$. However, some Members do not support such extrapolation beyond the range of the data, i.e. using the risk coefficient at concentrations lower than where effects have been demonstrated.

The effects on mortality of air pollution at concentrations above a cut-off of 7 μg/m³ annual average $PM_{2.5}$ are 151,000 life years lost, equivalent to 13,000 attributable deaths UK-wide in 2013. This shows that a little less than half of the larger estimate without a cut-off (of 330,000 life years lost, equivalent to 29,000 deaths) is based on concentrations which do not require extrapolation, i.e. this portion of the larger number is more firmly established in evidence. Some Members do not support the use of these lower 'above cut-off' numbers as an answer to the burden question: they consider that, by ignoring any effect on mortality of air pollution when annual average $PM_{2.5}$ is lower than 7 μg/m³, these 'above cut-off' results are necessarily an under-estimate of the full mortality effect.

b Calculation from the single pollutant coefficient for $NO_2$. This results in an estimate of a mortality burden equivalent to 22,000 attributable deaths associated with a loss of 252,000 life years in the UK in 2013, without a cut-off. The estimated effect is equivalent to 16,000 deaths, associated with 181,000 life years lost, if a cut-off of 5 μg/m³ is used. Similar issues of interpretation apply as for quantification based on $PM_{2.5}$, above. For $NO_2$, the overall estimate without a cut-off is lower than for $PM_{2.5}$; but the percentage of that estimate which does not require extrapolation is higher, at approximately 70%.

The single-pollutant estimate for $NO_2$ should not be added to the figure for $PM_{2.5}$ due to double counting. Also, because any single-pollutant estimate is likely to underestimate the effect of the mixture as a whole, the higher of these two single-pollutant estimates is preferred. For estimation without cut-off, this is an effect equivalent to 29,000 deaths in 2013, associated with 330,000 life years lost, using $PM_{2.5}$ as a marker. For estimation with cut-off, it is equivalent to 16,000 attributable deaths, associated with 181,000 life years lost, using $NO_2$ as a marker.

### 9.2.2 Coefficients from two or multi-pollutant models

Four separate calculations were undertaken, each using adjusted coefficients for both $NO_2$ and $PM_{2.5}$ derived using information from one of four available informative studies. For each study, the percentage reduction in $NO_2$ coefficient on adjustment for PM was applied to the unadjusted summary $NO_2$ coefficient used in (b) above. Similarly, the percentage reduction in $PM_{2.5}$ coefficient on adjustment for $NO_2$ was applied to the unadjusted summary $PM_{2.5}$ coefficient used in (a) above. The estimated burdens obtained using these mutually adjusted

summary coefficients were then summed (within each study) to give an estimated burden of the air pollution mixture.

Estimates without a cut-off gave results from the four studies of 373,000, 363,000, 416,000 and 328,000 life years lost based on Jerrett et al. (2013), Fischer et al. (2015), Beelen et al. (2014) and Crouse et al. (2015a), respectively. Corresponding numbers of equivalent deaths UK-wide in 2013 were 32,000; 31,000; 36,000 and 28,000. Analyses above a cut-point gave corresponding estimates of 224,000; 211,000; 222,000 and 207,000 life years lost and equivalent deaths of 19,000; 18,000; 19,000 and 18,000 across the same four studies respectively.

We have not estimated the burden in terms of loss of life-expectancy from birth. However, given that the mortality burden estimates reported above, expressed as attributable deaths or years of life lost, are similar to those in our previous report (COMEAP, 2010), it is likely that burdens expressed as loss of life-expectancy from birth would also be similar to our previous estimates. These figures were: an average loss of between three and four months of life expectancy in Scotland and Northern Ireland, and between six and seven months in England and Wales.

**Table 9.3: Illustrative estimates of the mortality burden of anthropogenic air pollution in the UK in 2013, based on associations with $NO_2$ and PM**

| Mortality burden of air pollution in the UK in 2013 | | | | | | |
|---|---|---|---|---|---|---|
| **General method for approximating burden of air pollution mixture** | **Single-pollutant (sp)[1] summary estimate for $NO_2$ or $PM_{2.5}$[2]** | | **Combining pairs of mutually-adjusted coefficients ($NO_2$ adjusted for $PM_{2.5}$ and *vice versa*)[3]** | | | |
| **Specific method (concentration-response functions) for approximating burden of air pollution mixture** | **$NO_2$ sp summary estimate (this report) HR 1.023 (1.008, 1.037)** | **$PM_{2.5}$ sp summary estimate (Hoek et al., 2013) HR 1.06 (1.04, 1.08)** | **Jerrett et al. (2013) Adj $NO_2$ HR 1.019 Adj $PM_{2.5}$ HR 1.029** | **Fischer et al. (2015) ($PM_{10}$) Adj $NO_2$ HR 1.016 Adj $PM_{10}$ HR 1.033** | **Beelen et al. (2014) Adj $NO_2$ HR 1.011 Adj $PM_{2.5}$ HR 1.053** | **Crouse et al. (2015a) ($+O_3$) Adj $NO_2$ HR 1.020 Adj $PM_{2.5}$ HR 1.019** |
| **Number of "attributable" deaths[4]** | 22,000 | 29,000 | 32,000 | 31,000 | 36,000 | 28,000 |
| **Years of life lost[4]** | 252,000 | 330,000 | 373,000 | 363,000 | 416,000 | 328,000 |
| **"Central" estimates of calculations using cut-offs for quantification: (5 µg/m³ for $NO_2$; 7 µg/m³ for $PM_{2.5}$)** | | | | | | |
| **Number of "attributable" deaths[4]** | 16,000 | 13,000 | 19,000 | 18,000 | 19,000 | 18,000 |
| **Years of life lost[4]** | 181,000 | 151,000 | 224,000 | 211,000 | 222,000 | 207,000 |

1. sp = single pollutant (as indicator of a mixture).

2. $PM_{2.5}$ refers to anthropogenic $PM_{2.5}$.

3. Coefficients are the summary coefficients reduced by the percentage reduction from unadjusted to adjusted coefficients from each study (see Table 5.2).

4. Rounded to nearest 1,000

With the exception of results based on coefficients from Crouse et al. (2015a), which were additionally adjusted for ozone, the estimates obtained by combining calculations using mutually-adjusted pollutant estimates are all higher than those obtained using unadjusted single-pollutant coefficients. This suggests that, if it is assumed that the multi-pollutant model results can be taken at face value, there is not complete overlap of the associations of mortality with $NO_2$ and $PM_{2.5}$ concentrations. Note that this conclusion does not require that $NO_2$ itself is responsible for this increase, although it may contribute. It could simply be a better reflection than $PM_{2.5}$ of effects of some traffic pollutants.

The results also suggest that the previous burden calculations by COMEAP (2010) for $PM_{2.5}$ may have underestimated the burden of air pollution to some extent, if they are regarded as a reflection of the air pollution mixture as a whole. They are however consistent with the qualitative conclusion of COMEAP's Interim Statement (2015) on quantification of $NO_2$ that "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". Indeed the quantitative results from the four studies, if taken at face value, indicate what "similar to or only a little higher than" means in practice. Nonetheless, the many uncertainties and limitations of the methods used to generate each estimate should be recognised.

### 9.2.3 Discussion of some methodological issues

We acknowledge that there are a number of methodological issues which, when performing calculations in this way, contribute to uncertainty in burden estimates. Nonetheless, we consider that these have been addressed to some extent by the studies selected and approach taken. For example:

Correlated pollutants: Studies with high correlation between PM and $NO_2$ were not selected when considering percentage reductions.

Possible interaction between $PM_{2.5}$ and $NO_2$: We do not know the extent to which there may be an interaction between the effects of $PM_{2.5}$ and $NO_2$, i.e. whether the coefficient for $PM_{2.5}$ changes depending on the concentrations of $NO_2$ (and other associated pollutants), and vice-versa. The relevant cohort studies did not report the required information to assess whether such an effect, if present, was statistically significant or to be able to quantify the possible effects on burden estimates. However, there is no evidence that the effect of any interaction, taken in conjunction with the adjusted coefficients representing the effects of the individual pollutants, would have a significant effect on the overall burden estimates.

Exposure misclassification: In certain situations, when pollutants are highly correlated and the accuracy with which exposures can be estimated varies between pollutants, there is the possibility of some 'transfer' of effect from the pollutant with greater misclassification (measurement error) to the one for which estimated exposure more accurately represents 'true' exposures, even if the former relationship was causal. There are many aspects to potential errors in estimating exposure, including spatial variation and errors arising due to infiltration indoors and of people's movements throughout the day. Whether these contributions are larger or smaller for $NO_2$ relative to PM is unclear.

Transferability of relationships between locations: Transferability depends on the nature and extent of the differences between the study location (and its pollution and other characteristics, including population, death rates etc.) and corresponding characteristics of the location where the results are being applied, in this instance the UK. It is not clear how much uncertainty this might have introduced into our estimates. Nonetheless, we think that there is less uncertainty in using pairs of adjusted coefficients to jointly estimate the effect of a mixture, than in using individual adjusted coefficients (or pairs of adjusted coefficients) to estimate separately the effects associated with the $NO_2$ or $PM_{2.5}$, because it is possible to be more confident about the estimated effect of a mixture while retaining doubts about the independent contribution of individual components which contribute to the overall summed estimate.

## 9.3 Summary of results

For a reduction in all traffic-related pollutants, consistent with a sustained 1 μg/m$^3$ reduction of $NO_2$, we estimate that about 1.6 million life years could be saved in the UK over the next 106 years, and that life expectancy (at birth) would be increase by around 8 days.

For a 1 μg/m$^3$ reduction in $NO_2$, without a corresponding reduction in concentrations of other traffic-related pollutants, we estimate that about 420,000 to 903,000 life years could be saved in the UK over the next 106 years, and that life expectancy (at birth) would be increased by around 2 to 5 days. We emphasise that these are indicative results because of the need to estimate, using expert judgement, the extent to which observed associations between $NO_2$ and mortality are caused by $NO_2$ rather than other pollutants.

Using an approach of undertaking several individual exploratory calculations, the range of estimates of the mortality burden of the air pollution mixture (based on associations with $PM_{2.5}$ and $NO_2$) in 2013 in the UK is an effect equivalent to 28,000 to 36,000 deaths at typical ages, associated with a loss of 328,000 – 416,000 life years. The range reflects the higher of the two estimates obtained by using single-pollutant coefficients as well as estimates based on reductions of $NO_2$ and $PM_{2.5}$ coefficients in four different studies following mutual adjustment. It does not take into account uncertainties such as those reflected in the confidence interval around the unadjusted coefficient.

Lower results (an effect equivalent to 16,000 – 19,000 deaths and an associated loss of 181,000 – 224,000 life years) are obtained when cut-offs for quantification are implemented. These figures avoid extrapolating the concentration-response relationships to concentrations lower than those which have currently been studied, and therefore represent the portion of the estimated burden in which there is greatest confidence.

There are uncertainties in these estimates, but we have not been able to fully quantify that uncertainty.

# Chapter 10
# Views of the dissenting group

## 10.1 Introduction

As indicated in the Executive Summary, a number of differences of opinion arose during the preparation of this report. Members failed to resolve these differences by discussion and it was agreed that Richard Atkinson, Robert Maynard and Ross Anderson should prepare a Minority Report setting out their views and indicating those points in the fore-going chapters from which they wished to disassociate themselves. The current chapter and its two annexes comprise that Minority Report. It will be seen that the key area of disagreement related to burden calculations. It should not be thought that the authors of the Minority Report disagree with all the views expressed in the fore-going chapters: on the contrary they agree with many of the views set out and with many of the conclusions and recommendations. These agreements/disagreements are noted in the fore-going chapters.

## 10.2 Background

In 2010 COMEAP published a report quantifying the mortality burden associated with long-term exposure to particulate air pollution represented by a widely used metric of the ambient aerosol: $PM_{2.5}$ (COMEAP, 2010). The burden calculation used a coefficient (Hazard Ratio (HR)) associating $PM_{2.5}$ with the risk of mortality recommended by an earlier COMEAP report (COMEAP, 2009a). The recommended coefficient came from a US cohort study (Pope et al., 2002) and was unadjusted for co-pollutants. COMEAP recognised that the coefficient could not be guaranteed to reflect only the effects of $PM_{2.5}$: the possibility that it also represented the effects of gaseous air pollutants, including $NO_2$, was considered but, at that time, it was felt that the evidence supporting an effect of $NO_2$ was weak.

Evidence associating $NO_2$ with an increased risk of mortality has accumulated since 2010. The WHO REVIHAAP review (WHO, 2013a) is the most recent, comprehensive and impartial (i.e. non-governmental, non-advocacy) review of the literature. The main lines of evidence to support a causal role of $NO_2$ were based on short-term exposure studies – epidemiological, human chamber and toxicological. REVIHAAP concluded 'As there is consistent short-term epidemiological evidence and some mechanistic support for causality, particularly for respiratory outcomes, it is reasonable to infer that $NO_2$ has some direct effects.' With respect to effects of long-term exposure to $NO_2$ it was more cautious concluding that: 'It is much harder to judge the independent effects of $NO_2$ in the long-term studies because, in those investigations, the correlations between concentrations of $NO_2$ and other pollutants are often high, so that $NO_2$ might represent the mixture of traffic-related air pollutants. In this case, chamber studies do not apply and toxicological evidence is limited. However, some epidemiological studies do suggest associations of long-term $NO_2$ concentrations with

respiratory and cardiovascular mortality and with children's respiratory symptoms and lung function'.

