Report of a Workshop to Identify Needs for Research on the Health Effects of Nitrogen Dioxide - London, 2-3 March 2011

Workshop convened by the Air Pollution Group, Health Protection Agency and commissioned by the Policy Research Programme of the Department of Health

ABSTRACT

It is clear from epidemiological and laboratory studies that air pollution has adverse effects on health. However, understanding whether ambient concentrations of nitrogen dioxide (NO_2) have direct adverse effects on health has proved to be difficult, because levels in ambient air correlate closely with those of other pollutants, notably particles. This difficulty arises because NO_2 and particles have similar sources, such as traffic.

Knowing whether or not current concentrations of outdoor NO_2 have direct adverse health effects is becoming increasingly important. One reason for this is that the UK, like many other EU countries, is finding it difficult to comply with legally binding EU limit values for NO_2 in outdoor air. Member States failing to comply face the possibility of large fines. This has re-focussed attention on the uncertainties in the evidence base underpinning the assessments of the possible impacts of NO_2 on health, including the derivation of the World Health Organization (WHO) guideline on which the legally binding limits are based.

The Health Protection Agency (HPA) and Department of Health (DH) recognised the important policy implications of these data gaps in preventing confident evaluation of the public health importance of ambient levels of NO_2. In March 2011, DH's Policy Research Programme commissioned a workshop, organised by the HPA, to consider this issue. This brought national and European experts together with officials from relevant Government departments with policy or advisory responsibilities in this area. The main aim of the workshop was to develop ideas for future research that would help disentangle the possible adverse health effects of NO_2 from those of other pollutants, notably particles. Invited speakers set out the issues and outlined the available scientific evidence. Proposals for different types of scientific investigation were then discussed and research recommendations agreed.

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EXECUTIVE SUMMARY

Nitrogen oxides[1] make an important contribution to the ambient mixture of air pollutants especially in urban areas. They also contribute to ozone formation and react to produce secondary aerosol components of particulate matter.

Long-term average concentrations of oxides of nitrogen in most urban areas of the UK have declined since the 1990s. However, this trend has levelled off, and in some areas (e.g. at roadsides) concentrations are slowly increasing. An important reason for this is the failure of the European emission standards (which define requirements for emissions from motor vehicles) to deliver the expected reductions in emissions of oxides of nitrogen (NO_X) from road vehicles, particularly from light-duty diesel vehicles. Over the past decade the number of these vehicles has increased significantly in the UK. Another factor contributing to the increase in concentrations at some roadside locations in recent years is an increase in directly emitted nitrogen dioxide (NO_2) related to some forms of particle emission control on diesel vehicles.

Demanding standards for outdoor concentrations of NO_2 were set in Directive 1999/30/EC, in an effort to limit the adverse effects on health of NO_x. These include an EU annual average limit value of 40µg/m^3, which has been difficult to meet at roadsides. Questions about the basis of this standard and the benefits to health likely to be delivered by its achievement have been raised. From the available evidence, it has not been clear whether current ambient concentrations of NO_2 have direct adverse effects on health. Instead, it is often suggested that epidemiological associations between concentrations of NO_2 and adverse health effects might reflect the effects of other toxic air pollutants (mainly particulate matter) in the air pollutant mix. Concentrations of NO_2 and particulate matter are closely correlated, as they are emitted from the same sources, e.g. traffic. Therefore, disentangling the possible adverse health effects of NO_2 from those of particulate matter, and other components of the traffic-dominated mixture of outdoor air pollutants, has proved difficult.

The World Health Organization (WHO) acknowledged the uncertainties in the evidence when recommending a concentration of 40 µg/m^3 (annual average) as a health-based air quality guideline (AQG) for outdoor concentrations of NO_2. Despite these uncertainties, this value was later adopted in the European Union (EU) as a legally binding standard (limit value). It is also of note that, in deriving the WHO guidelines, expert groups of the WHO were required not to take account of policy issues relating to feasibility or cost of achievement or the locations at which it should apply, but to make recommendations on health criteria alone.

Many other EU countries are also finding it difficult to comply with the limit values for NO_2. Increasingly expensive or restrictive measures will be required to comply with this legislation in the required timescales and Member States failing to comply face the possibility of large fines. This has re-focussed attention on the uncertainties in the

[1] Nitrogen dioxide (NO_2) and nitric oxide (NO) are oxides of nitrogen and together are referred to as NO_X.

evidence base underpinning the assessments of the possible impacts of NO_2 on health, including the derivation of the WHO guideline on which the legally binding limits are based. This has been seen by some as unsatisfactory, partly because it was based on studies of indoor exposure to NO_2 from gas cooking.

The Health Protection Agency (HPA) and Department of Health (DH) recognised the important policy implications of these gaps in the evidence base in preventing confident evaluation of the public health importance of ambient levels of NO_2. In March 2011, DH's Policy Research Programme commissioned a workshop, organised by the HPA, to consider this issue. This brought national and European experts together with officials from relevant Government departments with policy or advisory responsibilities in this area. The intention was that, by generating new thinking with regard to these issues, ideas for a research agenda that would help disentangle the possible adverse health effects of NO_2 from those of other pollutants would be developed.

As might be expected, the difficult issues outlined above, and in more detail in the following pages, have not been answered with certainty. However, a number of important discussion points have been noted and a series of recommendations for research have been made. These are summarized below; more details may be found in the following chapters.

Key discussion points

1 The WHO annual average air quality guideline for NO_2 is based on studies of the adverse effects on health of children of indoor exposure to raised concentrations of NO_2 produced by gas cooking. Such evidence could be regarded as a less than ideal basis for an annual average EU limit value for outdoor concentrations of this pollutant[2].

2 In deriving an annual average air quality guideline for NO_2, WHO expert groups had acknowledged the areas of uncertainty in the evidence on long-term exposure to NO_2. However, these uncertainties did not appear to have been reflected in the subsequent regulatory process which resulted in adoption of WHO guideline values as limit values in EU legislation for this pollutant.

3 Nitrogen dioxide has been less thoroughly studied than particulate matter in the past decade or so. This is, in part, due to the surging interest in the adverse health effects of small particles. As a result, little progress has been made in understanding the possible independent adverse effects of ambient NO_2 on health. It is for this reason that WHO, in successive evaluations of the evidence, has been unable to improve upon the AQG which was established in the mid 1990s. It was also noted that, when interpreting the findings of epidemiological studies which had found associations between both NO_2 and particles and adverse effects on health,

[2] It was noted that in more recent reviews of the AQG, the WHO had considered evidence on long-term exposure to outdoor NO_2. Consideration of that evidence did not lead to a change in the WHO annual average guideline for NO_2.

the default assumption seems to be that particles and not NO_2 are responsible for such effects.

4 A limited number of studies has considered NO_2 and PM_{10} together (in two-pollutant regression models). The few studies of short-term effects published until 2002 were systematically reviewed by the Committee on the Medical Effects of Air Pollutants (COMEAP) (see Appendix 4 of COMEAP, 2006[3]) to assess the strength of the evidence for associations with NO_2 and PM_{10} respectively, and this analysis found NO_2 associations to be somewhat more robust against adjustment for PM_{10} than associations with PM_{10} were against adjustment for NO_2. Two pollutant analyses of other metrics of particulate matter and NO_2 have not been reviewed systematically. Some epidemiological associations between long-term exposure to NO_2 and health outcomes are available, e.g. associations with mortality as demonstrated in cohort studies conducted in Europe (Brunekreef, 2007). However, for reasons discussed in this report, questions remain regarding the causal nature of these associations. Toxicological data have been of limited help in addressing the issue of causality as the concentrations at which adverse effects have been demonstrated in such studies are well above those examined in the epidemiological studies. Direct comparison of these two bodies of evidence is further hindered by differences in the health outcomes investigated.

