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“Review of evidence on health aspects of air pollution – REVI HAAP”

First results
“Review of evidence on health aspects of air pollution – REVIHAAP Project”

First results

This publication arises from the project REVIHAAP and has received funding from the European Union.
ABSTRACT

This document presents answers to 22 questions relevant for the review of European policies on air pollution and addressing health aspects of these policies. The answers were developed by a large group of scientists engaged in the WHO project “Review of evidence on health aspects of air pollution – REVIHAAP”. The experts reviewed and discussed the newly accumulated scientific evidence on health effects of air pollution, formulating science-based conclusions and drafting the answers. Extensive rationale for the answers, including the list of key references, will be provided in the final report from the project. The review concludes that a considerable amount of new scientific information on health effects of particulate matter, ozone and nitrogen dioxide, observed at levels commonly present in Europe, has been published in the recent years. This new evidence supports the scientific conclusions of the WHO Air Quality Guidelines, last updated in 2005, and indicates that the effects can occur at air pollution concentrations lower than those serving to establish the 2005 Guidelines. It also provides scientific arguments for the decisive actions to improve air quality and reduce the burden of disease associated with air pollution in Europe.

This publication arises from the project REVIHAAP and has been co-funded by the European Union.

Keywords

AIR POLLUTANTS
AIR POLLUTION – ADVERSE EFFECTS
ENVIRONMENT AND PUBLIC HEALTH
EVIDENCE BASED PRACTICE
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**Introduction**

The World Health Organization (WHO) Regional Office for Europe is implementing projects “Evidence on health aspects of air pollution to review EU policies – REVIHAAP”, and “Health Risks of Air Pollution in Europe – HRAPIE” with financial support from the European Commission (EC). These projects will provide scientific evidence-based advice on health aspects of air pollution in support of the comprehensive review of European Union (EU)’s air quality policies scheduled for 2013.

The advice provided by the REVIHAAP and HRAPIE projects is formulated in the form of responses to twenty-six key policy-relevant questions asked by the European Commission. These questions cover general aspects of importance for air quality management, as well as specific topics concerning health aspects of individual air pollutants. While some of the questions directly address policies, the recommendations stemming from the REVIHAAP and HRAPIE projects are based solely on scientific conclusions on health aspects of air pollution, and do not consider other issues which are relevant for policy formulation.

A Scientific Advisory Committee (SAC) of eight scientists, experienced in previous reviews conducted by WHO and representing key areas relevant for the projects (epidemiology, toxicology, atmospheric sciences) has been put together to guide and oversee the projects. The review is conducted by a group of 29 invited experts from top academic institutions across the world, representing various relevant scientific disciplines. These experts, working in small groups, reviewed the accumulated scientific literature, drafted succinct answers to the questions and longer rationales to the answer emerging from the research results. Answers to questions D were prepared using conclusions from answers to questions A-C. Thirty-two invited external reviewers, as well as the SAC members provided detailed comments on the completeness of the reviewed literature, validity of conclusions reached and the clarity of the answers. The authors used the comments to revise the text subject to further review. A full list of SAC members, expert authors, and external reviewers is provided at the end of this document. All submitted a WHO Declaration of Interests to ensure unbiased process of the review.

Besides the discussion conducted by electronic means of communication, direct discussion on the answers and evidence in their support was held at two WHO Experts Meetings (taking place in WHO/ECEH office in Bonn, Germany on 21-23 August 2012 and 15-17 January 2013). During the second meeting, the final text for the first twenty-
two answers covered under the REVIHAAP project was adopted. These are being presented in this document.

A full WHO technical report for project REVIHAAP is being developed, and will include answers to questions along with rationales, the list of references cited and some introductory remarks. This document will be available in the spring 2013.

Further work proceeds in order to document critical data gaps (questions A7 and C9), as well as emerging issues on health risks from air pollution related to specific source categories (e.g. transport, biomass combustion, metals industry, refineries, power production), specific gaseous pollutants or specific components of PM (e.g. size-range like nano-particles and ultra-fines, rare-earth metals, black carbon (EC/OC)) (question D3). As well, concentration-response functions (CRFs) to be included in cost–benefit analysis will be identified in response to question D5. This work under the HRAPIE project will be concluded by September 2013, although preliminary findings will be made available to the EC earlier to ensure suitable use for the review of the EU’s air quality policies.
A. Health effects of particulate matter

1. Question A1

What new evidence on health effects has emerged since the review work done for the WHO Air Quality Guidelines published in 2005, particularly with regards to the strength of the evidence on the health impacts associated with exposure to PM$_{2.5}$? Based on this new information, do the scientific conclusions given in 2005 require revision?