Recent reviews by the US EPA (US EPA, 2016) and Health Canada (Health Canada, 2016) concluded that the evidence for long-term $NO_2$ concentrations and total mortality was suggestive, but not sufficient, to infer a causal relationship. It is widely recognised that $NO_2$ acts, in part, as a marker of traffic-related pollutants including ultrafine particles. COMEAP's own assessment of the evidence (COMEAP, 2015b) based upon authoritative reviews and additional evidence concluded 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'.

The $NO_2$ subgroup has undertaken a quantitative systematic review of cohort studies reporting HRs for long-term $NO_2$ concentrations and all-cause mortality. This review included an assessment of studies reporting results from two pollutant models incorporating $NO_2$ and $PM_{2.5}$. This review found:

a. Based upon 10 cohort studies, the random-effects summary HR for $NO_2$ from single pollutant models was 1.021 (95% CI: 1.006, 1.036) per 10 $\mu g/m^3$

b. There was substantial heterogeneity ($I^2$=97%) between these 10 estimates

c. There was substantial evidence of effect modification by level of covariate adjustment: 1.008 (95% CI: 0.993, 1.024) in studies controlling for the required individual confounding factors vs 1.031 (95% CI: 1.025, 1.037) per 10 $\mu g/m^3$ in those that did not

d. Six studies reported results from two-pollutant models containing $NO_2$ and $PM_{2.5}$. Correlations between $NO_2$ and $PM_{2.5}$ were high in 2 studies (0.79 and 0.85), moderate in 2 studies (0.2-0.7 and 0.55) and weak (-0.08) in one study. One study used $PM_{10}$ rather than $PM_{2.5}$

Part of the Terms of Reference for the $NO_2$ working group requested:

a. Consideration of how, and under what circumstances, the association between long-term average concentrations of $NO_2$ and mortality should be used …. to quantify the mortality burden attributable to $NO_2$

b. Make recommendations of concentration-response coefficients and quantify the association between long-term average concentrations of $NO_2$ and mortality. Potential quantification questions:

    a. What is the mortality burden to public health in the UK from the effects of long-term exposure to average concentrations of $NO_2$?

    b. What would be the public health benefit of a 1 $\mu g/m^3$ reduction of annual mean $NO_2$ or a reduction to the annual limit value?

c. Comment on any associated uncertainty

This note presents the arguments why burden calculations for long-term concentrations for $NO_2$ and mortality should not be recommended.

## 10.3 The purpose of burden calculations

The COMEAP 2010 report (COMEAP, 2010) estimated the mortality burden of long-term anthropogenic $PM_{2.5}$ concentrations, expressed as the numbers of attributable deaths in England and Wales in 2008. The report asked the following rhetorical question: 'Why then consider burden of disease, which we do not use (or advise using) for assessing the benefits of protective policy?'. Two main reasons were given in the report: (1) the effects of air pollutants on health had become 'a topic of general discussion in the UK, Europe and elsewhere' and 'the underlying purpose [of burden calculation] seems to be to assess the significance of outdoor air pollution as a public health problem, so that by highlighting its importance, the impetus for action can be increased'; and (2) the number of deaths attributable to air pollution was seen to be a more intuitive measure and more easily understood by the general public than an estimate of total or average years of life lost across the population for a given level of air pollution.

The mortality burden published in the 2010 COMEAP report has had the desired effect of highlighting the importance of particulate air pollution to the general public. The burden calculation of 29,000 attributable deaths has been widely quoted in the media and other publications despite numerous caveats relating to its meaning and use described in the report. It is clear that qualifying burden estimates with caveats has no influence on how the burden calculations are interpreted and used by others. Furthermore, there remains widespread ignorance as to what "attributable deaths" mean.

At the time the COMEAP report (COMEAP, 2010) was published it was widely accepted that $PM_{2.5}$ caused premature mortality and that the evidence for a causal role for gaseous pollutants was very limited. The message therefore was relatively straightforward. The current scenario for $NO_2$ (and $PM_{2.5}$), is far more complex. It is now acknowledged that the previously reported mortality effects of $PM_{2.5}$ were likely to be in part due to other correlated pollutants possibly including $NO_2$. Similarly, it is acknowledged that associations between $NO_2$ and mortality represent associations between $NO_2$ and closely correlated pollutants including $PM_{2.5}$. Separating the contributions of the measured (and unmeasured) pollutants is difficult due to the limitations of the data and the statistical models and the paucity of studies investigating this issue.

COMEAP'S original advice to avoid burden calculation (COMEAP, 2010) is therefore particularly relevant given the increased complexity when considering multiple pollutants. At the meeting of the COMEAP Quantification Sub-group (QUARK) in September 2016 it was recognised that the use of HRs derived from multi-pollutant models in (multi-pollutant) burden calculations presents significant conceptual and methodological challenges. It was recognised that QUARK needed to undertake substantial further work in this area. Given that these issues are not well understood at the present time we believe it would be premature to present joint burden calculations for multiple pollutants until the QUARK working group has completed its study of the issues and concluded its work.

COMEAP needs to balance the need to engage with the public with the requirement to provide sound scientific advice including assessment of the uncertainties to Defra. It is recognised by COMEAP (COMEAP, 2016) that in providing an estimate of the number of deaths attributable to $NO_2$ it is possible that it will be misinterpreted and added to the burden estimate for $PM_{2.5}$ (Defra, 2015). COMEAP should resist the temptation to produce 'headline' results justified by an obligation to inform public debate when the evidence base for such

calculations is limited, highly uncertain and complex. Experience with the COMEAP $PM_{2.5}$ report shows that caveats and explanations are largely ignored.

In our view there is an important difference between the level of conviction needed to accept that an association reported by epidemiological studies is likely to represent a causal association and that needed to allow a reliable estimate of the quantitative effects of exposure to be made. The question of causality is considered next followed by an assessment of the evidence needed to enable the reliable calculation of a HR for input to burden calculation.

## 10.4 Evidence for causality

WHO (WHO, 2013a), the US EPA (US EPA, 2016) and Health Canada (Health Canada, 2016) have concluded that $NO_2$ might have a causal relationship with adverse health effects. This was also the conclusion of COMEAP (COMEAP, 2015b). The weight of evidence supporting this conclusion came from short-term studies, especially time-series studies which indicated that in multi-pollutant models, $NO_2$ tended to be robust to adjustment for PM. The terms of reference of the $NO_2$ quantification working group did not include a re-examination of the specific question of the causality of the long-term associations observed in mortality cohort studies. Without such consideration, any estimation of burden based on this evidence might be open to question on two counts:

a The above mentioned reviews were candid about their reliance mainly on short-term exposure evidence from epidemiological and toxicological studies. They were less certain about the causality of long-term exposure associations and noted that this was inferred, in part, indirectly from the short-term evidence

b The current COMEAP Working Group, having commissioned a detailed and up-to- date analysis of available cohort evidence had the opportunity to revisit the causality question but did not do so

Our approach to making a causal judgement follows the guidelines provided by WHO (WHO, 2000). Scientific judgment relating to causality begins with determining whether an association can be explained by 1) chance and/or 2) confounding. If this is not the case, the conventional approach is to apply what are referred to as Bradford Hill's criteria as a framework for making a judgement (in fact he used the terms "aspects" and "viewpoints") (Hill, 1965). The nine viewpoints are: strength of association, consistency of evidence, specificity of effect, temporality, biological gradient (dose response), plausibility, coherence, experiment and analogy. None, apart from temporality are necessary and none sufficient. Bradford Hill emphasised that consideration of these viewpoints was not to establish scientific proof but to come to a decision concerning the control of a hazard *"…..to help us make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more likely than cause and effect"*.

Professor Anderson (at the time a COMEAP member but not a member of the $NO_2$ Working Group) has undertaken an assessment of the evidence and this is given in full in Annex A. This evidence was considered by COMEAP at its June meeting. To date, the $NO_2$ Working Group has not responded to Professor Anderson outlining their agreement (or otherwise) with the arguments presented.

Professor Anderson's conclusions were:

a "The causal basis for estimating the burden of $NO_2$ on mortality and loss of life expectancy is weak and insufficient."

b "There is a stronger case for using the $NO_2$ coefficient to represent the burden of the urban pollution mixture as a whole. Superficially this addresses one of the main problems which is the high correlation between the pollutants. However, the pollution mix is likely to vary, perhaps considerably, across the populations studied in the work comprising the cohort evidence and the validity of transferring these coefficients either individually or as summary estimates to the UK population has not been considered."

## 10.5 Uncertainty in the estimation of the HRs in two pollutant models

In order to calculate mortality burden associated with a pollutant, a suitable HR and estimate of precision are required. It is now acknowledged that the previously reported mortality effects of $PM_{2.5}$ were likely to be in part due to other correlated pollutants including $NO_2$. Similarly, it is acknowledged that associations between $NO_2$ and mortality represent associations between $NO_2$ and closely correlated pollutants including $PM_{2.5}$. Separating the contributions of the measured (and unmeasured) pollutants is therefore necessary to derive HRs suitable for quantifying the mortality burden for individual pollutants. Without such estimates burden calculations will misrepresent the mortality associated with each pollutant leading to double counting of attributable deaths and the incorrect attribution of health effects. This in turn will have a detrimental effect on the evaluation of policy scenarios.

It has been suggested that a coefficient for "$NO_2$" reflecting the effects of the urban mixture of air pollutants in the UK might be used. The term "$NO_2$" has been proposed as a means of indicating that a coefficient expressed in terms of $NO_2$ concentration actually represents the effects of a mixture of closely correlated pollutants of which $NO_2$ is one member. Within a particular location this may be a reasonable assumption. However, the transferability of coefficients to other locations is questionable. The studies on which a coefficient is based were undertaken in locations in which the relationship between $NO_2$ and other pollutants is likely to have varied, indeed we know that this is so. It seems to us to be unwise to refer to "the urban mixture of air pollutants" as though it were a constant mixture: it is more likely to be a variable mixture. This conclusion is based on the considerable heterogeneity between the findings of the studies in this area (HRs vary substantially between locations reflecting different unit toxicity) and the different correlations between pollutants in study locations. For example, in England & Wales the correlation between modelled $NO_2$ and $PM_{2.5}$ is high, over 0.8, whereas in other locations the correlations are lower (Table 10B.1, Annex B to this Chapter). Furthermore, the spatial resolution of the modelled pollutant concentrations may vary between studies and therefore may not be readily transferable from one location to another. Appropriate adjustments to HRs may need to be estimated and applied to account for differential measurement error between studies. Hence the adjusted HRs for $NO_2$ and $PM_{2.5}$ derived in one study location may not be readily transferable to England & Wales for use in burden calculations.

Variation in pollution mixtures between locations also means that HRs derived in one location cannot simply be transferred to another location for the purposes of burden calculations. This is especially true if adjusted HRs are used since the *relative* scaling is important when comparing HRs. The scaling factor is the pollution increment used to calculate the HR for the pollutant. When comparing associations between health and different air pollutants the scaling factors for each pollutant should represent the ranges of concentrations in each pollutant to which the local population is exposed. The metric most commonly chosen in air pollution epidemiology is the inter-quartile range. A second issue is the possibility of extrapolating beyond the range of the data, that is, using HRs calculated in a location with particular pollution concentration ranges to another location with broader ranges in pollution concentrations, particularly if the population weighted exposures vary too. Again, this is of particular concern in the context of multi-pollutant models especially if the relative pollutant burdens are compared and inferences drawn. Extrapolating beyond the range of the data distorts burden calculations. This issue was recognised by COMEAP in their burden calculations for $PM_{2.5}$ (COMEAP, 2010). The 2010 report recognised that the burden calculation based upon the removal of all anthropogenic $PM_{2.5}$ extrapolated below the lowest concentration recorded in the study from which the HR came. A second burden calculation, using the lowest recorded concentration in that study was also reported and produced a burden estimate that was 61% lower.

Currently the epidemiological evidence from cohort studies of long-term exposure to pollutants including $PM_{2.5}$, $NO_2$ and other correlated pollutants is limited to six studies (Annex B to this Chapter). Correlations between $NO_2$ and $PM_{2.5}$ were high in 2 studies, one study used concentrations of $PM_{10}$ rather than $PM_{2.5}$ and in one study the correlation was -0.08 suggesting potential problems with the exposure estimation. The impact of the correlation between the pollutants can be seen in Figure 10B.1, Annex B to this chapter, – the confidence intervals for the $NO_2$ coefficients widen upon adjustment in all studies, except Fischer et al. The changes in the HRs derived from two-pollutant models compared with those from single pollutant models are unconvincing as, in all but one study, the confidence interval for the adjusted coefficient encompasses the confidence interval for the unadjusted coefficient. Estimates of the attenuation/increase of single pollutant HRs after adjustment for a co-pollutant are therefore very uncertain.

The table of two pollutant model results (Table 10B.1, Annex B to this Chapter) includes in the final column the product of the mutually adjusted HRs. In all but one study, the combined HRs are close to the single pollutant HR for $NO_2$ or $PM_{2.5}/PM_{10}$. Indeed, when the imprecision in the estimates are assessed it cannot be concluded that the combined (adjusted) HRs represent an association with mortality different from that for an individual pollutant (albeit $NO_2$ in some studies and PM in others).