5 Vehicle test-cycles intended to represent real-world conditions are in need of re-examination because they underestimate emissions of NO_x. It was noted that this was underway. Without further research and measurement, there may not be confidence in the effectiveness of the latest (Euro 6 and Euro VI) vehicle emission limits in delivering real improvements in NO_x emissions.

Research recommendations

There is a need for further research to investigate the relative importance of the adverse effects of ambient NO_2 on health in relation to other constituents of the urban (traffic-dominated) air pollution mixture. The following research recommendations are likely to contribute to this and will help inform policy development in this area.

1 An innovative approach to the re-examination of the results of existing epidemiological studies is urged. Existing information, including that held in databases such as APED[4], can be used in novel ways to gain more insight in the relative importance of NO_2 and other constituents of urban air pollution mixtures, particularly where these change over time.

2 New epidemiological studies should focus on improved assessments of outdoor exposure to NO_2 and involve better characterisation of mixtures of air pollutants.

[3] Committee on the Medical Effects of Air Pollutants (2006) *Cardiovascular Disease and Air Pollution*. Available at (accessed June 2011): http://www.comeap.org.uk/documents/reports.html
[4] APED: Air Pollution Epidemiology Database which is managed by St George's, University of London.

Studies capitalizing on policy-driven interventions such as the development of low emission zones, are also needed.

3 Chamber studies that better reflect the health outcomes and likely exposure patterns in epidemiological studies are needed. Studies focusing on comparisons of the effects of different air pollutants, and of different components of the pollution mixture emitted from one source (e.g. traffic), are needed. Such studies should also investigate increased duration of exposure[5] and sensitive sub-groups of the population.

4 Toxicological studies comparing the potency of ultra-fine particles, other pollutants and NO_2 in the same experimental system would allow appropriate comparisons to be drawn. Studies are needed on free radical-driven reactions following NO_2 exposure, and those exploring differences in sensitivity to air pollutants. Studies are also needed on the effects of combinations of pollutants (e.g. adding or removing NO_2 to/from filtered and unfiltered diesel exhaust exposures).

All this represents a large programme of research. A collaborative approach, between groups in the UK and abroad and between the specialties of epidemiology and toxicology is recommended.

Ongoing research projects of relevance to the issues considered in this workshop are noted, e.g. the ESCAPE[6] project, and the TRAFFIC project within the joint initiative[7] on Environmental Exposures and Health.

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[5] For example, exposure for a few hours but repeated over a longer time period.
[6] ESCAPE: European Study of Cohorts of Air Pollution Effects (http://www.escapeproject.eu/)
[7] Joint initiative on Environmental Exposure and Health by the Medical Research Council (MRC), Natural Environment Research Council (NERC), Department of Health (DH), Economic and Social Research Council (ESRC), and Department for Environment, Food and Rural Affairs (Defra).

CONTENTS

1 INTRODUCTION

1.1 Background to the workshop

The effects of short-term exposure to high concentrations of nitrogen dioxide (NO_2) are well established (MAAPE, 1993). However, establishing that short- and long-term exposure to ambient concentrations of NO_2 is causally associated with adverse effects on health has proved more difficult. Disentangling the possible adverse health effects of NO_2 from those of the other components of the traffic-dominated mixture of outdoor air pollutants has proved difficult. A number of epidemiological studies have reported associations between ambient concentrations of NO_2 and adverse effects on health but some workers have suggested that the findings are confounded by the close correlation between NO_2 and fine particles (WHO, 2006; US EPA, 2008; COMEAP, 2009). There are few studies which show that long-term average outdoor concentrations of NO_2 are associated with adverse effects on health.

It has been argued that whether NO_2 acts, by itself, to damage health or whether it acts as a surrogate for a mixture of pollutants that damages health is unimportant: in either case reducing concentrations of NO_2 should be of benefit to health. The latter part of the argument cannot be sustained unless it is further argued that reductions in concentrations of NO_2 will be accompanied by proportional reductions in the other components of the mixture for which NO_2 is acting as a surrogate.

It can be argued that reducing emissions of oxides of nitrogen (NO_x) would be of benefit to health by virtue of the secondary effects of reducing the formation of ozone and of nitrates in secondary particles. This is accepted, though there may be more cost effective means of achieving reductions in these secondary pollutants.

Meeting the EU annual average limit value (LV) for NO_2 in urban areas in the UK at present requires the reduction of emissions of NO_x from vehicles. Showing that such reductions would be directly beneficial to health will be difficult unless some direct effect of exposure to NO_2 can be demonstrated. That reductions in emissions of NO_x will, by reducing the formation of nitrate, aid in reducing exposure to particles is clear, but this will not help in demonstrating that reductions in urban concentrations of NO_2, will be directly beneficial to health. If it was known that the only benefit associated with reducing emissions of NO_x was delivered by a reduction in secondary particles then a LV based on particle concentrations rather than on NO_2 concentrations would seem more appropriate.

These points are now critically important because many European Union (EU) Member States, including the United Kingdom (UK), are experiencing difficulties in meeting the EU annual average limit value for NO_2 at roadside locations in urban areas: 40µg/m^3, annual average concentration, to be achieved by 1 January 2010 (Directive 2008/50/EC). To meet it, efforts to reduce emissions of NO_x, and thereby concentrations of NO_2, will be needed. Technical measures will be very expensive and non-technical ones (such as radical restrictions on traffic and, in particular, reduction of diesel car numbers) are not well accepted by society. It would be very difficult to justify large expenditure unless a significant benefit to health can be expected.

The issue is further complicated by questions about the basis of the EU annual average LV. The LV is based on the annual average World Health Organization (WHO) air quality guideline for NO_2 that, in turn, adopted a recommendation by the International Programme on Chemical Safety (IPCS) based on studies of indoor air pollution (IPCS, 1997; WHO, 2000). The EU Directive effectively requires compliance with the LV at the roadsides. This is where concentrations of NO_2 are highest.

The need for Member States to submit air quality plans to the European Commission for time extensions to meet the annual average LV for NO_2 and the review of the EU Air Quality Directive scheduled for 2013 are raising the profile of the issues related to understanding the effects of long-term exposure to ambient levels of NO_2 on health.

1.2 Objectives and key questions

The interactive workshop, conducted over a day and a half (2-3 March 2011), brought together a range of experts from the academic community and policy makers from the UK and EU (including the EC and WHO) to explore various facets of the issues, given the available evidence, of considering whether or not ambient concentrations of NO_2 have direct adverse effects on health and of whether meeting the EU annual average LV for NO_2 would confer benefits to health. The aim of the workshop was, by generating new thinking with regard to the issues described in Section 1.1, to develop ideas for a research agenda that would help disentangle the possible adverse health effects of NO_2 from those of other pollutants.

To facilitate discussion the number of participants was restricted to approximately 30. A list of participants is attached as Appendix A.

Key questions were devised by the organisers to help define important issues for discussion.

Three broad questions:

i How much benefit to health does compliance with the EU annual average limit value for NO_2 confer?
ii How cost-efficient is compliance with this limit value?
iii What research do we need to put in hand to answer these questions?