Answer:

Since the Air Quality Guidelines, Global Update 2005 were issued, many new studies from Europe and elsewhere on both short and long-term exposure to PM$_{2.5}$ have been published. These studies provide considerable support for the scientific conclusions in the 2005 Guidelines and suggest additional health outcomes to be associated with PM$_{2.5}$. Among the major findings to date are the following:

1. Additional support for the effects of short-term exposure to PM$_{2.5}$ on both mortality and morbidity based on several multicity epidemiologic studies;
2. Additional support for the effects of long-term exposures to PM$_{2.5}$ on mortality and morbidity based on several studies of long-term exposure conducted on large cohorts in Europe and North America;
3. An authoritative review of the evidence for cardiovascular effects, conducted by cardiologists, epidemiologists, toxicologists and other public health experts, concluded that long-term exposure to PM$_{2.5}$ are a cause of both cardiovascular mortality and morbidity;
4. Significantly more insight has been gained into physiological effects and plausible biological mechanisms linking short- and long-term PM$_{2.5}$ exposure with mortality and morbidity as observed in epidemiological, clinical and toxicological studies;
5. Additional studies linking long-term exposure to PM$_{2.5}$ to several new health outcomes including atherosclerosis, adverse birth outcomes and childhood respiratory disease;
6. Emerging evidence also suggests possible links between long-term PM$_{2.5}$ exposure and neurodevelopment and cognitive function as well as other chronic disease conditions such as diabetes.

The scientific conclusions of the 2005 WHO Guidelines about the evidence for a causal link between PM$_{2.5}$ and adverse health outcomes in humans have been confirmed and strengthened and, thus, clearly remain valid. As the evidence base for the association between PM and short-term, as well as long-term, health effects has become much larger and broader, it is important to update the current WHO Guidelines for PM. This is particularly important as recent long-term studies are showing associations between PM and mortality at levels well below the current annual WHO air quality guideline level for PM$_{2.5}$ which is 10 µg/m$^3$. Further discussion is also provided in section D.
2. Question A2

<table>
<thead>
<tr>
<th>What new health evidence is available on the role of other fractions/metrics of PM, such as smaller fractions (ultra-fines), black carbon, chemical constituents (metals, organics, in-organics, crustal material and PM of natural origin, primary/secondary) or source types (road traffic including non-tailpipe emissions, industry, waste processing …) or exposure times (e.g. individual or repeated short episodes of very high exposure, 1h, 24h, yearly)?</th>
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**Answer:**

Since the 2005 WHO Guidelines, a considerable number of new studies have been published providing evidence on the health effects of size fractions, components or sources of PM. Health effects are observed with short-term (e.g. hours or days) and long-term (e.g. years) exposures to airborne particles.

**A. Other fractions/metrics of PM than PM$_{2.5}$ or PM$_{10}$**

1. The 2005 Global Update Report noted that, while there was little indication that any one property of PM was responsible for the adverse health effects, toxicological studies suggested that fossil fuel and biomass combustion processes may be a significant contributor to adverse health outcomes. Since then, further information has become available to amplify the earlier conclusions. Epidemiological and toxicological studies have shown PM mass (PM$_{2.5}$, PM$_{10}$) comprises fractions with varying types and degrees of health effects suggesting a role for both the chemical composition (e.g. transition metals and combustion derived primary and secondary organics) and physical properties (size, particle number and surface area);

2. There are three important components – black carbon, secondary organic aerosols, and secondary inorganic aerosols – for which there is substantial exposure and health research finding associations and effects. They each may provide valuable metrics for the effects of mixtures of pollutants from a variety of sources.
   a. New evidence links black carbon particles with cardiovascular health effects and premature mortality for both short-term (24 hours) and long-term (annual) exposures. In studies taking black carbon and PM$_{2.5}$ into account simultaneously associations remained robust for black carbon. Even when black carbon may not be the causal agent, black carbon particles are a valuable additional air quality metric to evaluate the health risks of primary combustion particles from traffic including organics, not fully taken into account with PM$_{2.5}$ mass.
   b. No new toxicological evidence has been presented to support a causal role for inorganic secondary aerosols such as ammonium, sulfates and nitrates. However, epidemiological studies continue to report associations between sulfates or nitrates and human health. Neither the role of the cations such as ammonium, nor the interactions with metals or absorbed components such as organics has been well documented in epidemiological studies (See answer...
C8). Even when secondary inorganic particles may not be the causal agents, they are a valuable additional air quality metric to evaluate the health risks.