The interpretation of the results of these studies is also problematic because of well documented statistical limitations including:

a If the concentrations of the pollutants are closely correlated, then the capacity of the statistical model to distinguish their effects is limited. This is generally accepted

b If the relationships between measured concentrations and exposures to the pollutants differ then the two-pollutant model may produce unreliable results. This is especially the case if the concentrations of the various pollutants have been measured at different spatial scales

c In the presence of differential measurement error there is a danger that the effect of the less well measured but causal pollutant could be transferred to the better measured but non-causal pollutant

d Interactions between pollutants are not usually investigated/reported and hence main effects may be misleading

Annex B to this Chapter provides further information. That these problems could be causing the results of the two-pollutant models to be unreliable is certain; what is not known is the extent to which they are playing a part. It is therefore recommended that in the presence of such uncertainty burden calculations, which require further assumptions (and hence uncertainty) should be avoided as it risks misleading the public and providing incorrect scientific advice to Defra.

## 10.6 If an impact calculation is acceptable then why is a burden calculation opposed?

Those in favour of undertaking a burden calculation for "$NO_2$"as a marker of $NO_2$ and closely correlated pollutants have asked why it is that we who oppose such a calculation appear to be content that a calculation of the impact of policies that will reduce emissions of $NO_2$ and, perhaps, co-pollutants should be done. This is an important question that identifies what might be regarded as an inconsistency in our thinking. Our position is as follows.

When two, or several, policies that will reduce emissions of $NO_2$ and closely correlated pollutants are to be compared it is necessary to estimate the likely benefits, or impact, of each policy. A first level approach is to compare cost with efficacy, i.e. with the reduction in emissions. But if it is required that the benefit, or impact, should be represented in terms of effects on health then some means of converting the reductions in emissions via a model linking emissions with concentrations and a further model linking concentrations with effects is required. This latter model involves the use of the coefficients we have been discussing. In our view the reliability of the coefficient used is of less importance if a purely comparative approach, comparing the effects of a variety of policies, is intended than if a specific approach, calculation of burden, is the objective. This is based on the perception that whether the coefficient is too large or too small matters little when it is used to compare policies. It matters, on the contrary, a great deal if the absolute burden to health is being estimated. We think that an unadjusted coefficient should be used for calculations of comparative impacts. If we thought that a reliable adjusted coefficient could be produced then that too could be used, but we are, as explained above, not convinced by the methods used for producing an adjusted coefficient.

It might be asked whether we would support the use of an unadjusted coefficient to compare the effects of policies designed to reduce emissions of $NO_2$ alone. In principle the answer is yes but we stress, again, that though in a comparative sense the results would be useful, in an absolute sense they would be likely to be very misleading.

## 10.7 Summary

a We think that the results of the $PM_{2.5}$ burden calculation undertaken in 2010 need to be restated in more precise terms. Taking only the widely quoted figure

of 29,000 attributable deaths in 2008 as an example we suggest: long- term exposure to particulate pollution well represented by $PM_{2.5}$ and to an unknown extent those pollutants less well represented by $PM_{2.5}$, was associated with a burden of 29,000 attributable deaths in 2008. Some of this burden might be contributed by pollutants closely associated with $NO_2$ and, perhaps, by $NO_2$ itself. It is possible, perhaps likely, that the total burden imposed by long-term exposure to the ambient mixture of air pollutants exceeded 29,000 attributable deaths in 2008

b We cannot, at present, estimate the burden imposed by particulate matter well represented by $PM_{2.5}$ alone. This would require a coefficient for $PM_{2.5}$ that had been adjusted for pollutants well represented by $NO_2$.We do not have such a coefficient

c Similarly, we cannot estimate burden imposed by pollutants well represented by $NO_2$. This would require a coefficient for this group of pollutants that had been adjusted for $PM_{2.5}$.We regard such coefficients as might be produced to be unreliable

d It follows that we do not support the calculation of a total burden imposed by long-term exposure to pollutants well represented by $PM_{2.5}$ and to pollutants well represented by $NO_2$

e We support the use of an unadjusted coefficient for "$NO_2$" in impact analysis where the objective is comparison of the impact of policies. However, for such an exercise we note that it is sufficient to compare impacts in terms of "$NO_2$" concentrations

f If a burden calculation based on "$NO_2$" is undertaken then it is possible, perhaps likely, that it will be assumed, despite the provision of many very necessary caveats, that this will be misunderstood as indicating that we think that long-term exposure to $NO_2$ itself is having an effect on the risk of mortality. We are not persuaded of this. The evidence for causality of this relationship is, in our view, weak and certainly weaker than that for particulate matter. What evidence there is for an effect of $NO_2$ is based on studies that have not and could not distinguish between the possible effects of $NO_2$ itself and closely correlated pollutants

g Most of the studies that provide evidence for a link between $NO_2$ and closely correlated pollutants and mortality have been undertaken not in the UK but in other countries. This raises the question of transferability of results. COMEAP has met this problem in the past and has often concluded that the findings of studies conducted in other countries can be transferred to the UK. This we think is sensible when broad questions, such as whether the ambient aerosol has an effect on health, are considered but we are much less sure when we come to separating out the effects of individual pollutants. It seems to us a particularly difficult problem when the composition of the mixture represented by $NO_2$ might vary between locations

h The uncertainty in the estimation of the HRs in two-pollutant models and the limited evidence base available at present precludes their use in quantification exercises

# Annex A to Chapter 10: Evidence for a causality in the associations between long-term exposure to $NO_2$ and all-cause mortality in cohort studies

*HR Anderson*

## 10A.1 Evidence for causality

WHO (REVIHAAP) and USEPA have concluded that it is likely that $NO_2$ may have a causal relationship with adverse health effects. This was also the conclusion of COMEAP. [COMEAP 2015]. The weight of evidence supporting this conclusion was based on short-term studies, especially time-series studies in which indicated that in multi-pollutant models, $NO_2$ tended to be robust to adjustment for PM. The terms of reference of the COMEAP $NO_2$ working group did not include a re-examination of the specific question of the causality of the long-term associations observed in cohort studies. Without such consideration, any estimation of burden based on this evidence might be open to question on two counts:

a The above mentioned reviews were candid about their reliance mainly on short-term exposure evidence from epidemiological and toxicological studies. They were less certain about the causality of long-term exposure associations and this was inferred, in part, indirectly from the short-term evidence.

b The current COMEAP $NO_2$ Working Group, having commissioned a detailed and up-to- date analysis of available cohort evidence had the opportunity to revisit the causality question but did not do so.

### 10A.1.1 Conclusions of REVIHAAP

The WHO REVIHAAP review is the most recent, comprehensive and impartial (i.e. non-governmental, non-advocacy) source of opinion in this area. The main lines of evidence to support a causal role of $NO_2$ are based on short-term exposure studies – epidemiological, human chamber and toxicological. The causal argument for long-term associations with mortality is less convincing as it "borrows" almost entirely from evidence based on short-term associations as there is little direct supporting evidence. REVIHAAP did however conclude that there was sufficient evidence for causality for this pollution-outcome pair to be included in sensitivity analyses of health-impact assessments. It was designated Group B (pollutant outcome pairs for which there were more uncertainties about the data used for quantification of effects) in the HRAPIE report on estimates for quantification. The recommended estimate, based on a meta-analysis, for $NO_2$ Annual Mean >20μg/m$^3$ for mortality age 30+ was 1.055 (95% CI 1.031 – 1.080).

### 10A.1.2 Reconsideration of the causality of long-term exposure evidence in the light of newer studies and detailed meta-analysis

REVIHAAP followed the WHO Guidelines for assessing environmental hazards in that there was a systematic review of the literature with meta-analysis as appropriate. But there was no formal process for agreeing causality using the usual approach applying Bradford Hill's "aspects/viewpoints" as recommended by an earlier WHO report (WHO 2000). Since REVIHAAP, more evidence has accumulated and thanks to the work of the $NO_2$ Working Group we now have an up-to-date and detailed meta-analysis that provides not only potential estimates for quantification but also better epidemiological evidence relating to the causal

argument. What follows is a systematic assessment of the causality of long-term ambient $NO_2$ – mortality associations using the WHO (2000) guidelines.

Scientific judgment relating to causality begins with determining whether an association can be explained by 1) chance and/or 2) confounding. If this is not the case, the conventional approach is to apply what are referred to as Hill's "criteria" as a framework for making a judgement (in fact he used the terms "aspects" and "viewpoints") (Hill, 1965). The nine viewpoints are: strength of association, consistency of evidence, specificity of effect, temporality, biological gradient (dose response), plausibility, coherence, experiment and analogy. None, apart from temporality are necessary and none sufficient. Hill emphasised that consideration of these viewpoints was not to establish scientific proof but to come to a decision concerning the control of a hazard *"…..to help us make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more likely than cause and effect".*

This framework will now be applied specifically to long-term exposure studies. The evidence from short-term studies is important indirectly and will be referred to as appropriate. In short, most authorities including REVIHAAP, considered that the evidence for short-term associations is consistent with an independent effect of $NO_2$ and we agree with this and for the purposes of the present argument will take it for granted. The relevance of this to the long-term exposure argument will be dealt with below.

### 10A.1.3 Chance

We are accustomed to small risks in air pollution epidemiology. Often, associations that are unlikely to be null (based on 95% confidence intervals) are only obtained after meta-analysis of a number of studies. The Working Group analysis shows that the size of the association is less than that proposed by HRAPIE based on cohort evidence available at the time, namely an HR for 10 $\mu g/m^3$ of $NO_2$ of 1.055 (95% CI 1.031-1.080). HRs based on the Working Group analyses were over 50% lower at 1.023 (1.008-1.037) using a random effects model. There was substantial heterogeneity with 97% of the variability explained by variations between the studies rather than by chance. The lower confidence interval of this estimate is much nearer to the null than the estimate used by HRAPIE. Refinement by restricting the analysis to studies with individual confounder control reduced the estimate further to 1.011 (0.995 – 1.027) which is just overlapping the null (1.00). Chance could also play a part through small study bias. The standard analysis of small study bias (which was hampered somewhat by low power) showed some asymmetry and the "corrected" estimate using the Trim and Fill method was 1.010 (1.009 – 1.012), 50% lower than the "uncorrected" estimate of 1.023. While a number of other factors could be responsible for this result, small study bias and consequent inflation of the "true" estimate cannot be excluded.

### 10A.1.4 Confounding and bias

a The possibility of confounding due to socioeconomic and lifestyle factors (SES) which are correlated with air pollution is a strong one. The authors of the cohort studies were aware of this and controlled for such factors at individual or ecological levels. The sensitivity analysis comparing estimates with individual confounder control with those without indicated that the more optimum approach, that of individual level confounder control, gave considerably smaller estimates. The HR was 1.011 (95% CI: 0.995, 1.027) in studies controlling for the required individual confounding factors vs 1.031

(95% CI: 1.025, 1.037) per 10 μg/m$^3$ in those that did not. In addition, in population cohort studies of this type it is most unlikely that relevant individual confounders have been accounted for in their entirety by a single SES estimate which means that the "real" estimate could be even lower. This is especially important when the estimate is already small and bordering on the null. For example, in the English cohort study (personal communication), adjustment for covariates including SES but excluding individual smoking gave a HR for $NO_2$ of 1.026 (95% CI: 1.001-1.052) per 10 μg/m$^3$. Adding individual smoking measures reduced the HR to 1.022 (0.995-1.049).

b An even more important problem is that of confounding by one or more of the pollutants associated with the same sources as $NO_2$. REVIHAAP noted that $NO_2$ was highly correlated with a number of other pollutants, some of which were, in theory, contenders for causing health effects (black carbon, air toxics, CO etc.) and which, even if they were available for analysis, would present statistical difficulties in determining independent (in a statistical sense) effects. Even when other correlated pollutants are available for multi-pollutant analysis there are difficulties in interpreting results because pollutants differ in their degree of exposure misclassification and spatial resolution and the example of $PM_{2.5}$ and $NO_2$ was cited by REVIHAAP. A related problem which is not often discussed is that the correlation between $NO_2$ and the other pollutants varies over short and long time-scales and from place to place. This has implications for the transferability of the HR from one locality to another and for the likely benefits of policies directed at $NO_2$ per se. Premature mortality related to pollution may have its origins in exposures very different from that which obtained at the time of the cohort study. Bias due to these factors may partly explain why there is such a high heterogeneity between studies and variations in the results of multi-pollutant models. While exposure misclassification is likely to bias results downwards this argument should be used sparingly when the prima facie estimate is already weak.

### 10A.1.5 Hill's viewpoints

Some additional insights can be gained by consideration of Hill's viewpoints.

#### *Strength of association*

Strength of association is largely a combination of size and significance. These have been discussed above and it is concluded that the estimates are not strong or statistically secure in significance terms.

#### *Consistency of evidence*

Of the 14 studies considered for meta-analysis, 12 show positive estimates and 8 have lower 95% confidence limits above 1.00. There is a high degree of heterogeneity $I^2$ 97.0% for the more representative population samples and 85.7% for the three specific age group cohorts. This suggests limited consistency. The heterogeneity could reflect a number of factors. As mentioned previously we have explored the effect of the level of confounder control in the UK cohort study by comparing the effects of controlling at an individual level for smoking with using an area indicator of SES: this concluded that estimates were smaller when individual level confounders were used. Until other reasons for heterogeneity are identified the causal argument is weakened.

### *Specificity*

The associations are not very different from those with other pollutants such as $PM_{2.5}$. This includes an association with lung cancer. The implication for causality is neutral or weak.

### *Temporality*

Not relevant as mortality does not cause $NO_2$ pollution.