More focussed questions:

i What does the evidence say about the primary effects on health of long-term exposure to NO_2?
ii What does the evidence say about the effects of intermittent exposure to long-term average concentrations of NO_2?[8]

[8] More precisely, what does the evidence say about the effects of intermittent exposure to short-term peaks super-imposed on long-term average concentrations of NO_2?

iii What does the evidence say about the likely causality of associations between effects on health and long-term average concentrations of NO_2?
iv What research do we need to disentangle the possible primary effects of NO_2 from the effects of particles?
v How reliable is the surrogacy argument as a basis for improving health by reducing long-term average concentrations of NO_2?
vi Does the evidence point to sub-groups of greater than average sensitivity or susceptibility to NO_2?
vii What is the relationship between reducing concentrations of NO_2 (as monitored for compliance with the limit value) and reducing exposures to NO_2?
viii Would it be possible to improve monitoring with a view towards improving the link between exposure and long-term average concentration and thus improving the prediction of benefits?
ix What research do we need to do to be able to calculate the benefits to health of reducing the annual average concentration of NO_2 (as monitored to assess compliance with the annual average limit value)?
x What is the likelihood of our answering these questions by taking only studies of the effects of outdoor exposure to NO_2?
xi Has any new evidence appeared since the last WHO air quality guideline review that suggests the current long-term air quality guideline might be usefully revised?

1.3 Agenda

The agenda, attached as Appendix B, was divided into a series of 30-minute presentations, with sufficient time allocated for corresponding discussion:

i The Policy-Science Interface, by Professor Martin Williams.
ii Standards, Emissions and Concentrations, by Dr David Carslaw.
iii Evidence from Epidemiological Studies, by Professor Ross Anderson.
iv Evidence of Direct Health Effects from Toxicological Studies, by Professor Frank Kelly.
v Key Issues on Nitrogen Dioxide, by Professor Bert Brunekreef.

In addition to the main speakers, four participants were identified, on the basis of their expertise and interests, to act as discussants during the first day of the workshop. Their role was to draw attention to specific aspects of the issues around NO_2 that were related to the main theme of each presentation.

Discussions on the first day of the workshop focussed on the series of scientific presentations. The earlier presentations provided valuable context to the latter ones on the epidemiological and toxicological evidence. The second day began with a reflection on the key themes to emerge from the previous day. It also saw discussion of the key questions put to participants and the identification of research needs.

1.4 Structure of the report

The main body of the report, given as Chapter 3, is organised to reflect the series of scientific presentations: sub-chapters provide a summary of each speaker's presentation followed by a record of the key points to emerge in the corresponding discussion. Presentations made during the workshop are available at www.hpa.org.uk.

Chapter 4 provides a synthesis of the key discussion points, as well as answers to some of the questions put to participants. Questions relating to research needs have been addressed in the final chapter on research recommendations.

2 SETTING THE SCENE: DESCRIBING THE ISSUES

The workshop began with welcome and opening remarks from the Chair, Dr Robert Maynard.

Initial comments from representatives from Department for Environment, Food and Rural Affairs (Defra) and the European Commission were invited:

- Defra outlined the challenge facing Member States: attempting to meet the EU annual average LV for NO_2 in the UK (and other Member States) required pursuit of costly policy measures for controlling ambient NO_2 with little knowledge of the potential benefits to health such measures could deliver. Defra hoped that the workshop would provide new perspectives about the complexities of the issues pertaining to NO_2.
- The European Commission took the opportunity to inform participants of its plans to undertake a major review of the Thematic Strategy on Air Pollution. That process would see a request from the Commission to the WHO to reconsider whether new evidence on ozone, particulate matter and NO_2 might warrant revision of the WHO air quality guidelines. The Commission will consult Member States and stakeholders on their concerns regarding air quality. Meetings with stakeholder groups will be held from 2011 until 2013, when the review and possible revised EU legislation is published.
- Both representatives welcomed the timely workshop and the funding provided by the Department of Health's Policy Research Programme.

The Chairman gave an opening presentation which provided participants with the following:

i the purpose of the workshop
ii a description of the issues (see Section 1.1)
iii the historical context leading to EU legislation for NO_2
iv the key questions to be addressed (see Section 1.2)
v the deliverables from the workshop

The central issue related to whether NO_2 had:

- *Primary health effects* - effects of exposure to NO_2, *per se*.
- *Secondary health effects* - the effects of ozone and nitrate particles: formation dependent on NO_2.
- *An association with health "effects"* by virtue of its acting as a surrogate, an index or marker, for other pollutants.

The availability of evidence on these categories of possible adverse health effects of NO_2 was questioned. Focus on the health effects of other pollutants, especially particulate matter, and a lack of funding for research on NO_2 had played a significant role in the decline in research efforts, and thus much needed evidence, on NO_2. Consequently, policy development on this pollutant had been impacted adversely. The lack of concentration-response functions (which could be regarded as causal) linking long-term average concentrations of ambient NO_2 and health, independently of effects of particulate matter, did not allow evaluation of policy measures using cost-benefit methods. This was used to support the commonly held view that perhaps NO_2 was an unimportant pollutant in terms of adverse effects on health. Belief in the efficacy of reducing surrogates had also contributed to the decline in research efforts on NO_2. It has been argued that whether NO_2 acts, *per se*, to damage health or whether it acts as a surrogate for a mixture of pollutants that damages health is unimportant: in either case reducing concentrations of NO_2 should be of benefit to health. The latter part of the argument cannot be sustained unless it is further argued that reductions in concentrations of NO_2 will be accompanied by proportional reductions in the other components of the mixture for which NO_2 is acting as a surrogate.

3 SCIENTIFIC PRESENTATIONS

This chapter provides a summary of the scientific presentations followed by a record of the key points which emerged in the corresponding discussion.

3.1 Presentation 1: The policy-science interface

Professor Martin Williams, King's College London

Summary
Areas of uncertainty relating to NO_2 that were of particular importance to the policy process were outlined:

i the science: uncertainty regarding whether NO_2 had a causal role in adverse effects on health
ii the size of the effect
iii the evaluation of policy measures

In deriving an annual average air quality guideline for NO_2, WHO expert groups had appropriately acknowledged the areas of uncertainty in the evidence on long-term exposure to NO_2. However, these uncertainties had not been adequately reflected in the subsequent regulatory process which involved adoption of WHO guideline values as limit values in EU legislation for this pollutant by the European Union.

Difficulties in achieving reductions in emissions of NO_x in urban areas were considered in detail. Despite good reasons for controlling ambient NO_2 and NO_x, it was argued that it was not necessary to control levels of ambient ozone via an annual average LV for NO_2; controls for emissions of NO_x, as in the EU National Emissions Ceilings Directive and the CLRTAP[9] Gothenburg Protocol, are more appropriate. However, the current regulatory system which defined requirements for emissions from motor vehicles, i.e. the so-called ‘Euro standards’, was <u>not</u> adequate to reduce real-world emissions of NO_x from diesel vehicles in urban areas. Comparisons of real-world data with those from EU regulatory test-cycles of engines revealed a disparity: for diesel vehicles, the reductions demonstrated in the regulatory tests had not occurred in the real-world. It appears that the regulatory test-cycle does not adequately reflect driving conditions in the real-world.

A comparison of trends in levels of ambient NO_2 between the UK and US was presented. Data showed that until 2002, the UK had experienced significant reductions in NO_x. Since then the trend had flattened as a result of an influx of diesel vehicles. This trend was also seen in other EU Member States. Additional data showed that emissions of primary NO_2 had increased in the UK. Trends for the US however showed a different picture: levels of NO_2 continued to decline owing to much less use of diesel vehicles.

Further points, including options for modification of the compliance regime for the EU annual average LV, were noted:

- Provision of a different compliance date by which the LV should be achieved.
- By analogy with the short-term LV where temporal percentiles are used to give some flexibility, using spatial percentiles to provide flexibility with respect to where the EU annual average LV is met.
- Tackling the surrogacy argument - it did not help the policy process to suggest that NO_2 was a marker for traffic-generated air pollutants given that the legal limit and measures to reduce emissions were specific to an individual pollutant.
- Further research to address the issue of causality was crucial.
- Analogies with the US were drawn - the annual average Federal standard of 100 $\mu g/m^3$ for NO_2 was considerably less stringent than the EU annual average limit value (and had been reviewed twice since 1971) as was the annual average value in California (57 $\mu g/m^3$). California had also regulated primary NO_2 in vehicle emissions which the EU has not as yet done.