c. There is growing information on the associations of organic carbon with health effects, and organic carbon primary emissions are one of the important contributors to the formation of secondary organic aerosol (a significant component of the PM$_{2.5}$ mass). The evidence is insufficient to distinguish between the toxicity of primary and secondary organic aerosol.

3. The new evidence suggests that short-term exposures to coarse particles (including crustal material) are associated with adverse respiratory and cardiovascular health effects, including premature mortality. Data from clinical studies are scarce; toxicological studies report that coarse particles can be equally toxic compared to PM$_{2.5}$ on a mass basis. Difference in risk between coarse and fine PM can at least partially be explained by differences in intake and different biological mechanisms.

4. There is increasing, though as yet limited, epidemiological evidence on the association between short-term exposures to ultrafine (<0.1 µm) particles and cardiorespiratory health as well as the central nervous system. Clinical and toxicological studies have shown that ultrafine particles in part act through mechanisms not shared with larger particles that dominate mass-based metrics such as PM$_{2.5}$ or PM$_{10}$.

B. Source types

1. A variety of air pollution sources have been associated with different types of health effects. Most evidence is accumulated so far for an effect of carbonaceous material from traffic (see also Question C1). More limited number of studies suggest that also traffic-generated dust, including road, brake and tyre wear, contribute to the health effects.

2. Coal combustion results in sulfate-contaminated particles for which there is strong evidence of adverse effects from epidemiological studies.

3. Health relevant sources also include shipping (oil combustion) power generation (oil and coal combustion), and metal industry (e.g. nickel).

4. Based on most recent studies, exposure to particles from biomass combustion, most notably residential wood combustion, may be associated not only with respiratory but also with cardiovascular health.

5. Desert dust episodes have been linked with cardiovascular hospital admissions and mortality in a number of recent epidemiological studies.

C. Exposure times (e.g. individual or repeated short episodes of very high exposure, 1h, 24h, yearly)

1. There is further evidence from epidemiological studies that long-term (years) exposure to PM$_{2.5}$ is associated with both mortality and morbidity. The evidence base is weaker for PM$_{10}$, and hardly any long-term studies are available for coarse particles.

2. There is also strong evidence from epidemiological studies that daily (24-hour average) exposures to PM are associated with both mortality and morbidity.
immediately and in subsequent days. Repeated (multiple day) exposures may result in larger health effects than the effects of single days.

3. While acute and long-term effects are partly interrelated, the long-term effects are not the sum of all short-term effects. Effects of long term exposure are much greater than those observed for short-term exposure suggesting that effects are not just due to exacerbations but may be also due to progression of underlying diseases.

4. There is significant evidence from toxicological and clinical studies using combustion derived particles that peak exposures of short duration (ranging from less than an hour up to a few hours) lead to immediate physiological changes, which is supported by epidemiological observations.

3. **Question A3**

| EU legislation currently has a single limit value for exposure to PM$_{2.5}$ which is based on an annual averaging period. Based on the currently available health evidence, is there a need for additional limit values (or target values) for the protection of health from exposures over shorter periods of time? |

**Answer:**

Since the last WHO review in 2005 when a 24-hour guideline for PM$_{2.5}$ of 25 µg/m$^3$ was set, the evidence for associations between 24-hour average exposures to PM$_{2.5}$ and adverse health effects has increased significantly. Thus, the 2005 WHO Guidelines support to establish 24-hour Limit Values in addition to an annual Limit Value has been strengthened. Single- and multicity studies from the United States report associations with both mortality and hospital admissions due to cardiorespiratory health problems. In the absence of monitoring of PM$_{2.5}$ in Europe until recently, the evidence from Europe is more limited, but where there are studies, the results are less consistent. The following points need to be considered in the legislation decisions:

1. Although the short-term effects may contribute to chronic health problems, those affected by short-term exposures are not necessarily the same as those suffering from the consequences of long-term exposures;
2. Not all biological mechanisms relevant to acute effects are necessarily relevant for the long-term effects and vice versa;
3. In periods with high PM$_{2.5}$ concentrations health relevant action may be taken by citizens, public authorities and other constituencies;
4. Areas that have relatively moderate long-term average concentrations of PM$_{2.5}$ may still have episodes of fairly high concentrations.