### *Biological gradient*

This refers to dose-response or in the present case exposure – response. In a causal relationship one would expect more effects as exposure increased. This has been comprehensively dealt with in the Working Group Report. Those studies that have reported estimates have found positive linear associations. This is consistent with causality due to $NO_2$ or with some closely correlated causal pollutant.

### *Plausibility*

This refers to biomedical mechanistic attributes. For short-term exposure studies there is substantial mechanistic evidence to support the possibility of toxic effects on the respiratory system at concentrations that may be encountered in the ambient situation though less for effects at the average concentrations to which most of the population are exposed. Some of these effects may be short-term patho-physiological defence mechanisms which are reversible. There is evidence of interaction with allergens and respiratory viruses. There is far less toxicological evidence relating to long-term exposure which is necessarily limited to long-term animal exposure experiments. There is no evidence of a direct connection between those effects identified in toxicological studies and actual disease that would be reflected in shortened life expectancy.

Given the relatively stronger and plausible evidence for $NO_2$ and short-term effects on daily mortality it is important to consider the possible role of these on the results of cohort studies. In other words, could the results of long-term exposure studies be explained by an accumulation of short-term effects. This is plausible if some short-term effects have a major effect on life expectancy. Hypothetically, this might occur if some of the increase in deaths identified in daily time-series studies are of patients who had a temporary vulnerability (severe pneumonia, exacerbation of COPD, heart attack) and if it had not been for the additional effect of air pollution would have got better and lived to die another day. In other words their death was brought forward by a significant amount. In this context it is perhaps relevant to compare the HRs for time-series with those from cohort studies. In cohorts providing $PM_{2.5}$ HRs the ratio of the cohort to time-series HR tends to be about 10:1 (6% vs 0.5%). This has been held to indicate that the mortality in cohorts is due to more than just the sum of the short-term exposure mortality effects. For $NO_2$ the ratio of cohort to time-series estimates is 3:1 (Based on Working Group estimate of 2.3% vs 0.71 of Mills et al., 2016). This provides some support for the idea that the more plausible short-term mechanisms maybe contribute relatively more to the long-term exposure associations with $NO_2$ than they do to the $PM_{2.5}$ associations.

### *Coherence*

Coherence refers to how the evidence hangs together with the totality of other evidence. The concept overlaps with others we have been considering.

### *Experiment*

Not relevant – no evidence

### *Analogy*

Other respiratory toxicants in ambient pollution have been found to have health effects, so it reasonable in principle to predict an effect of $NO_2$

## 10A.2 Summary

a The latest summary coefficient relating long-term exposure to $NO_2$ to mortality in cohort studies is considerably smaller, and the lower 95% confidence limit nearer the null, than when assessed by REVIHAAP and HRAPIE. There is a strong possibility that it may have been inflated by uncontrolled confounding by social and lifestyle factors as well as by correlated pollutants

b Consideration of other aspects of the causal argument provides little additional support for causality

## 10A.3 Conclusions

a The causal basis for estimating the burden of $NO_2$ on mortality and loss of life expectancy is weak and insufficient

b There is a stronger case for using the $NO_2$ coefficient to represent the burden of the urban pollution mixture as a whole. Superficially this addresses one of the main problems which is the high correlation between the pollutants. However, the pollution mix is likely to vary considerably across the populations comprising the cohort evidence and the validity of transferring these coefficients either individually or as summary estimates to the UK population has yet to be considered

c Estimating mortality impacts of $NO_2$ would be more secure using the daily mortality time-series evidence because the case for causality is stronger. This was Group A in the HRAPIE recommendations

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# Annex B to Chapter 10: Derivation, interpretation and use of adjusted coefficients from two pollutant models

*R Atkinson*

## 10B.1 Statistical issues in multi-pollutant models

In multi-pollutant models incorporating $NO_2$ and $PM_{2.5}$, the coefficient for $NO_2$ describes the association between $NO_2$ concentrations and the health outcome adjusting for the simultaneous change in $PM_{2.5}$ and other covariates in the model. A two-pollutant model containing covariates plus $NO_2$ and $PM_{2.5}$ assumes the relationship between $NO_2$ and mortality holds irrespective of the value of $PM_{2.5}$ and vice versa. If the coefficient of $NO_2$ varies with the level of $PM_{2.5}$ then we have an interaction. A consequence of a (statistically significant) interaction is that the main effects (adjusted $NO_2$ coefficient and adjusted $PM_{2.5}$ coefficient) in the two pollutant models are not readily interpretable. Hence, the first step in identifying the hazard ratio (HR) for $NO_2$ adjusted for $PM_{2.5}$ (and vice versa) is to establish that the interaction term is statistically non-significant. This limitation in the context of air pollution epidemiology has been noted previously.(1).

The second issue in deriving adjusted coefficients from two-pollutant models relates to the correlation between the pollutants. If two variables in a regression model are perfectly correlated then one of these variables provides no further information over and above that provided by the other and either can be dropped from the regression model. If they are strongly correlated then the statistical model may be unstable. This means that the regression coefficients may be sensitive to changes in the model specification and data i.e. the magnitude of the estimates may vary substantially (even changing sign). Also, the standard errors may be inflated in models with correlated variables. Another possibility is that individually the coefficients may not be statistically significant but jointly they may be – this would be indicated by the confidence region for both variables. It is still possible however that the correlation causes minimal problems. These issues are well documented in the statistical literature. Techniques to identify co-linearity in the models are available (eg variance inflation factors) and statistical techniques to adjust for co-linearity (eg ridge regression) exist.

A further issue is the potential impact of exposure measurement error on the estimation of the coefficients in multi-pollutant models. In large scale, air pollution epidemiological studies individual exposures to air pollution are not measured directly, instead they are estimated from models based upon monitored data/land use/atmospheric chemistry.(1, 2) These errors are potentially very important as they can lead to bias in effect estimates and loss of precision which, if serious enough, can invalidate any inference.(3) These issues can be exacerbated in multi-pollutant models.(1)

Whilst HRAPIE recommended an adjusted HR it should be noted that a number of publications have highlighted the difficulties with multi-pollutant models. See Greenbaum et al. for example.(4) The issue is also recognized by authors of original research. For example, the publication from the Canadian group (5) concluded: *"Correlations between the pollutants do, however, make it challenging to tease out the independent contributions to risk of mortality of each pollutant."* The authors go on to propose an alternative: *"Our cumulative risk estimates, however, describe associations with the overall mixture of pollutants more effectively than do the estimates from the multiple-pollutant models.*

*These observations suggest that efforts should be made to model the toxicity of atmospheric mixtures when modelling population burden of disease attributable to air pollution exposure."*

## 10B.2 Assessment of the available evidence

Results from the six studies in our review are tabulated in the report but are included here for ease of reference.

None of the models in the six studies in our review test for interaction terms between $NO_2$ and $PM_{2.5}/PM_{10}$. This is an important limitation when interpreting results from these multi-pollutant models.

Correlations between $NO_2$ and $PM_{2.5}$ were high (0.79 and 0.85) in 2 studies (6,7), moderate (0.2-0.7 and 0.55) in 2 studies (8,9) and weak (-0.08) in one study (10). In the single study using $PM_{10}$ rather than $PM_{2.5}$ (11), the correlation between $PM_{10}$ and $NO_2$ was 0.58. The estimated coefficients for $NO_2$ and $PM_{2.5}$ in the Cesaroni or Carey studies have limited meaning because of the high correlation (0.79 and 0.85 respectively) between the pollutants. The impact of the correlation between the pollutants can be seen in Figure 10B.1 – the confidence intervals for the $NO_2$ coefficients widen upon adjustment in all studies, except Fischer et al. The changes in the HRs derived from two-pollutant models compared to those from single pollutant models are unconvincing as, in all but one study, the confidence interval for the adjusted coefficient encompasses the confidence interval for the unadjusted coefficient.

The table of two pollutant model results (Table 10B.1) includes in the final column the product of the mutually adjusted HRs. In all but one study, the combined HRs are close to the single pollutant HR for $NO_2$ or $PM_{2.5}/PM_{10}$. Indeed, when the imprecision in the estimates are assessed it cannot be concluded that the combined (adjusted) HRs represent an association with mortality different to that from an individual pollutant (albeit $NO_2$ in some studies and PM in others).

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**Table 10B.1: Hazard ratios (95% CI) from single and two pollutant models for $NO_2$ and $PM_{2.5}$ or $PM_{10}$ (HRs are expressed per IQR)**

| Study | Cohort | Corr $NO_2/PM_{2.5}$ | $NO_2$ IQR (µg/m3) | $NO_2$ | $NO_2$ adj $PM_{2.5}$/ $PM_{10}$ | %[5] | $PM_{2.5}$/ $PM_{10}$ IQR (µg/m³) | $PM_{2.5}$/ $PM_{10}$ | $PM_{2.5}$/ $PM_{10}$ adj $NO_2$ | %[5] | Combined $NO_2$ adj/ PM adj HR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cesaroni et al. (2013)** | Rome | 0.79 | 10.7 | 1.029 (1.022, 1.036) | 1.026 (1.015, 1.037) | **10** | 5.7 | 1.023 (1.016, 1.031) | 1.004 (0.994, 1.015) | **82** | 1.030 |
| **Carey et al. (2013)[1]** | CPRD | 0.85 | 10.7 | 1.022 (0.995, 1.049) | 1.001 0.959, 1.044) | **95** | 1.9 | 1.023 (1.000, 1.046) | 1.023 (0.989, 1.060) | **0** | 1.024 |
| **Beelen et al. (2014)[2]** | ESCAPE | 0.2-<0.7 | 10.0 | 1.015 (0.993, 1.036) | 1.007 (0.967, 1.049) | **53** | 5.0 | 1.070 (1.016, 1.127) | 1.060 (0.977, 1.150) | **14** | 1.067 |
| **Fischer et al. (2015)[3]** | DUELS | 0.58[4] | 10.0 | 1.027 (1.023, 1.030) | 1.019 (1.015,1.023) | **29** | 2.4 | 1.019 (1.016, 1.022) | 1.010 (1.007, 1.013) | **46** | 1.029 |
| **HEI (2000)[4]** | ACS CPS II | -0.08 | 81.4 | 0.95 (0.89, 1.01) | 0.90 (0.84, 0.96) | **105** | 24.5 | 1.15 (1.05, 1.25) | 1.22 (1.11, 1.33) | **-42** | 1.09 |
| **Jerret et al. (2013)** | ACS CPS II | 0.55 | 7.7 | 1.031 (1.008, 1.056) | 1.025 (0.997, 1.054) | **19** | 5.3 | 1.032 (1.002, 1.062) | 1.015 (0.980, 1.050) | **53** | 1.040 |

Notes: (HR reported to 3 decimal places taken from publication or provided by personal communication)

1 $PM_{2.5}$ results –personal communication

2 Based on 14 cohorts in which correlation between $NO_2$ and $PM_{2.5}$ was less than 0.7. HRs are presented per 10 µg/m³ $NO_2$ and 5 µg/m³ $PM_{2.5}$

3 $PM_{10}$

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

5 % reduction in ln(HR)

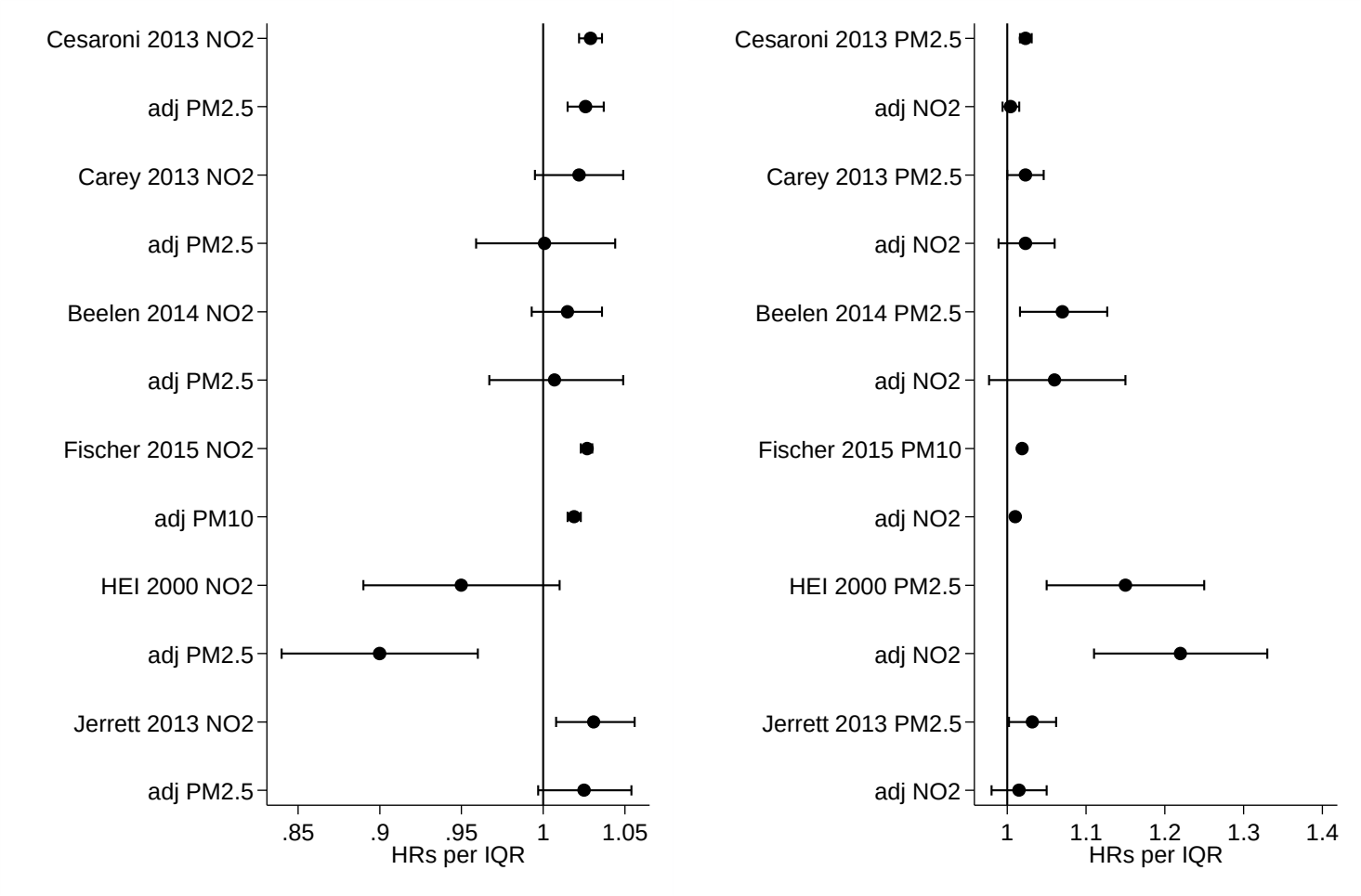


**Figure 10B.1: Hazard ratios (95% CI) from single- and two-pollutant models for $NO_2$ (A) and $PM_{2.5}/PM_{10}$ (B) HRs are expressed per IQR or selected increments in multi-centre studies**