[9] CLRTAP: the Convention on Long-Range Transboundary Air Pollution.

Key discussion points

- *Discussant*: Dr Michal Krzyzanowski, World Health Organization
    - The historical context which led to the WHO recommended annual average air quality guideline of 40 µg/m^3 for NO_2 was recapped. Despite several reviews of the evidence on long-term exposure to NO_2, WHO expert groups had arrived at similar conclusions, and there remained uncertainty regarding which constituents of traffic emissions were responsible for the observed adverse effects on health. The recommended guideline figure of 40 µg/m^3 was derived from studies of indoor air; this was an unsatisfactory approach to devising a guideline for outdoor NO_2. However, WHO expert groups had acknowledged the accompanying uncertainties in arriving at this figure.
    - Differences between guidelines and standards were stressed: the WHO had made great efforts to explain these.
    - The lack of credible concentration-response functions for NO_2 had contributed to the widespread belief that perhaps NO_2 was an unimportant pollutant in terms of adverse effects on health because quantification and costing of risks could not be undertaken.
    - The significant imbalance in research between particles and NO_2 was highlighted and the need for high quality research where both particulate matter (PM) and NO_2 (rather than PM only) were measured, was stressed.
    - The increase in research on the health effects of the urban mixture of traffic-generated pollutants, and the focus this had placed on using NO_2 as a surrogate of that mixture, was noted. Questions were raised regarding the extent to which these studies had contributed to a better understanding of the health effects of NO_2, *per se*, as well as their usefulness to the current policy framework which regulated on an individual pollutant basis. The recent conclusion by the Health Effects Institute (HEI) from its review of the evidence on the health effects of traffic-generated pollutants was noted: there was no single surrogate that could best represent the mixture of traffic-generated pollutants (Health Effects Institute, 2010).
- The importance of separating the scientific process of risk assessment from the negotiating process which produced legislation was raised. The latter had tended to adopt the recommended guidelines from WHO expert groups. It was argued that a lack of appropriate scientific evidence could not be used as the basis for not taking action to provide protection to health. In such circumstances, alternative information, e.g. evidence from indoor air studies, could be used as the basis for policy development/action.
- Some participants drew attention to a disparity in the current EU approach: the annual average LV, not the 1-hour (i.e. short-term), for NO_2 was the main policy driver despite stronger evidence on short-term exposure to NO_2.

- Although the WHO and US EPA had reviewed the same evidence base, the US EPA derived much less stringent legislation for annual average concentrations of ambient NO_2.
- More imaginative thinking about controlling traffic was suggested as there was perhaps no perfect surrogate for the mixture of traffic-generated pollutants.
- A need for bridging the gap between the scientific process of the WHO and the negotiating process in the European Union which led to EU legislation was expressed. The crucial issue was on the handling of scientific uncertainty in the negotiating process.

3.2 Presentation 2: Standards, emissions and concentrations

Dr David Carslaw, King's College London

Summary
Data showed a significant reduction in concentrations of NO_x in the UK and London from the late 1990s; however, since 2002 there had been a weak decline. Concentrations of ambient NO_2 in London showed a different trend: there had been increases at many sites. Furthermore, trends in primary NO_2 in the UK showed that the ratio of NO_2/NO_x had increased over the past decade, with the ratio for London being, on average, higher than those for the rest of the UK. Data from 2008 showed that a similar proportion of sites in the UK and Europe exceeded the EU annual average LV for NO_2 of 40 µg/m^3.

Policy makers had expected European legislation on emissions from vehicles to deliver considerable reductions in ambient concentrations of NO_x and NO_2. UK emission inventory projections of NO_x suggested that a 5-6% reduction in NO_x per year in urban areas of the UK was to be expected. However, measurements showed that approximately a 1-2% reduction per year had actually occurred. Therefore, there was disagreement between modelled projections and measured ambient concentrations. Defra recently funded Dr Carslaw to undertake an investigation of this disparity[10]. Using novel remote sensing technologies, measurements of emissions of NO_x from 72,000 individual vehicle exhausts in five urban areas between 2008 and 2010, were made. The techniques also allowed a wide range of data on each vehicle, e.g. on number plates, to be assembled. Re-calculation of NO_x emissions using measurement data was thus possible and enabled comparison with inventory projections.

The project's analysis of data on emissions of NO_x from petrol and diesel cars per year revealed important differences: whilst a substantial reduction in emissions of NO_x from petrol vehicles had occurred since the early 1990s, emissions of NO_x from diesel cars had increased, or at best had been stable for about the past 25 years. Examination of

[10] See report: Carslaw, D., Beevers, S., Westmoreland, E., Williams, M., Tate, J., Murrells, T., Stedman, J., Li, Y., Grice, S., Kent, A. and Tsagatakis I (2011). *Trends in NOx and NO_2 emissions and ambient measurements in the UK*. Version: 3rd March 2011. Available at: http://uk-air.defra.gov.uk/library/reports?report_id=645 (accessed April 2011).

the same data according to classes of European emission standards showed that catalytic converters had been effective in delivering progressive reductions in emissions of NO_x from petrol vehicles. More importantly, the analysis showed that emissions of NO_x from diesel cars had been relatively stable across successive Euro classes. Emissions of NO_x by year for diesel Light Duty Vehicle, Heavy Goods Vehicles, and buses showed a similar picture, though important caveats were highlighted. Overall, the European emission standards had provided little evidence of the much anticipated reduction in emissions of NO_x from diesel vehicles.

The analysis of the distribution of the UK vehicle stock by Euro class was interesting: a large stock of older petrol cars (Euro classes 1 and 2) which may be emitting larger amounts of NO_2 had been present in the UK fleet. This had been coupled with increased use of modern diesel cars, which were high emitters of NO_x and NO_2. This finding had implications for future trends in NO_2 in the UK.

Key discussion points

- *Discussant*: Professor Roy Harrison OBE, University of Birmingham
    - Nitrogen dioxide is both a primary and a secondary pollutant which complicates the optimisation of abatement policies.
    - The UK projections of NO_x emissions made in the 1990s were over-optimistic in regard to reductions in NO_x from road traffic, which is the major source in urban areas.
    - The UK projections of future NO_2 were based upon NO_2-NO_x relationships and were slow to recognise the change in those relationships caused by an increased ratio of NO_2/NO_x in road traffic emissions.
    - Locations where levels of NO_2 were highest were considered. Street canyons present a particular problem, but concentrations can differ greatly between opposite sides of the road, and according to the extent of shading, which reduces photolysis of NO_2.
- It was noted that the findings presented by Professor Harrison should be taken into account in the implementation of policy. The disparity between the locations of monitoring sites used in epidemiological studies and those used to assess compliance was noted: epidemiological studies used monitoring data from background sites whilst compliance was assessed using data from both background and roadside sites. The way in which background concentrations act as a surrogate for personal exposure in the population (and thus health effects) will be different from the way in which roadside concentrations would be related to personal exposure.
- A crucial policy message from Dr Carslaw's presentation was discussed: there had been a large number of vehicles in the UK fleet that were not performing as expected owing to problems with the European emission standards. This could <u>not</u> be addressed by changing the regulatory test-cycle; devising other policy measures to increase turnover in the fleet, and thus reducing inertia in the system, was needed.

3.3 Presentation 3: Nitrogen dioxide - evidence from epidemiological studies

Professor Ross Anderson, King's College London and St George's, University of London

Summary
An overview of general concepts in the field of epidemiology was used to draw participants' attention to:

i differences in the weight of observational evidence required for taking action to protect public health from that needed for scientific acceptance of a causal association.
ii the paradigm of multi-factorial causation of disease - this provided support for the theoretical case for a causal role of NO_2 in adverse effects on health. This paradigm could help explain: why small exposures could have clinically important effects; the lack of thresholds in exposure response relationships; and, the variation of effects between individuals and between populations.

Data from epidemiological studies of varying designs on NO_2 were used to illustrate that:

i A limited number of studies of short-term effects has considered NO_2 and PM_{10} together (in two-pollutant regression models). The few studies published until 2002 were systematically reviewed by COMEAP (see Appendix 4 of COMEAP, 2006[11]) to assess the strength of the evidence for associations with NO_2 and PM_{10} respectively, and this analysis found NO_2 associations to be somewhat more robust against adjustment for PM_{10} than associations with PM_{10} were against adjustment for NO_2. Two pollutant analyses of other metrics of particulate matter (PM) and NO_2 have not been reviewed systematically.
ii Consistent and statistically significant associations between long-term exposure to NO_2 and mortality had been demonstrated in cohort studies conducted in Europe (Brunekreef, 2007). However, questions regarding their causal nature remained. These associations were indicative of a single source, i.e. traffic, as they were based on studies of within-city (vehicular traffic-dominated) exposure contrasts. Furthermore, those associations had not been adjusted for important measures of particulate pollution, i.e. PM composition, and/or $PM_{2.5}$, and/or ultrafine particle counts, with which NO_2 is closely correlated.

It was argued that there had been a lack of symmetry in the appraisal of epidemiological evidence considered by WHO expert groups. The repeated use of caveats by WHO to indicate that the reported associations with NO_2 might be due to particles was raised. Similar caveats had not been used in discussion of the epidemiological evidence on particles despite evidence where its use was warranted. There was some speculation

[11] Committee on the Medical Effects of Air Pollutants (2006) *Cardiovascular Disease and Air Pollution*. Available at (accessed June 2011): http://www.comeap.org.uk/documents/reports.html

about the extent to which current opinions of NO_2 as not causing the observed adverse health effects were based on science or prejudice.

The scientific rationale for WHO air quality guidelines were not consistent across pollutants: there had been disparity in the contributions of epidemiological and toxicological evidence to WHO guidelines. For example, whilst evidence from epidemiological studies underpinned the short-term guideline for particulate matter, that for NO_2 was based on toxicological studies despite the availability of credible associations of adverse effects of NO_2 on health from time-series studies.

It was also noted that it was perhaps unlikely that epidemiological associations with co-pollutants could be disentangled.

Key discussion points

- *Discussant*: Dr Heather Walton, King's College London
    - A health impact calculation relating to a 1 µg/m^3 reduction in annual average concentration of NO_2 in the UK was presented. The calculation attempted to scope the possible size of the impacts for several scenarios in the epidemiological evidence:

        i the reported adverse effects on health were due to NO_2 alone;
        ii the reported adverse effects on health were due to particles alone;
        iii the reported adverse effects were due to both pollutants.

    The calculation used coefficients from McConnell *et al* (2003) which reported coefficients linking annual average outdoor concentrations of NO_2 with respiratory symptoms in children, the outcome on which the WHO annual average guideline is based. The full calculation is available in Dr Walton's presentation at www.hpa.org.uk[12].

- Difficulties in using two- or multi-pollutant regression models to disentangle the health effects of closely correlated pollutants were discussed. It was advised that caution should be exercised in the interpretation of results from these models. Results from time-series studies covering distinctly different time periods had suggested the presence of (unmeasured) co-varying factors, which could be responsible for the reported findings of an adverse effect on health. This was illustrated in time-series studies on sulphur dioxide (SO_2) which had reported increases in risk estimates amidst dramatic reductions in concentrations of ambient SO_2 (Buringh *et al*, 2010). Examination of temporal trends in pollutant concentrations and estimates from time-series studies would help identify points of

[12] The calculation has been further developed in a presentation at the 2011 Annual UK Review Meeting on Outdoor and Indoor Air Pollution held at the Institute of Environment and Health (IEH), Cranfield University on the 10 & 11 May 2011. The revised calculation will be available in due course: http://www.cranfield.ac.uk/health/researchareas/environmenthealth/ieh/page19562.html (accessed June 2011).

divergence in the data; similar analyses had been undertaken in the Netherlands for Black Smoke (Fischer *et al*, 2009).

- Two- or multi-pollutant regression models for estimating effects of NO_2 would be most useful if all plausibly causal pollutants were included in the analyses. It was noted that PM_{10} had often been used in these models; different results may be obtained if it were possible to adjust for PM composition, and/or $PM_{2.5}$, and/or ultrafine particle counts in these models, as correlations between such alternative measures and PM_{10} may be poor. Use had been made of PM_{10} because there was limited availability of measurement data for ultrafine particles and other metrics of particulate matter.

- There was general acknowledgement of an emphasis on particulate matter, rather than NO_2, being causally associated with the effects on health of the air pollutant mix; more detailed studies of the relative importance of the different components of the urban air pollution mix (which includes NO_2) were considered important. The emphasis on particulate matter had been driven (in part) by the findings on $PM_{2.5}$ from the American Cancer Society (ACS) II cohort study (Pope *et al*, 2002). This study made a significant contribution to the scientific acceptance of a causal association between long-term exposure to fine particles (measured as $PM_{2.5}$) and mortality, a finding which has since been confirmed by several other studies. The absence of an equivalent large-scale study designed to assess the effects of NO_2 on mortality and morbidity makes it difficult to establish the independent role of NO_2 in causing adverse effects on health at current ambient levels. Professor Brunekreef informed participants of the potential of the ESCAPE[13] project in this context. ESCAPE will utilise health and confounder data from existing European cohort studies to assess the effects of long-term population exposure to (mainly) fine particles, particle composition, and NO_x on a range of health outcomes for a variety of spatial contrasts. The project is currently underway and is expected to be completed by mid-2012. It is funded by the European Commission to help inform the review of the Air Quality Directive in 2013.

3.4 Presentation 4: Nitrogen dioxide - evidence of direct health effects from toxicological studies

Professor Frank Kelly, King's College London

Summary

The presentation began with consideration of the theory that it is the oxidant/free-radical properties of air pollutants that were responsible for their adverse effects on health. Findings from various types of toxicological studies were presented: (i) in vitro; (ii) animal; (iii) controlled human exposures. Effects of NO_2 had been demonstrated in each type of toxicological study but only at concentrations considerably higher than those

[13] ESCAPE: European Study of Cohorts of Air Pollution Effects (http://www.escapeproject.eu/)

found in the ambient air[14]. This therefore made it difficult to determine whether there was a direct toxic effect of ambient NO_2. Furthermore, very few studies of longer-term exposure were available and there were few studies which examined interactions between NO_2 and other pollutants.