# Chapter 11
# Recommendations for further research

In our Statement in March 2015 on the health effects of $NO_2$, we noted that a Department of Health-funded workshop in 2011 (HPA, 2011) had identified needs for research on the health effects of $NO_2$ and that the WHO REVIHAAP project (WHO, 2013a) had also made recommendations to address data gaps in relation to the health effects of $NO_2$. We agreed that the studies recommended, and other research, would be valuable. We think that the types of studies listed below would be particularly useful to help address some of the difficulties we encountered when considering the link between long-term exposure to $NO_2$ and mortality.

## 11.1 To reduce some of the uncertainties associated with understanding and estimating the effects of long-term exposure to $NO_2$ upon health

a Further toxicological studies to underpin knowledge of the causality of adverse effects and their specificity to $NO_2$. These might include

i. Studies comparing the potency of ultrafine particles, other pollutants and $NO_2$ in the same experimental system to allow appropriate comparisons to be drawn and the possibility of interaction to be investigated

ii. Chamber studies to compare the effects of different constituents of traffic-related pollution

iii. Studies on the effects of combinations of pollutants (eg adding or removing $NO_2$ to/from filtered and unfiltered diesel exhaust exposures)

iv. Studies on markers of cardiovascular effects, in susceptible animal models or in epidemiological studies

b Further multi-pollutant epidemiological studies, preferably carried out in circumstances where $NO_2$ and PM concentrations are weakly correlated, or allowing comparison of areas with different ratios of $NO_2$ to PM concentrations. Examples include spatio-temporal studies and interrupted time-series studies taking advantage of the changes in $NO_2$ to $PM_{2.5}$ ratios over time. New epidemiological studies using two- or multi-pollutant models to examine mortality effects associated with between-community and within-community variations in $NO_2$ concentrations would be valuable, as this

approach reduces correlations between $NO_2$ and PM metrics. Studies on cause-specific (eg cardiovascular or respiratory) mortality, as well as all-cause mortality, would be valuable

c Better understanding of the errors in exposure assessment, including how well measured or modelled concentrations approximate to personal exposures, how big any biases may be, and the variance and the correlation of the errors for the different pollutants

## 11.2 To improve quantification of the effects associated with exposure to air pollution mixtures

d The availability of results from two- / multi-pollutant models provides an opportunity to consider a wider multi-pollutant context which includes $NO_2$, $PM_{2.5}$ and ozone. A move to a multi-pollutant approach may help to estimate a total mortality burden attributable to the ambient air pollution mixture in the UK. This has been explored to some extent in Chapter 5 but further work is necessary to refine the approach

e Development or clarification of appropriate statistical methods eg for understanding when multi-pollutant models become unstable, for pooling multi-pollutant model results, for estimating the uncertainties in ratios (including of coefficients from single- and multi-pollutant models). This also requires more details to be provided in study publications, including covariance information from the multi-pollutant model results. With the wider use of publication of supplementary material, there should be no problem with providing this type of additional detail

## 11.3 Exploring heterogeneity of the HR used to derive the summary coefficient

f We have noted substantial between-study variability in the reported unadjusted (i.e. single-pollutant) HRs associating annual average $NO_2$ and mortality. Possible reasons include baseline population risk, other population characteristics, concentrations and sources of co-pollutants, methods of exposure assessment, and model specification including potential confounders. An investigation of these and other factors, and how they impact on the HRs, is required to improve our estimation of the summary HR and its precision, and to improve our understanding of their relevance to the transferability and interpretation of results from elsewhere to health impact assessment in the UK

# Chapter 12
# Summary and conclusions of the majority and those with dissenting views

## 12.1 Introduction

This Chapter summarises the views of the majority of the Committee on the evidence linking long-term average concentrations of $NO_2$ with mortality risk. It sets out our recommendations for using this evidence to quantify the impacts (benefits) of reducing ambient concentrations of $NO_2$, either with or without proportionate reductions in other traffic-related air pollutants. The exploratory approach that we used to estimate the mortality burden on the basis of associations reported with long-term $NO_2$ and $PM_{2.5}$ concentrations is also explained. The results of applying these recommendations to the UK population are then summarised.

Although there was agreement amongst all Committee Members on many points, a number of points of disagreement arose between Members of the Committee during the course of our work. These points were discussed at length but some proved to be impossible to resolve. Professors H Ross Anderson and Robert Maynard, and Dr Richard Atkinson, disagree with a number of the statements, conclusions and recommendations listed below. Their views, outlining the reasons for this, are presented following the views of the majority of the Committee (in section 12.3).

## 12.2 Views of the majority of the Committee

### 12.2.1 Conclusions regarding evidence

#### *12.2.1.1 Cohort studies: Associations from single-pollutant models*

Our conclusions on the evidence from associations examined in single-pollutant models in cohort studies are:

We have concluded that there is epidemiological evidence from cohort studies that shows an association between long-term (annual) average concentrations of $NO_2$ and an increase in all-cause mortality.

Meta-analyses of coefficients from single pollutant models from 11 studies (after exclusion of studies on specific age groups) gave a random-effects summary hazard ratio of 1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ increment in $NO_2$.

There is substantial heterogeneity between the 11 coefficients selected for meta-analysis. Higher coefficients were obtained from studies with weaker control for individual confounders (although the number of studies available for this analysis was small) and there is a possibility of small study bias. This heterogeneity needs fuller investigation.

Associations were observed in studies with $NO_2$ concentrations as low as 5 μg/m$^3$ $NO_2$. The available evidence does not suggest that a threshold for effects exists at the population level. However, as only some of the studies have included formal tests for this, the possibility of a threshold cannot be ruled out.

#### *12.2.1.2 Causality: Evidence from two- or multi-pollutant models in cohort studies*

The association of $NO_2$ with mortality is not necessarily caused by $NO_2$ itself: it almost certainly also reflects an effect of other pollutants correlated with $NO_2$. When assessing the possibility of a causal effect of long-term exposure to $NO_2$ on mortality, we considered whether the reported associations were independent of associations of mortality with other pollutants, especially PM. We used the limited number of cohort studies which examine associations of mortality with both $NO_2$ and PM simultaneously in two- or three-pollutant models to do this. Our views are:

There are some difficulties in interpreting the results of the coefficients reported from two-pollutant models. Two-pollutant model results can be particularly subject to bias from measurement error when the correlation between the pollutants is high. This may lead to ascribing associations to the wrong pollutant (effect transfer). This is less likely when correlations between pollutants are lower. Our conclusions from two-pollutant models have been based on studies with correlations less than 0.7.

In the few studies which report coefficients from both single- and two-pollutant models, the associations of mortality with $NO_2$ concentrations are fairly robust to adjustment for effects associated with PM concentrations. Although coefficients were reduced by adjustment for PM, associations remained and statistical significance was often retained.

Available two-pollutant models for $NO_2$ and PM suggest there is likely to be some association with long-term average concentrations of $NO_2$ that is independent of the association with PM mass and vice versa.

As noted in our interim statement (COMEAP, 2015a): "….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."

Few studies have examined possible confounding by ozone or noise or other pollutants. We note that the correlation between $NO_2$ and ozone can be negative, implying that adjustment for ozone might increase the estimated $NO_2$ coefficient.

#### 12.2.1.3 Causality: other evidence

We considered other evidence including epidemiological time-series studies, studies on human volunteers and toxicological studies:

There is evidence from time-series studies of associations between all-cause mortality and hourly and daily $NO_2$ concentrations. These remain robust to adjustment for PM mass. There are few studies that have controlled for other traffic-related pollutants, so confounding by ultrafine particles, or by other pollutants which are not routinely measured, cannot be ruled out.

Animal studies and studies on human volunteers provide some support for the view that short-term exposure to $NO_2$ can cause respiratory effects. This does not mean that effects are necessarily large or affect all individuals. Available studies only explore effects down to the high end of concentrations experienced by some people in some microenvironments. There are few toxicological studies on the cardiovascular effects of $NO_2$, and those available provide at best weak evidence for long-term exposure to $NO_2$ having a causal role in cardiovascular effects.

#### 12.2.1.4 Causality: overall conclusions

The summary coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ $NO_2$ has not been adjusted for $PM_{2.5}$ or $PM_{10}$ or other pollutants. It reflects the combination of: (i) any causal effect of $NO_2$, (ii) a component of the effect on mortality of any other air pollutants (including PM) and environmental hazards (for example, noise) with which $NO_2$ is correlated, and (iii) any effect of residual confounding or small study bias.

Therefore, a possible interpretation of an unadjusted coefficient for $NO_2$ is that it reflects any causal effect of $NO_2$ and also, to some extent, the effects of other pollutants with which $NO_2$ is correlated. These include $PM_{2.5}$, other fractions of PM, and other components of the air pollution mixture (eg ultrafine particles, Black Carbon, Volatile Organic Compounds etc.).

A coefficient for $NO_2$ adjusted for $PM_{2.5}$ is likely to reflect any effect of $NO_2$ and also, to some extent, other pollutants with which $NO_2$ is closely correlated but it would exclude (as far as possible) effects associated with $PM_{2.5}$ concentrations and other components of the air pollution mixture that are more closely correlated with $PM_{2.5}$ concentrations than with $NO_2$ concentrations. Nonetheless, the possibility of residual confounding, effect transfer etc. need to be borne in mind when interpreting adjusted coefficients.

The extent to which the unadjusted coefficient for $NO_2$ reflects a causal effect of $NO_2$ itself is unknown.

However, in our opinion it is unlikely to be close to either 0% (because of the aggregate of short-term effects, and the likely effect on respiratory mortality) or 100% (because of confounding).

### 12.2.2 Conclusions regarding methods for quantification

#### 12.2.2.1 Cut-offs for quantification

The association between long-term average $NO_2$ and mortality is based on studies which, necessarily, do not include very low annual average $NO_2$ concentrations. We considered two

approaches to setting a lower limit to the $NO_2$ concentrations where the resulting coefficients could be applied when quantifying the benefits of interventions or, if appropriate, the mortality burden of implied by current pollution concentrations. These are:

Using a cut-off for quantification, based on the lower end of concentrations in studies in which associations have been shown, estimates the portion of the predicted benefits of interventions (or, if appropriate, burden) in which there is greatest confidence, because no extrapolation beyond the range of data is involved. As associations were observed in cohort studies with concentrations of $NO_2$ as low as 5 $\mu g/m^3$ annual average, we consider this to be an appropriate cut-off.

Further extrapolation down to zero estimates the additional benefit (or effect) that is likely under the assumption that the same concentration-response relationship holds below concentrations that have currently been studied. Without such extrapolation any benefit (or effect) below 5 $\mu g/m^3$ annual average $NO_2$ remains unquantified.

We recommend quantifying to both zero and to 5 $\mu g/m^3$ annual average $NO_2$.

#### *12.2.2.2 Coefficients for impact calculations*

Because of the difficulties in apportioning associations observed in epidemiological studies to individual pollutants, we consider analysis to be most robust when evaluating the effects associated with a mixture of pollutants, where possible. However, this may not always be what is needed (for example when evaluating an intervention primarily aimed at reducing emissions of specific pollutants) and, in view of this, we have considered

a. How to quantify the benefits of interventions on the basis of reductions of a mixture of pollutants (eg a mixture of traffic-related pollutants)
b. How to quantify the benefits of interventions on the basis of reductions in $NO_2$ concentrations (eg. interventions affecting $NO_x$ emissions alone)
c. Whether to estimate the mortality burden attributable to $NO_2$ itself
d. How to estimate the mortality burden attributable to the overall air pollutant mixture

##### Impact assessments to quantify the benefits of reducing a mixture of traffic-related pollutants, using unadjusted coefficients

Assessment of the likely impacts (health benefits) of interventions intended to reduce air pollution are needed to undertake cost-benefit assessment of policy options. This report is concerned only with benefits that are mediated via changes (reductions) in ambient pollutant concentrations. It does not address issues such as the health benefits of active travel. Our views are:

The unadjusted coefficient from single-pollutant models represents the effects of the mixture of pollutants (often traffic-related) that are correlated with $NO_2$ including any effect of $NO_2$ itself. We consider that, as a result, the unadjusted single pollutant coefficient is most appropriately used to assess the impacts of benefits of reductions in emissions of the mixture of traffic-related pollutants.