Key discussion points

- *Discussant*: Professor Jon Ayres, University of Birmingham
    - Comparison of toxicological data with findings from epidemiological studies was limited owing to a mismatch in the health outcomes examined in these two bodies of evidence. Volunteer studies had demonstrated an effect of NO_2 on young subjects suffering from asthma only at concentrations much higher than those experienced in ambient air whilst epidemiological studies of similar (short-term) exposures reported associations for deaths from cardiovascular disease and Chronic Obstructive Pulmonary Disease (COPD) - i.e. in older individuals - but not from asthma.
    - NO_2 can act as a potentiator of allergen responses and such potentiation may be relevant when considering asthma exacerbations.
    - The ultrafine hypothesis (Seaton *et al* (1995); Seaton and Dennekamp, 2003) was revisited: that epidemiological associations with low concentrations of NO_2 represented adverse health effects of ultrafine particles rather than NO_2 *per se*. The robustness of associations of NO_2 with adverse health effects should therefore be investigated in two- or multi-pollutant regression models including particle metrics other than particle mass, e.g. particle number concentration, or alternatively, particle metrics which are closely correlated with particle numbers, and which would be able to represent the ambient mixture of particulate pollutants arising from the same emission source as NO_2. Participants suggested that Elemental Carbon was a good indicator of the particle mixture related to traffic pollution. Additional insights may be obtained by exploiting data from situations (spatial and temporal) where there are different relationships between particle number concentrations and NO_2.
    - Findings of epidemiological studies on long-term exposure to NO_2 could either represent ‘true’ toxic effects of low levels of this pollutant or reflect exposure to peak concentrations. Difficulties in resolving this issue were noted. A method of personal monitoring of NO_2 that could detect peaks was needed (two week averages had been used in those studies of indoor air which used personal monitoring). The pattern of peaks could then be simulated in chamber studies.

[14] It was noted that some concentrations of NO_2 in microenvironments do exceed the lower end of the range of concentrations at which effects had been demonstrated in toxicological studies.

  - For policy purposes, focus should be placed on controlling sources but, as raised by participants, this would not help with understanding how to control an expanding number of sources.

- Attempts to rank NO_2, particulate matter and ozone on the basis of toxicological evidence of effects at near ambient levels had been met with difficulties:
  - questions about the classification of particulate matter arose.
  - direct comparison of the toxicological data on each pollutant in the same experimental system had not been previously undertaken.
- Data on nitrosation of tyrosine residues in lavage fluid could help identify possible independent responses/effects of NO_2 as this (response) could not be triggered by particles. Measurement of nitrosation was regarded as a biomarker of exposure and effect for NO_2 and would demonstrate the ability of NO_2 to overcome host defences.

3.5 Presentation 5: Key issues on nitrogen dioxide

Professor Bert Brunekreef, Utrecht University

Summary
Using European data, Professor Brunekreef began by highlighting the high correlations which existed between particles (soot) and NO_2. Changes to these correlations could occur as a result of changes in the mixture of ambient pollutants. This would have implications for the interpretation of results from epidemiological studies.

An overview of the ESCAPE project was presented as it had potential to deliver important insights on the effects of traffic-generated pollutants on health. In attempting to disentangle the possible independent adverse effects of NO_x from those of other pollutants in that mixture, ESCAPE will identify: (i) locations where correlations between NO_2 and particles differed; and (ii) locations with different concentration ratios of these pollutants. Initial data from the project had showed:

- relatively similar levels of $PM_{2.5}$ across the countries examined.
- differences in levels of NO_2 across the locations.
- differences in Pearson correlations for annual mean concentrations of NO_2 with $PM_{2.5}$ and $PM_{2.5}$ Absorbance.

Findings from various epidemiological studies were referenced in building a case against the use of studies on indoor air to develop guidelines and standards for NO_2 in outdoor air. The complexities of the mixture of indoor air pollutants were illustrated; it was shown to be as complex as the mixture outdoors, with less information available on the indoor mixture. Studies had showed that pollutants/factors, other than particles (e.g. nitrous acid), could also account for the reported associations of NO_2. Differences in ratios of concentrations of air pollutants between indoor and outdoor environments were also noted. These observations raised the need for caution in assuming that the reported associations of adverse health effects with NO_2 in indoor studies were due to NO_2 *per se*.

A comparison of standards for NO_2 for the EU and US showed that, despite consideration of the same evidence base, annual mean standards for the EU were far more stringent that those for the USA (i.e. the US EPA and Californian EPA standards). Interestingly, the US EPA was responsible for preparing the first draft of the IPCS (1997) Environmental Health Criteria for Oxides of Nitrogen, on which current stringent EU standards are based. The IPCS's recommendations were based on a meta-analysis of epidemiological studies of indoor NO_2 conducted in children (Hasselblad *et al*, 1992). Careful re-examination of that meta-analysis showed that:

- the combined estimate, though positive, was of borderline statistical significance.
- the study with the largest sample size in the meta-analysis, i.e. Neas *et al* (1991), reported only one statistically significant finding (for lower respiratory symptoms) across the wide range of health outcomes examined, and the one significant finding was included in the meta-analysis. Lower respiratory symptoms were reported for 20-30% of the study populations and likely included occasional wheeze and chest colds.

Professor Brunekreef concluded by demonstrating that the differences in the one hour standards were much smaller between the US and the EU, and that in fact, the one hour standard in the US for all practical purposes was far more stringent than the annual mean standard.

Key discussion points

- The lack of consistency in the assessment of the evidence across pollutants was reiterated: in reference to the WHO guideline for SO_2, the need for a long-term guideline for NO_2 was questioned, given the availability of robust time-series evidence which could be used to strengthen the short-term guideline. Some participants disagreed: a long-term guideline had been recommended to reflect different health effects of NO_2. Therefore agreement between the two guidelines was not needed.

- Guidelines were usually defined at concentrations where adverse health effects were not expected. However, the recommended figure of 40 $\mu g/m^3$ fell within the range of indoor NO_2 levels produced by gas cooking which were found to be associated with lower respiratory symptoms in children.

4 SYNTHESIS OF THE DISCUSSION

This section of the report presents a synthesis of the key points of discussion at the workshop.

On the Policy-Science Interface

Two important issues were identified:

i The World Health Organization (WHO) annual average air quality guideline (AQG) for NO_2 is based on studies of the adverse effects on health of children of indoor exposure to raised concentrations of NO_2 produced by gas cooking. Such evidence could be regarded as a less than ideal basis for an annual average EU limit value for outdoor concentrations of this pollutant[15].

ii The WHO acknowledged the uncertainties in the evidence when recommending a concentration of 40 µg/m^3 (annual average) as a health-based guideline for outdoor concentrations of NO_2. Despite these uncertainties, this value was later adopted by the European Union (EU) as a legally binding standard (limit value). The recent new information on real-world vehicle emissions has made the task of compliance more difficult than anticipated for virtually all Member States, including the UK. Now that NO_2 is changing relative to other components of the air pollution mixture produced by traffic, policy makers are faced with difficult questions about the direct benefits to health of controlling NO_2 specifically. This makes a re-evaluation of the independent role of NO_2 in producing health effects urgent.

This suggests a need to bridge the gap between the scientific process of the WHO and the negotiating process of the European Union, and to incorporate scientific uncertainty in the process of agreeing limit values.

Re-evaluation of the existing evidence is likely to be of little help in dealing with the first of the issues outlined above: new evidence would be required in order for progress to be made. It is therefore crucial to define what scientific research would be most useful for policy development and the points at which that evidence would become available to the policy process. It was agreed that there had been a mismatch between the cycles for research funding and policy development. Aligning these would improve the flow of evidence from research to policy.

On Emissions and Concentrations

Significant reductions in concentrations of NO_x in the UK and London had been achieved in the period until 2002. Since then, the trend has flattened and has not declined as projected[16].

Achieving reductions in NO_x and NO_2 relies on current controls, i.e. European emission standards, for reducing emissions of NO_x from vehicles. The Euro standards have <u>not</u> delivered the anticipated reductions in emissions of NO_x from diesel vehicles. It is likely that this has resulted from a mismatch between testing conditions in the EU regulatory test-cycle and real-world driving conditions. Furthermore, emissions of primary NO_2 have increased in the UK. Addressing these issues remains an action for the policy process.

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[15] It was noted that in more recent reviews of the AQG, the WHO had considered evidence on long-term exposure to outdoor NO_2. Consideration of that evidence did not lead to a change in the WHO annual average guideline for NO_2.

[16] See report: Carslaw, D., Beevers, S., Westmoreland, E., Williams, M., Tate, J., Murrells, T., Stedman, J., Li, Y., Grice, S., Kent, A. and Tsagatakis I (2011). *Trends in NOx and NO_2 emissions and ambient measurements in the UK*. Version: 3rd March 2011. Available at (accessed April 2011): http://uk-air.defra.gov.uk/library/reports?report_id=645.

Recent work has revealed an important policy area for the UK which has implications for future trends in NO_2: not only is there a large stock of diesel vehicles in the UK fleet which are emitting more than was anticipated, there is also currently a large stock of older petrol cars (Euro classes 1 and 2) in the UK vehicular fleet which may be emitting larger amounts of NO_2 than had been previously thought.

On Epidemiological and Toxicological Evidence
NO_2 had been less thoroughly studied than particulate matter. The need for high quality research where both particulate matter (PM) and NO_2 (rather than PM only) were measured, was stressed.

In time-series studies of mortality and hospital admissions, NO_2 often has robust associations with the studied health outcomes. In addition, epidemiological associations of long-term exposure to NO_2, e.g. from cohort studies on mortality conducted in Europe (Brunekreef, 2007), are available. However, questions regarding the causal nature of these associations remain, in view of the high correlations with other components of the air pollution mixture arising from the same emission source. Toxicological data have been of limited help in addressing the issue of causality as the concentrations at which adverse effects had been demonstrated in such studies were well above those examined in the epidemiological studies. Direct comparison of these two bodies of evidence was further hindered by differences in the health outcomes investigated.

4.1 Answers to questions

Q1: What does the evidence say about the primary effects on health of long-term exposure to NO_2?

A1: Despite the availability of some evidence of epidemiological associations of adverse effects of long-term exposure to NO_2 on health, whether these associations should be regarded as causal remains uncertain.

Q2: What does the evidence say about the effects of intermittent exposure to long-term average concentrations of NO_2?[17]

A2: Some evidence from chamber studies showed that individuals responded to peak concentrations. It was noted that some ambient concentrations of NO_2 occasionally get near to those examined in the chamber studies. The importance of exposure to peaks over decades was however unknown. Areas of complexity in these investigations were however noted:

i the rate of recovery after short-term exposure - for the outcomes considered in these studies, it was speculated that the recovery time was likely to be short.

[17] More precisely, what does the evidence say about the effects of intermittent exposure to short-term peaks super-imposed on long-term average concentrations of NO_2?

Multiple challenges to the same concentration could lead to a subsequent lack in response, suggesting reduction in response suggesting adaptation occurred.

ii the possibility for continuity of a disease process after cessation of exposure which initiated that process.

iii effects observed in chamber studies do not reflect the effect of long-term exposure, which is likely to represent the accumulation of small amounts of damage.

Q3: What does the evidence say about the likely causality of associations between effects on health and long-term average concentrations of NO_2?

A3: see A1.

Q4: What research do we need to disentangle the possible primary effects of NO_2 from the effects of particles?

A4: See Chapter 5.

Q5: How reliable is the surrogacy argument as a basis for improving health by reducing long-term average concentrations of NO_2?

A5: Using NO_2 as a surrogate for the urban mixture of traffic-generated pollutants in a regulatory context would only be feasible if the ratio between concentrations of NO_2 and the active component of that mixture remained constant. This criterion is unlikely to be satisfied, given that technologies and strategies to control emissions affect pollutants differently. Recent research demonstrating changes in primary emissions of NO_2 confirm this.

Q6: Does the evidence point to sub-groups of greater than average sensitivity or susceptibility to NO_2?

A6: Chamber studies revealed that asthmatic individuals were more sensitive to NO_2 than other individuals and thus formed a susceptible subgroup of the population. Exploring the variation in susceptibility in responders in chamber studies was suggested.

The remaining questions were not addressed.

5 RESEARCH RECOMMENDATIONS

The following list of research needs is designed to investigate whether or not ambient concentrations of NO_2 have direct adverse effects on health.

5.1 Epidemiological studies

5.1.1 Re-evaluation of existing epidemiological studies

Re-evaluation of the existing epidemiological evidence had not, so far, led to progress in understanding the effects of NO_2 on health. In order for any re-examination to deliver new inferences from existing evidence, more critical and imaginative evaluation is required.

A number of areas where this might be achieved were discussed, but focus was placed on the application of the database of estimates from ecological time-series studies, e.g. APED[18], to more focussed questions on the issue. For example:

- temporal trends in concentrations and estimates of NO_2 should be examined to identify possible differences in concentration-response relationships over time. Points of divergence in the data could highlight the presence of co-varying factors, which could be responsible for observations of adverse effects on health. The work might enable the identification of independent associations of effect by investigating differences in coefficients for NO_2 in time-series studies according to different relationships between concentration ratios of NO_2/NO_x and NO_2/PM. This is particularly important given changes in the urban mixture of ambient pollutants: changes in trends for NO_x and NO_2; increases in emissions of primary NO_2 from diesel vehicles; and changes in the concentration ratio of NO_2 to particulate matter.

Further to the examination of temporal trends, exploiting spatial differences in ambient concentrations of the mixture of traffic-dominated ambient pollutants provides a further opportunity to attempt to disentangle any possible independent adverse effects of NO_2 from those of particulate matter.

It was noted that such critical inferential reviews would require significant input from experts in the field.

5.1.2 New epidemiological studies

- Improved exposure assessment in new epidemiological studies would be important. Exposure misclassification might be greater for NO_2 than for PM_{10} and $PM_{2.5}$ in places, and spatial variability in exposure might account for the heterogeneity in reported associations for NO_2. Studies should report results for all relevant pollutants, not just particles.

- Recommendations made in the context of evaluating existing epidemiological studies, regarding investigating temporal trends and spatial variation in concentrations and estimates of NO_2 to identify possible differences in concentration-response relationships over time and possible independent adverse effects of NO_2, also apply to new studies. It will be important to ensure that the relevant pollutant concentration ratios are recorded.

- Examination of ratios of background to roadside concentrations of NO_2 would help understand exposure patterns, and to design appropriate regulatory limits.

- Characterising the nature of exposure to co-pollutants at the personal level.

- Better characterisation of the mixture of indoor air pollutants might aid understanding of existing epidemiological evidence on indoor NO_2.

[18] APED: Air Pollution Epidemiology Database, which is managed by St George's, University of London.

- Being alert to opportunities to examine the effects of interventions such as Low Emission Zones and zones with reduced speed limits for vehicular traffic.
- Studies to examine the effect modification of air pollution on health by genetic make-up.

The following studies are vital to understanding any possible mechanisms of action of NO_2.

5.2 Chamber studies

- Comparisons of the exposures between ambient pollutants, mainly NO_2, ozone and particles (with characterization of their physical and chemical properties) are needed. Investigations of two- and multi-pollutant exposures are needed. Exposures examined should overlap with levels seen in ambient mixture, and consider the pattern of peaks in personal exposure. Good understanding of the pattern of peaks in personal exposure may require developments in personal monitoring.
- The need for increased duration of exposure in studies, e.g. exposure for a few hours but repeated over a longer time period.
- Investigation of a range of possible sensitive groups to allow direct comparison with findings from epidemiological studies.
- A need to address the mismatch in the health outcomes examined in chamber and epidemiological studies remains.
- Use of "omics" to identify biomarkers of exposure by examining initial signalling responses. Nitrosation of tyrosine in proteins could be used as a potential biomarker of exposure and effect for NO_2.
- Examination of interactions of pollutants with allergens.