As noted in our Interim Statement (COMEAP 2015a.) "….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."

Interventions that reduce emissions of the mixture of traffic-related pollutants will reduce PM concentrations. An alternative calculation of benefits associated with this reduction of the mixture could be performed by using the unadjusted single-pollutant coefficient for $PM_{2.5}$ to predict the expected mortality benefits associated with the reduction in $PM_{2.5}$ concentrations.

As either of the calculations using the unadjusted $NO_2$ or $PM_{2.5}$ coefficient is likely to underestimate the full benefits of an intervention, the higher of the two values calculated from these two approaches can be used as the value likely to under estimate the predicted benefits the least.

Using a single pollutant coefficient for $NO_2$ and a single-pollutant coefficient for $PM_{2.5}$ and adding the results, would overestimate the combined effects associated with the two pollutants.

### Impact assessments to quantify the benefits of reducing concentrations of $NO_2$ itself

Assessing the benefits of reductions in concentrations of $NO_2$ requires the derivation of a coefficient to represent the effects of $NO_2$ only. Such a coefficient is needed to undertake cost-benefit assessment of policy options that primarily target reductions in emissions of $NO_x$ and have little or no impact on other pollutants.

We wished to adjust the summary single-pollutant coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ annual average $NO_2$ for effects associated with other pollutants. However, there are no validated statistical approaches for adjusting a summary effects estimate obtained by meta-analysis of unadjusted single-pollutant coefficients.

The view of the majority of the Committee is, therefore, that application of expert judgement is currently the best available approach for deriving a coefficient linking mortality with long-term exposure to $NO_2$ and, despite its limitations, is good enough to be used for quantification provided the uncertainties are noted.

Consequently, we have applied the judgement of Committee Members to reduce the summary coefficient obtained from meta-analysis of coefficients from single-pollutant models to derive a coefficient intended to represent mortality associated with long-term exposure to $NO_2$ itself. We recommend use of 25-55% (mid-point of range 40%) of the unadjusted coefficient 1.023 (95% CI: 1.008, 1.037) per 10 $\mu g/m^3$ annual average $NO_2$.

Several strands of evidence were used in coming to this view, including

a coefficients from four studies that had reported coefficients from both single- and multi-pollutant models and in which concentrations of $NO_2$ were not highly correlated with those of PM

b time-series evidence

- evidence from toxicological and chamber studies, which provides stronger evidence for a causal link between $NO_2$ and respiratory effects than cardiovascular effects

Nonetheless, there is considerable uncertainty regarding the suggested range of 25-55%.

This reduced coefficient may be used for assessing the benefits of reductions in concentrations of $NO_2$ itself, without corresponding reductions in concentrations of other traffic-related pollutants.

Adding estimates of the mortality benefits of interventions obtained using either the unadjusted or reduced coefficients for $NO_2$ recommended in this report to assessments based on an unadjusted concentration-response function for $PM_{2.5}$ will lead to an over-estimate of potential benefits.

#### *12.2.2.3 Impact calculations – other considerations*

##### Cessation lag

There is likely to be some delay in the reduction of mortality risk following a reduction in pollution, and this cessation lag needs to be reflected in impact calculations. In the absence of any direct evidence to indicate an alternative, it was considered appropriate to use the same cessation lag as that recommended by COMEAP (2010) for quantification of the mortality benefits of reductions of particulate matter.

##### Assessing the effects of reductions in nitrate particles

One consequence of reducing $NO_x$ emissions is a reduction in the formation of nitrate particles. Because this effect occurs some distance from the source of the $NO_x$ emissions, nitrate concentrations would not be expected to be correlated with those of $NO_2$. Therefore, the health effects of nitrate particles arising from $NO_x$ emissions would not be represented by the associations with $NO_2$ concentrations reported from epidemiological studies.

The mortality benefits arising from reductions in nitrate concentrations can therefore be included as a separate component in health impact assessments, to be added to the predicted benefits associated with reductions in $NO_2$ concentrations calculated using either the unadjusted or reduced coefficient.

#### *12.2.2.4 Burden estimates*

The mortality burden on the current population attributable to long-term exposure to air pollution can be useful in communicating the size of the effect on public health.

The majority of Committee Members, including all signatories of the Dissenting View, did not support the use of the reduced $NO_2$ coefficient (25-55% of the unadjusted coefficient) to generate an estimate of the burden of mortality attributable to current exposure to $NO_2$ itself.

Because burden estimates are intended to convey the size of the effect of air pollution on public health, an estimate of the overall effect of the air pollution mixture was considered sufficient.

Whist recognising the uncertainties involved, we decided it was appropriate to attempt to estimate the burden of mortality in the UK attributable to the air pollution mixture, on the basis of associations reported with PM and $NO_2$.

We propose reporting a range of possible values of the mortality burden, derived:

a Using summary single-pollutant (i.e. unadjusted) coefficients for either $PM_{2.5}$ or $NO_2$ and also

b By four separate estimations, each undertaken using information from one of the four available multi-pollutant cohort studies with moderate correlations between annual average $NO_2$ and PM concentrations. For each study, the percentage reduction in $NO_2$ coefficient on adjustment for PM is applied to the unadjusted summary $NO_2$ coefficient used in (a) above. Similarly, the percentage reduction in $PM_{2.5}$ coefficient on adjustment for $NO_2$ is applied to the unadjusted summary $PM_{2.5}$ coefficient. The estimated burdens obtained using these mutually adjusted summary coefficients are then summed to give an estimated burden of the air pollution mixture.

### 12.2.3 Conclusions regarding quantification

For a reduction in all traffic-related pollutants, consistent with a sustained 1 $\mu g/m^3$ reduction of $NO_2$, we estimate that about 1.6 million life years could be saved in the UK over the next 106 years, and that life expectancy (at birth) would be increase by around 8 days.

For a 1 $\mu g/m^3$ reduction in $NO_2$, without a corresponding reduction in concentrations of other traffic-related pollutants, we estimate that about 420,000 to 903,000 life years could be saved in the UK over the next 106 years, and that life expectancy (at birth) would be increased by around 2 to 5 days. We emphasise that these are indicative results because of the need to estimate, using expert judgement, the extent to which observed associations between $NO_2$ and mortality are caused by $NO_2$ rather than other pollutants.

Using an approach of undertaking several individual exploratory calculations, the range of estimates of the mortality burden of the air pollution mixture (based on associations with $PM_{2.5}$ and $NO_2$) in 2013 in the UK is an effect equivalent to 28,000 to 36,000 deaths at typical ages, associated with a loss of 328,000 – 416,000 life years. The range reflects the higher of the two estimates obtained by using single-pollutant coefficients as well as estimates based on reductions of $NO_2$ and $PM_{2.5}$ coefficients in four different studies following mutual adjustment. It does not take into account uncertainties such as those reflected in the confidence interval around the unadjusted coefficient.

Lower results (an effect equivalent to 16,000 – 19,000 deaths and an associated loss of 181,000 – 224,000 life years) are obtained when cut-offs for quantification are implemented. These figures avoid extrapolating the concentration-response relationships to concentrations lower than those which have currently been studied, and therefore represent the portion of the estimated burden in which there is greatest confidence.

There are uncertainties in these estimates, but we have not been able to fully quantify that uncertainty.

## 12.3 Views of the dissenting group

Members who dissent from the views outlined in Section 12.2 above (Professors H Ross Anderson and Robert Maynard, and Dr Richard Atkinson) have provided the following summary outlining their areas of disagreement with the conclusions reached by the majority of Members of COMEAP. These views are explained in more detail in Chapter 10

### 12.3.1 Statement of disagreement with the conclusion of the majority

Our disagreement with the majority view concerns the following issues

a Causality

b The decision to estimate the burden of mortality and the decision to present a burden estimate which extrapolates down to zero concentration of $NO_2$

c The use and interpretation of two-pollutant models

d The inadequate consideration of uncertainties, including those indicated by the heterogeneity within the evidence

In more detail:

a In our view there is insufficient evidence to infer a causal association between long-term average ambient concentrations of $NO_2$ and risk of death

b We regard the results of two-pollutant models as too uncertain for use in differentiating associations between long-term average ambient concentrations of $NO_2$ and PM and the risk of death

c We do not agree with the proposed method for arriving at an estimate of the association between $NO_2$ and mortality separate from particle mass concentrations and pollutants derived from the same sources as $NO_2$

d We regard the evidence for a causal effect of exposure to long-term average ambient concentrations of $NO_2$ on the risk of death as too weak and imprecise to be used as a basis for a calculation of the burden imposed on public health in the UK by long-term average ambient concentrations of $NO_2$

e We think it very likely that basing mortality burden calculations on long-term average ambient concentrations of $NO_2$ will, despite listing caveats, mislead the public into believing that exposure to long-term average ambient concentrations of $NO_2$ is causally associated with an increased risk of death

f While we disagree with the calculation of mortality burden estimates, we very much disagree with estimating the burden down to concentrations lower than those contributing to the original risk estimates, i.e. extrapolating beyond the data. Further, we disagree with presenting two estimates (cut off and zero threshold) and inviting the reader to choose

g We recognise that statistically significant associations between long-term average concentrations of $NO_2$ and risk of death have been reported. In our view these associations are best regarded as representing the associations between a mixture of pollutants of which $NO_2$ is a member and risk of death

h Single pollutant models using $NO_2$ as an indicator of the ambient mixture have been examined using meta-analytical techniques and have yielded a summary coefficient of 1.023 (95% CI: 1.008, 1.037) per 10 μg/m$^3$ increment in long-term average ambient $NO_2$ concentration. In our view this coefficient could be used in impact calculations to assess the marginal benefits of measures to abate levels of pollution mixtures represented by $NO_2$

i The current evidence base indicates a high level of heterogeneity between the $NO_2$ coefficients reported in individual studies, all but one of which is based on an overseas population. This makes extrapolation to UK cities, which, in turn may also vary in the composition of the pollution mixture, subject to uncertainty. Hence, the size and precision of any summary estimate should be interpreted with caution

# Chapter 13
# Working Group Chairman's reflections on quantification of the health impacts of $NO_2$

When COMEAP was handed the task of recommending coefficients for use in quantification of the mortality effects of long-term exposure to $NO_2$, the task appeared difficult but tractable. COMEAP had already expressed the view that some of the effects attributed to it in epidemiological studies were plausibly caused by nitrogen dioxide itself. This perception and the fact that COMEAP had previously recommended coefficients linking both acute and chronic exposures to a number of other air pollutants to adverse health outcomes suggested that the task could be achieved without major debate and controversy. Unfortunately, this has not proved to be the case.

When the epidemiological evidence for adverse effects of airborne particulate matter started to emerge in the early 1990's there was a marked scepticism from the UK research community as to the causality of the reported associations. However, as more studies reported results consistent with the earlier research, and subsequently toxicological studies revealed plausible mechanistic explanations for the toxicity of particulate matter exposure, it was widely accepted that the epidemiological associations were in fact causal, and this belief underpins the development of policy in relation to particulate matter exposures in the UK. Following that acceptance, COMEAP has recommended coefficients for particulate matter for use both in estimation of public health burdens and development of policy for both acute and chronic exposures.

In comparison to many of the other risks of life, the relative risks associated with exposure to typical ambient air pollutant concentrations are relatively small, which has the consequence of rendering their estimation difficult and frequently uncertain, and consequentially also leads to reduced confidence in causality without good supporting evidence from other sources, such as toxicology. This should, of course, not be taken to imply that these effects lack importance because of their small size, since with very large exposed populations the public health effects are of considerable magnitude, despite the small increases in risk to the individual. Thus, for example, the numbers of premature deaths estimated to be associated with fine particle exposure in the UK exceed those due to road traffic accidents by more than one order of magnitude. Consequently, it is of considerable importance to have the means of quantitative estimation of the effects of air pollutants to which all, or at least a large proportion, of the population are exposed. $NO_2$ falls within that category since it is emitted from high temperature combustion processes, most notably motor vehicle traffic, and has its highest

concentrations typically in urban areas where the majority of the population are unavoidably exposed.

One consequence of the emission of $NO_x$ from road traffic is that its emission is normally accompanied by that of particulate matter, and hence in urban areas concentrations of the two pollutants are typically highly correlated. Were they to be perfectly correlated there would be no means by which an epidemiological study could distinguish the effects of the two pollutants from one another. The earlier work of COMEAP on the association of mortality with chronic particulate matter exposure took the view that the effects associated with the exposure-response coefficient for $PM_{2.5}$ were likely to include also some due to correlated pollutants, as in the mixture of emissions from road traffic.

Our approach initially was to meta-analyse the results of single pollutant models for $NO_2$. This produced a coefficient statistically significant at the 95% level but showed a high level of heterogeneity between the studies. Such a coefficient will reflect any effects of $NO_2$ but reflect also in part the effects of pollutants with which it is correlated. In order to adjust the coefficient for the effects due to correlated pollutants the Committee turned to studies that had used two pollutant models in which coefficients were determined both for $NO_2$ and for $PM_{2.5}$. The relevant studies varied considerably in their attribution of the mortality effects to each of the pollutants, but also varied appreciably in the strength of correlation between $NO_2$ and $PM_{2.5}$. However, a subset of those studies with less strong correlation between the pollutants appeared to offer a broadly consistent picture of the effects due to each pollutant and we have used the insights gained from those studies to make a first adjustment to the coefficient for $NO_2$ for the effects of $PM_{2.5}$.

Unfortunately adjustment for $PM_{2.5}$ is only part of the story. In the countries where the relevant epidemiological studies were conducted, the main source of $NO_2$ is from road traffic. This is also a source of a number of other pollutants known to be capable of affecting human health, which include polycyclic aromatic hydrocarbons and ultrafine particles. Although the latter are a component of $PM_{2.5}$, there is some limited evidence that they may exert effects independent of those parts of the $PM_{2.5}$ that contribute most to mass. Since, in most developed countries the major part of $PM_{2.5}$ mass derives from advected secondary pollutants, and not directly from local primary emissions, it is likely that primary traffic generated pollutants such as PAH and ultrafine particles correlate more strongly with concentrations of oxides of nitrogen ($NO_x$) than with $PM_{2.5}$ mass, and probably also with concentrations of $NO_2$. Consequently, there must be a strong possibility that some of the associations attributed to $NO_2$ in the epidemiological studies are in fact due to other co-emitted pollutants. Arguments are advanced in our report that there are good reasons to believe that the contribution of $NO_2$ itself is neither zero nor 100% of that associated with it in the epidemiological studies, and the majority of the committee took the view, based upon their collective knowledge, that after discounting effects due to $PM_{2.5}$ and other correlated pollutants, $NO_2$ accounts for between 25-55 % of the effects attributed to it. Through this means, a coefficient was generated which can be used to estimate tentatively the benefits of small reductions in $NO_2$ itself upon mortality.

Some scenarios for pollution abatement, such as reductions in overall levels of road traffic, involve reductions in both $NO_2$, $PM_{2.5}$ and the co-emitted pollutants such as PAH and ultrafine particles. The report makes recommendations as to how the benefits of mitigation policies affecting the mix of pollutants can be estimated from single pollutant coefficients for $NO_2$ and/or $PM_{2.5}$ although these appear bound to be underestimates of the true effects. However, it was clear to all Members that simply adding effects estimated from single pollutant

coefficients for $NO_2$ and $PM_{2.5}$ would seriously overestimate the benefits of mitigation measures affecting both pollutants. Coefficients which can be used to generate tentative estimates of the benefits of reduction of $NO_2$ alone are also proposed.

Since $NO_2$ and $PM_{2.5}$ are not perfectly correlated with one another, the use of either single pollutant coefficient will inevitably underestimate the effects of the mixture upon health and consequently the report includes our best estimate of the health burden of the pollutant mixture using results of two pollutant models, the upper range of which exceeds by a modest margin that estimated for $PM_{2.5}$ using a single pollutant model coefficient. This health burden reflects, as best we can, the effects of $PM_{2.5}$, $NO_2$ and other correlated pollutants as no attempt has been made to adjust the coefficients for the presence of the latter.

In its earlier deliberations COMEAP has managed to reach unanimity on a wide range of issues; however, this was not possible in the current report which presents both a case against the quantification of effects and a case for quantification, including the outcome of resultant calculations. A sizeable minority of the committee was opposed to quantification especially in regard of the burden (as opposed to impact), regarding the uncertainty around such estimates as being too great for them to be meaningful. Amongst the reasons for that uncertainty are the following:

a A number of factors detract from the confidence which can be placed upon the outcomes of the epidemiological studies. The existence of substantial unexplained heterogeneity is concerning, and there is evidence of possible small study bias resulting from non-publication of studies showing non-significant outcomes. There are also concerns around the fact that for two pollutant models in which measurement uncertainties differ between the pollutants, there can be an apparent transfer of effects from the less accurately measured pollutant to the more accurately measured pollutant. It is currently not possible to quantify the magnitude of such an effect for already published studies. Some Members were also concerned that differences in the pollutant exposure scenarios between published studies and those existing in the UK currently limited the transferability of results from those studies

b It is recognised that two pollutant models are unreliable in distinguishing the effects attributable to each pollutant when the two pollutants are strongly correlated with one another. This was addressed by focusing upon those studies with the lesser degree of correlation, but there are no firm guidelines as to what degree of correlation can or should be accepted, and what strength of correlation is so great as to wholly invalidate the study outcome as far as individual pollutants are concerned. Other factors related to exposure misclassification can affect the reliability of the results as well, and we had no information on these aspects

c The quantitative contribution of other co-emitted pollutants such as PAH and ultrafine particles remains unknown, precluding an evidence-based adjustment of coefficients to allow for their contribution to effects

d In the case of particulate matter, there is strong support for causality from toxicological studies which have examined possible mechanisms. In the case of $NO_2$, there is some mechanistic evidence relating to acute exposures, but very limited evidence in relation to chronic exposures. This is not due to a

predominance of negative studies, but rather to a scarcity of relevant research work. Some members were unconvinced that there was sufficient evidence to support the causality of associations with $NO_2$

- While there is no evidence to suggest existence of a threshold for effects, it remains uncertain whether a lower concentration exists below which effects of $NO_2$ are negligible. Published work includes studies of very low concentrations, but the available coefficients derive in the main from concentrations well above zero. There was therefore much discussion over whether calculations of the mortality burden should include concentrations down to zero, or to a counterfactual representing the point below which adequate evidence of effects is lacking. Our decision was to calculate the mortality burden using both approaches

There was a wide range of views across COMEAP as to the extent to which published work could guide us in the estimation and application of coefficients for quantification of effects for $NO_2$. One viewpoint within the Committee was that the uncertainties which surround $NO_2$ are simply too great to allow quantification of effects, and were such quantification to be conducted it would run the risk of being seriously misleading, except in certain very limited applications. This proved to be a minority view. A viewpoint held with equal conviction by others (the majority) was that the published epidemiology shows sufficient consistency and coherence to allow quantitative messages to be extracted, and therefore within wide uncertainty limits, effects of $NO_2$ alone could be estimated under certain circumstances. The two groups did not divide on disciplinary lines and each group was respectful of the arguments advanced by the other, but was not convinced by them. This report has been structured so as to draw out clearly the two sets of views and not to obscure in any way the divergences of view and the uncertainties inherent in estimation of the effects of chronic exposure to $NO_2$ upon mortality. The fundamental disagreement lies within the question of whether it is more beneficial to extract the maximum information from published work applying past knowledge and experience while acknowledging the considerable uncertainties in doing so, or whether it is wiser simply to take the view that those uncertainties, and the ways in which reporting might downplay them, are so great as to invalidate the entire process.

One recommendation upon which the membership of COMEAP is unanimous is that further research is required both on the toxicology and epidemiology of $NO_2$ exposures, as well as on the use of multi-pollutant models to derive quantitative estimates of the effects of the pollutants being considered. Our research recommendations are listed in Chapter 11.

# Chapter 14
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# Appendix 1
# Terms of Reference for the COMEAP QUARK working group on $NO_2$

## A1.1 Overview

This Appendix presents the Terms of Reference for the COMEAP Quantification Working Group on $NO_2$, drafted before the group started its work on this topic.

## A1.2 Summary

The Committee has been asked to fast-track its work on quantifying the association between long-term average concentrations of nitrogen dioxide ($NO_2$) and mortality. It is proposed that a working group is set up to expand on COMEAP's discussions so far, make recommendations, undertake quantification, and prepare a draft statement or report for consideration by the Committee at the November 2015 meeting so that a statement or report can be published in December 2015.

## A1.3 Introduction

COMEAP's 2013-2018 work programme includes the theme 'traffic-related pollution' which currently focuses on $NO_2$. As part of this work, COMEAP published in March a statement on the health effects of exposure to $NO_2$ and concluded that:

a. 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

b. 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

With the evidence associating ambient concentrations of $NO_2$ with adverse effects on health strengthening, $NO_2$ is a priority for local and national government. At the meeting of the COMEAP Strategy Group 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 a priority for the Committee's consideration. Feedback from PHE's Air Pollution and Public Health Advisory Group and other stakeholders has also identified this as a

priority. The relationship between long-term average concentrations of $NO_2$ and mortality is likely to have a substantial influence if included in cost-benefit analyses.

The Department for Environment, Food and Rural Affairs (Defra) will be 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 has been asked to fast-track its work on quantifying the association between long-term average concentrations of $NO_2$ and mortality.

## A1.4 Output

The intention is to produce a statement or report quantifying the association between long-term average concentrations of $NO_2$ and mortality and to comment on any associated uncertainty. Commentary on the extent to which this should be regarded as additional to the mortality effects of $PM_{2.5}$, and the inferences that can be drawn will also be important considerations.

## A1.5 Approach

The Committee has already begun discussions on considerations relevant to quantification. At the COMEAP meeting in March, Members discussed the paper COMEAP/2014/02, which invited them to consider the evidence associating long-term average concentrations of $NO_2$ with increased mortality risk, and to give their views on causality. Views were also requested on whether, and under what circumstances, this pollutant-outcome pair should be used in cost-benefit analyses of measures intended to reduce ambient air pollution, or to quantify the mortality burden attributable to ambient air pollution.

At the next COMEAP meeting in June, Members will be asked to consider other issues regarding quantification including the scale and type of exposure assessments, use of two-pollutant models, recommendations for selection of a coefficient for quantification and the likely extent of overlap between $PM_{2.5}$ and $NO_2$.

It is proposed that a small working group be established to expand on these views expressed by Committee Members, make recommendations, undertake quantification, and prepare a statement or report. The statement will aim to:

a. Explain the reasoning behind the focus on mortality associated with long-term exposure to $NO_2$
b. Summarise the hazard evidence for mortality (refer to Secretariat working paper COMEAP/2014/02)
c. Consider how and under what circumstances, the association between long-term average concentrations of $NO_2$ and mortality should be used in health impact assessment studies, cost-benefit analyses of measures intended to reduce ambient air pollution, or to quantify the mortality burden attributable to $NO_2$
d. Make recommendations of concentration-response coefficients and quantify the association between long-term average concentrations of $NO_2$ and mortality. Potential quantification questions:
    - What is the mortality burden to public health in the UK from the effects of long-term exposure to average concentrations of $NO_2$?

- What would be the public health benefit of a 1μg/m$^3$ reduction of annual mean $NO_2$ or a reduction to the annual limit value?

e. Comment on any associated uncertainty

PHE may undertake additional work to quantify local impacts associated with annual mean $NO_2$ concentrations, which could be published as a PHE report and/or in the scientific peer-reviewed literature.

## A1.6 Resources

The following will inform the considerations regarding quantification of mortality associated with long-term average concentrations of $NO_2$:

a. The Secretariat working papers prepared by Karen Exley and/or Alison Gowers for the June 2014, November 2014, March 2015 and June 2015 COMEAP meetings including:
   - COMEAP 2014 02 Considering the evidence for the effect of $NO_2$ on health
   - COMEAP 2014 06 Evidence for the effects of $NO_2$ on health
   - COMEAP 2014 07 $NO_2$ considerations relevant to quantification
   - COMEAP 2015 03 Long-term $NO_2$ and mortality
b. Members' views from the meetings listed above
c. Working paper 8 (Studies on a Small Spatial Scale) of COMEAP (2009) report *Long-Term Exposure to Air Pollution: Effect on Mortality*
d. The QUARK paper QUARK/MORT/2011/07 Quantification of PM at a local level, and related discussions
e. Discussion included in the response to REVIHAAP[18] question C4: "Based on currently available health evidence, what $NO_2$ metrics, health outcomes and concentration–response functions can be used for health impact assessment?"
f. Health risks of air pollution in Europe – HRAPIE project (2014)[19]
g. Relevant meta-analyses including the Hoek et al[20] and Faustini et al[21] papers
h. US EPA Integrate Science Assessment for Oxides of Nitrogen – Health Criteria (Second External review Draft, 2015)[22]Information from the HIEH HPRU meeting

[18] http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/review-of-evidence-on-health-aspects-of-air-pollution-revihaap-project-final-technical-report

[19] http://www.euro.who.int/__data/assets/pdf_file/0006/238956/Health-risks-of-air-pollution-in-Europe-HRAPIE-project,-Recommendations-for-concentrationresponse-functions-for-costbenefit-analysis-of-particulate-matter,-ozone-and-nitrogen-dioxide.pdf

[20] Hoek, Krishnan, Beelen, Peters, Ostro, Brunefreef and Kaufman (2013) Long-term air pollution exposure and cardio-respiratory mortality: a review Environmental Health 12:43 doi:10.1186/1476-069X-12-43

[21] Faustini, Rapp and Forastiere (2014)Nitrogen dioxide and mortality: review and meta-analysis of long-term studies European respiratory journal doi:10.1183/09031936.00114713

[22] http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=288043

(February 2015) on burden estimates in the context of mortality associated with long-term average concentrations of $NO_2$

i. Methodology used in the Transport for London's report for quantification of effects associated with $NO_2$ (once published)

j. Other relevant and recently published papers

k. Available modelled $NO_2$ exposure data for the UK and selected urban areas

## A1.7 Timescales

Due to an urgent need for this information, the intention is to fast track this item of work. A draft statement will be prepared for consideration by COMEAP at the November 2015 meeting with sign off by early December 2015. Table 1, below, details the proposed timescales and meetings. An initial face-to-face meeting with the working group is proposed sometime after the June COMEAP meeting. The Chair has requested that an additional COMEAP meeting is held between the June and November meetings to discuss the work. Work by correspondence is expected and 2-3 teleconferences will be scheduled, depending on availability of Members.