5.3 Toxicological studies

- Studies using toxicological data to examine the potency of NO_2, ozone and particles, alone and in combination, would help with drawing inferences from epidemiological studies.
- Examination of the oxidative stress hypothesis using exposure to ultrafine particles and gaseous pollutants in sensitive experimental models could be considered. This requires the construction of an ultrafine aerosol of environmental relevance prior to undertaking controlled exposure experiments. Work should assess the oxidative capacity of these pollutants individually and in combination in an attempt to understand the plausibility of pathways that might lead to health effects.

- Investigating the toxicity of filtered and unfiltered air, diesel emissions or concentrated ambient particles (CAPs) with NO_2 added at various environmentally relevant concentrations[19].

All this represents a large programme of research. A collaborative approach, between groups in the UK and abroad and between the specialties of epidemiology and toxicology is recommended.

The above research recommendations are likely to contribute to understanding the relative importance of ambient NO_2 to health in relation to other constituents of the urban (traffic-dominated) air pollution mixture, and help inform the development of policy for this pollutant.

It is important to take note of research currently underway that might overlap with the areas mentioned above. A list of ongoing research projects of relevance to the issues considered in this workshop is given below:

i **ESCAPE**: as mentioned on pages 12 and 14 of this report. For further information please refer to the project's website: (http://www.escapeproject.eu/). This project is due to come to a completion in June 2012.

ii The **TRAFFIC** project seeks to understand better the health problems caused by traffic particulate pollution in London. The work involves the development of a new hybrid-exposure model which should provide a more accurate assessment of individual exposure to pollution as people move through an urban environment (London). The project is being undertaken by a consortium of researchers from King's College London, Imperial College London, St George's, University of London and London School of Hygiene and Tropical Medicine, and is run by the Environmental Research Group at King's College London. Funding for the work has been received as part of the joint initiative on Environmental Exposure and Health by the Medical Research Council (MRC), Natural Environment Research Council (NERC), Department of Health (DH), Economic and Social Research Council (ESRC), and Department for Environment, Food and Rural Affairs (Defra). The project began in January 2011, and will run for four years.

iii The Department of Health is funding a project to use the epidemiological database, APED, which is managed by St George's, University of London, to conduct a systematic review (including meta-analysis) of time-series evidence for several pollutants including NO_2 and a meta-analysis of within community studies (specifically asthma prevalence) on NO_2. This will develop quantitative estimates for the association between NO_2 and various outcomes. These results are expected to be available in 2012.

[19] This recommendation also applies to chamber studies.

5.4 Other research recommendations

The following important area of research, not focusing on the health effects of NO_2, was also identified during the workshop.

- Vehicle test-cycles intended to represent real-world conditions are in need of re-examination because they underestimate emissions of NO_x. Without further research and measurement, there may not be confidence in the effectiveness of the latest (Euro 6 and Euro VI) vehicle emission limits in delivering real improvements in NO_x emissions.

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7 GLOSSARY OF TERMS AND ABBREVIATIONS

APED Air Pollution Epidemiology Database, which is managed by St George's (University of London)

AQG Air Quality Guideline

CAPs Concentrated Ambient Particles

CLRTAP The Convention on Long-Range Transboundary Air Pollution

EC European Commission

ESCAPE European Study of Cohorts of Air Pollution Effects

ESRC Economic and Social Research Council.

EU European Union

LV Limit Value

NO_x	Nitrogen dioxide (NO_2) and nitric oxide (NO) are oxides of nitrogen and together are referred to as NO_X.
NO_2	Nitrogen Dioxide
PM	Particulate Matter
$PM_{2.5}$	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
$PM_{2.5}$ Absorbance	The soot content of $PM_{2.5}$
PM_{10}	As above, with 10 micrometres
PNC	Particle Number Concentration
SO_2	Sulphur Dioxide
WHO	World Health Organization

8 ACKNOWLEDGEMENTS

We wish to thank the Policy Research Programme of the Department of Health for commissioning this important and timely meeting.

Participants of the workshop are thanked for their contributions. In particular, we are grateful to the speakers and discussants for their presentations of the evidence at the workshop and for their contributions towards the development of this report.

APPENDIX A List of participants

Professor Ross Anderson	St George's, University of London King's College London
Dr Richard Atkinson	St George's, University of London
Professor Jon Ayres OBE	University of Birmingham
Professor Bert Brunekreef	Utrecht University
Dr David Carslaw	King's College London
Dr Miriam Gerlofs-Nijland	National Institute for Public Health and the Environment (RIVM) The Netherlands
Professor Roy Harrison OBE	University of Birmingham
Dr Debbie Jarvis	Imperial College London
Irene Katsaiti	King's College London
Professor Frank Kelly	King's College London
Dr Klaas Krijgsheld	Dutch Ministry of Environment (VROM)
Dr Michal Krzyzanowski	WHO European Centre for Environment and Health
Dr Vina Kukadia	BRE Environment
Professor Duncan Laxen	Air Quality Consultants
Dr Heather Walton	King's College London
Professor Martin Williams	King's College London
André Zuber	European Commission. Environment Directorate-General

Helen Ainsworth	Department for Environment, Food and Rural Affairs
Dr Clare Bayley	Department for Environment, Food and Rural Affairs
Dr Karen Exley	Health Protection Agency
Iain Forbes	Department for Transport
Britta Gadeberg	Health Protection Agency
Alison Gowers	Health Protection Agency
Dr Jonathan Graves	Department of Health
Paul Holley	Department of Health
Dan Instone	Department for Environment, Food and Rural Affairs
Dr Robert Maynard CBE	Health Protection Agency
Inga Mills	Health Protection Agency
Isabella Myers	Imperial College London; Health Protection Agency
Dr Sotiris Vardoulakis	Health Protection Agency
Dr Ursula Wells	Department of Health, Policy Research Programme
Tim Williamson	Department for Environment, Food and Rural Affairs

APPENDIX B The agenda

Wednesday 2nd March, 2011

10.30 – 11.00	TEA AND COFFEE
11.00 – 11.10	Welcome and Introductory Remarks *Dr Robert Maynard (Chair of Workshop)*
11.10 – 11.20	Opening Remarks *Tim Williamson, Department for Environment, Food and Rural Affairs (Defra)* *André Zuber, European Commission*
11.20 – 11.35	Description of the Problem *Dr Robert Maynard*
The evidence:	
11.35 – 12.05	The Policy-Science Interface *Professor Martin Williams, King's College London*
12.05-12.30	Discussion
12.30 – 1.00	Standards, Emissions and Concentrations *Dr David Carslaw, King's College London*
1.00-1.30	Discussion
1.30 – 2.30	LUNCH
The evidence continued:	
2.30 – 3.00	From Epidemiological Studies *Professor Ross Anderson, St George's, University of London and King's College London*
3.00 – 3.30	Discussion
3.30 – 4.00	From Toxicological Studies *Professor Frank Kelly, King's College London*
4.00 – 4.30	Discussion
4.30 – 5.00	Synthesis of day's discussion
5.00 – 5.15	Closing Remarks from Chair
1930	DINNER (Park Plaza Riverbank, London)

3rd March, 2011

9.00 – 9.30	TEA AND COFFEE
9.30 – 9.40	Opening remarks from the Chair
9.40 – 10.00	Reflect on the problem and pick-up points from yesterday's discussion *Professor Bert Brunekreef, Utrecht University*
10.00 – 10.20	Discussion
10.20 – 11.00	Questions to be addressed
11.00 - 11.15	TEA AND COFFEE
11.15 – 11.45	Ideas for research
11.45 – 12.15	Paper for publication
12.15 – 12.30	Closing remarks from the Chair
1230	LUNCH & Departure