## A1.8 Funding

Funding may need to be sought for additional meetings. Funding may also need to be sought for modelling of $NO_2$ concentrations at the appropriate scale.

# Appendix 2
# Glossary of Terms and Abbreviations

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| **ACS** | American Cancer Society |
| **ACS CPS II** | American Cancer Society Cancer Prevention Study II: a prospective mortality study |
| **Adjusted coefficient** | In a regression model, when more than one explanatory variable (eg $NO_2$ and $PM_{2.5}$) is used to explain changes in the response variable (eg health outcome), the coefficients associated with the explanatory variables may be different from those obtained if separate models were fitted (eg $NO_2$ and health outcome, and $PM_{2.5}$ and health outcome). Coefficients are typically adjusted for factors (eg socio-economic status) which may be correlated with both the variable of interest (eg $NO_2$) and the studied health outcome, and which therefore have the potential to confound the association found with the variable of interest. In this report, "adjusted coefficient" is used to refer to coefficients obtained where both $NO_2$ and PM are included in the same analysis – ie the association of mortality with one pollutant, having adjusted for the association of mortality with the other pollutant |
| **Ambient air** | Outdoor air |
| **Anthropogenic** | Originating from human activity |
| **AHSMOG** | The Adventist Health Study of Smog |
| **Bias** | In this report, bias refers to a systematic difference between the true value of a coefficient associated with an explanatory variable (eg $NO_2$) in a regression model and the coefficient estimated based on the available data |
| **Black smoke (BS)** | Non-reflective (dark) particulate matter, measured by the smoke stain method |
| **BMI** | Body mass index |

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| **CanCHEC** | The Canadian Census Health and Environment Cohort |
| **CTS** | The Californian Teachers Study |
| **Cardiovascular disease** | Disorders of the heart and circulatory system |
| **Chamber Studies** | Studies involving the exposure of volunteers to controlled concentrations of gases or aerosols |
| **Chronic obstructive pulmonary disease (COPD )** | COPD is a collective term referring to chronic bronchitis and emphysema: long-term diseases of the airways of the lung, associated with increased production of phlegm and shortness of breath. COPD is often caused by cigarette smoking.. The narrowing of the airways in COPD usually becomes progressively worse over time. COPD symptoms can be worsened by infections or air pollution |
| **Coefficient** | The quantification of the association between an explanatory variable (eg $NO_2$) and the response (eg health outcome) in a regression model. Positive coefficients (>0) indicate that increases in the explanatory variable are associated with increases in the health outcome |
| **Cohort Studies** | Epidemiological studies following the health of individuals in a sample of the population (a cohort) over a period of time |
| **COMEAP** | Committee on the Medical Effects of Air Pollutants |
| **Concentration response function (CRF)** | A function that expresses the quantitative relationship between concentrations (eg of an air pollutant) and the (health) outcome of interest. This term is often used to refers to the function adopted to estimate effects associated with pollutants |
| **Confidence interval** | If it is possible to define two statistics t1 and t2 (functions of sample values only) such that, $\theta$ being a parameter under estimate,<br><br>$P(t1 \leq \theta > t2) = \alpha$<br><br>where $\alpha$ is some fixed probability (eg 0.95 or 95%), the interval between t1 and t2 is called a confidence interval. The assertion that $\theta$ lies in this interval will be true, on average, in a proportion $\alpha$ of the cases when the assertion is made. For example, 95% confidence intervals are calculated in such a way that, in the absence of bias, 95% of such intervals will include the parameter that is being estimated |

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| **Confounding factors/variables** | Factors which may affect the results of epidemiological studies looking at the effects of variables (eg air pollutants) on health. Factors such as smoking, employment, diet, gender, socio-economic status or ethnicity may be correlated with both the variable of interest (eg an air pollutant) and the health outcome studied. Unless they are adjusted for, these factors can affect (confound) the association found between the variable of interest and health outcomes. |
| **Correlation** | The quantification of the relationship between two variables; often used to refer to how close two variables are to having a linear relationship with each other. A correlation of zero indicates no relationship with values of +1 / -1 corresponding to perfect positive / negative correlation |
| **Counterfactual** | A theoretical baseline (reference) concentration against which the burden of existing concentrations of pollution are compared |
| **Covariance** | A measure of the joint variability of two variables, covariance describes the way that two variables deviate from their expected values (means). If two variables are independent then the covariance is zero. If the two variables are positively correlated then the covariance is >0. Covariance is closely related to correlation, which is the normalised version of covariance |
| **CPRD** | Clinical Practice Research Datalink. Provides anonymised primary care records for public health research. |
| **DUELS** | The Dutch Environmental Longitudinal Study |
| **Epidemiological studies** | Investigations of diseases conducted at a population level |
| **ESCAPE** | European Study of Cohorts for Air Pollution Effects |
| **EU** | European Union |
| **EU Limit Values** | EU Limit Values are legally binding EU parameters that must not be exceeded. Limit Values are set for individual pollutants and are made up of a concentration value, an averaging time over which it is to be measured, the number of exceedances allowed per year, if any, and a date by which it must be achieved. Some pollutants have more than one Limit Value covering different endpoints or averaging times. |
| **Exposure misclassification** | Exposure misclassification in this report refers to differences between the exposure metrics used in the |

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| | epidemiological study and the 'true' exposures of the population at risk. This includes differences between the 'true' concentrations and the measurements and/or modelled values used when estimating risks, and differences between concentrations and personal exposures.<br><br>Exposure misclassification is sometimes referred to as measurement error |
| **Hazard Ratio (HR)** | The ratio of the hazards (risk of death, or other health outcome) evaluated at different levels of an explanatory variable (eg exposure to a pollutant) |
| **HEI** | Health Effects Institute |
| **HRAPIE** | World Health Organization's health risks of air pollution in Europe – HRAPIE –project |
| **$I^2$** | A measure of heterogeneity. It is the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance) |
| **Intervention** | In this report, an intervention refers to an action to reduce exposure to ambient air pollution. |
| **LAQT** | London Air Quality Tool |
| **Land Use Regression (LUR)** | The land use regression model is an exposure assessment tool frequently used in air pollution epidemiological studies to estimate the concentration of air pollution at unmonitored locations |
| **Measurement error** | The difference between a measured value of a quantity and its true value. The measurement error referred to in this report is exposure misclassification (see definition above) |
| **Meta-analysis** | A statistical method used to combine the results of a number of individual studies |
| **Multi/two pollutant model** | A regression model containing two (or more) pollutants, plus other covariates (eg possible confounders such as socioeconomic status) |
| **Nitrogen dioxide ($NO_2$)** | A gas produced during combustion by the oxidation of atmospheric nitrogen |
| **Oxides of Nitrogen ($NO_x$)** | A mixture of gases that are composed of nitrogen and oxygen and produced during combustion. In atmospheric chemistry, $NO_x$ is used to refer to nitric |

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| | oxide (NO) and nitrogen dioxide ($NO_2$) |
| **Output area (OA)** | A geographical unit used for statistical purposes, with the size varying around about 120 households. |
| **Ozone ($O_3$)** | A strongly oxidant gas produced by reactions in the atmosphere |
| **Particle** | A minute portion of matter – frequently a very small solid or liquid particle (or droplet) of micrometre or nanometre dimensions |
| **PHE** | Public Health England |
| **PCM model** | Pollution Climate Mapping model. The models is used to produce background maps, 1 km x1 km grids of pollutant concentrations, for the UK |
| **PM** | Particulate matter |
| **$PM_{2.5}$** | The mass concentration of particles with a diameter of 2.5 μm or less (also known as fine particles).<br><br>Defined as the mass per cubic metre of particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of 2.5 micrometres |
| **$PM_{10}$** | As for $PM_{2.5}$ (above) with 10 micrometres. $PM_{10}$ includes $PM_{2.5}$. |
| **ppb** | parts per billion |
| **QUARK** | COMEAP Sub-group on Quantification of Air Pollution Risks in the UK |
| **Reduced coefficient** | In this report, "reduced coefficient" is used to refer to the estimated causal association between long-term exposure to $NO_2$ and mortality. Expert judgement was used take account of the likely extent of confounding, by $PM_{2.5}$ and other pollutants correlated with $NO_2$, of coefficients from single-pollutant models |
| **Relative risk (RR)** | Relative risk is used in this report to compare age-specific death rates in two groups that differ in terms of exposure or other characteristics, eg in terms of their average annual exposure to $NO_2$. It is derived as the ratio of age-specific death rates in the two groups (assuming other factors are equal) because exposure is expected to increase age-specific death rates by some multiplicative factor, estimated from epidemiological |

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| | studies. Relative risk is a measure of that factor |
| **REVIHAAP** | WHO's Review of Evidence on Health Aspects of Air Pollution project |
| **SES** | Social economic status |
| **Single pollutant model** | A regression model containing a single pollutant, plus other covariates (eg possible confounders such as socioeconomic status) |
| **Small study bias** | Refers to the possibility that small studies identified in a systematic review or meta-analysis may report systematically different effects to larger studies. Small study bias includes publication bias (bias due to the fact that small studies that show small or no effects are less likely to be published). |
| **Time-series studies** | Studies of the health effects of short-term exposure to air pollution. Time-series studies estimate the influence of daily variations in air pollutant concentrations on deaths (mortality) and illness by linking daily counts of health events (mortality, hospital admissions, visits to emergency departments, etc) within a geographically defined population with daily measures of air pollution and other variables |
| **Two/multi pollutant model** | A regression model containing two (or more) pollutants, plus other covariates (eg possible confounders such as socioeconomic status) |
| **µg/m³** | Micrograms per cubic metre. 1 µg = 1 millionth of a gram |
| **µm** | Abbreviation for micrometre or micron (a unit of length). 1 µm =one thousandth of a millimetre |
| **Unadjusted coefficient** | The coefficient from a regression model in which only a single explanatory variable is included (eg $NO_2$ with no other covariates or pollutants). As all studies report coefficients that are adjusted for the effects of potentially confounding covariates, it is commonly used (including in this report) to refer to a coefficient from a single, rather than two/multi-, pollutant model – ie the association with one pollutant, without having adjusted for the association with the other pollutant |
| **US EPA** | US Environmental Protection Agency |
| **WHO** | World Health Organization |

# Appendix 3
# Membership Lists

## Membership of the Committee on the Medical Effects of Air Pollutants

**Chair**

Professor Frank Kelly BSc PhD FRSB FKC

**Members**

Professor H Ross Anderson MD MSc FFPHM FRCP FMedSci *(until August 2016)*
Dr Richard Atkinson BSc MSc PhD PG Cert HE
Professor Alan R Boobis OBE PhD CBiol FSB FBTS
Dr Nicola Carslaw BSc MSc PhD
Ms Ruth Chambers MA MSc
Dr Beth Conlan BSc MSc PhD
Professor Jonathan Grigg BSc MBBS MRCP MD FRCPCH
Professor Roy Harrison OBE PhD DSc CChem FRSC FRMetS HonFFOM HonMFPH FRS *(co-opted)*
Dr Mike Holland BSc PhD
Mr J Fintan Hurley MA
Professor Debbie Jarvis MBBS MRCP MD FFPH
Dr Jeremy Langrish BA MA MB BCh MRCP PhD *(until 2015)*
Professor Robert L Maynard CBE FRCP FRCPath FFOM *(co-opted)*
Dr Mark Miller BSc PhD
Dr Brian G Miller BSc PhD CStat *(until May 2017)*
Professor Gavin Shaddick BSc MSc PhD *(co-opted)*
Dr Alison Searl BSc PhD MEnvS *(until November 2015)*
Mr John Stedman BA
Dr Heather Walton BSc DPhil
Professor Paul Wilkinson BA BM BCh MSc MFPHM FRCP

**Secretariat**

Dr Sotiris Vardoulakis BSc MSc PhD (Scientific) *(until May 2017)*
Ms Alison Gowers BSc MSc (Scientific)
Dr Inga Mills BSc MSc PhD (Scientific) *(until June 2016)*
Dr Karen Exley BSc MSc PhD (Scientific)
Dr Sani Dimitroulopoulou BSc PhD (Scientific) *(until May 2017)*
Dr Sarah Robertson BSc MSc PhD (Scientific)
Mrs Isabella Myers BSc MSc (Scientific) *(until June 2015)*

## Membership of the Committee on the Medical Effects of Air Pollutants Quantification Working Group on Nitrogen Dioxide

| | |
|---|---|
| Chair | Professor Roy Harrison OBE PhD DSc CChem FRSC FRMetS HonFFOM HonMFPH |
| Members | Dr Richard Atkinson BSc MSc PhD PG Cert HE<br>Dr Mike Holland BSc PhD<br>Mr J Fintan Hurley MA<br>Professor Frank Kelly BSc PhD FRSB FKC<br>Dr Brian G Miller BSc PhD CStat (*until May 2017*)<br>Mr John Stedman BA<br>Dr Heather Walton BSc DPhil |
| Secretariat | Dr Karen Exley BSc MSc PhD (Scientific)<br>Ms Alison Gowers BSc MSc (Scientific)<br>Dr Inga Mills BSc MSc PhD (Scientific) (*until June 2016*) |