In light of the above considerations, health impacts and the need to regulate concentrations both for short term averages (such as 24-hour average) and annual means is well supported by the scientific evidence.
4. **Question A4**

What health evidence is available to support an independent limit value for PM$_{10}$ (in parallel to (i) an annual average limit for PM$_{2.5}$ and (ii) multiple limits to protect from short term and long term exposures to PM$_{2.5}$)?

**Answer:**

There is a sizable scientific literature on the short-term and long-term health effects of PM$_{10}$ at concentrations below the current European limit values. The following arguments make it clear that PM$_{10}$ is not just a proxy measure of PM$_{2.5}$:

1. As reviewed above (A2), there is increasing evidence for the effects of coarse particles (PM$_{10-2.5}$). Short-term health effects of coarse particles have been observed independently of those related to fine particles (PM$_{2.5}$);
2. New European studies further strengthen the evidence of an association between long-term exposure to PM$_{10}$ and health – especially for respiratory outcomes – and of health benefits due to the reduction in long-term mean concentrations of PM$_{10}$ at levels far below the current EU limit value of PM$_{10}$;
3. Coarse and fine particles deposit at different locations in the respiratory tract, have different sources and composition and act through partly different biological mechanisms and result in different health outcomes.

Therefore, maintaining independent short-term and long-term limit values for ambient PM$_{10}$ in addition to PM$_{2.5}$ to protect against the health effects of both fine and coarse particles is well supported.

5. **Question A5**

EU legislation has a concentration limit value and an exposure reduction target for PM$_{2.5}$. To decide whether it would be more effective to protect human health through exposure reduction targets rather than limit or target values it is important to understand (amongst other things, such as exposure, cost effectiveness, technical feasibility) the shape of the concentration-response functions. What is the latest evidence on thresholds and linearity for PM$_{2.5}$?

**Answer:**

The issues of thresholds and linearity for the relation of health response to PM$_{2.5}$ exposure have been subject of several studies published since 2005. The power to assess these issues is particularly strong for short-term effect studies. Long-term exposure studies face greater methodological challenges to fully assess thresholds and linearity.

- **Thresholds:** For short-term exposure studies, there is substantial evidence on associations observed down to very low levels of PM$_{2.5}$. The data clearly suggest the
absence of a threshold below which no one would be affected. Likewise long-term studies give no evidence of a threshold. Some recent studies have reported effects on mortality at concentrations below an annual average of 10 µg/m³.

- Linearity: The European short term studies that have rigorously examined concentration-response functions have not detected significant deviations from linearity for ambient levels of PM_{2.5} observed in Europe. Few long-term studies have examined the shape of the concentration-response. There are however suggestions of a steeper exposure-response relation at lower levels (supra-linear) from analyses comprising studies from different areas across the globe and with different ranges and sources of exposure.

In the absence of a threshold and in light of linear or supra-linear risk functions, public health benefits will result from any reduction of PM_{2.5} concentrations whether or not the current levels are above or below the limit values.

6. Question A6

**Based on currently available health evidence, what PM metrics, health outcomes and concentration-response functions can be used for health impact assessment?**

*Answer:*

The evidence base supports quantification of the effects of several PM metrics and both, short-term and long-term exposures (see A1, A3 and A4). Specifically, a large body of evidence from cohort studies exists to support quantification of the effects of long-term exposure to PM_{2.5} on both mortality (all-cause and cardiovascular) and morbidity. In addition, studies of short-term exposure support quantification of the acute effects of PM_{2.5} on several morbidity outcomes.

There are other PM metrics for which response-functions have been published for at least some health outcomes, including PM_{10}, the coarse fraction of PM_{10}, black carbon, sulphate and others. Its use depends on the purpose of the HIA. Health impact assessors could use black carbon, as an indicator primarily for traffic-related PM using published short-term or long-term response functions. However, compared to PM_{2.5}, there are fewer studies and/or fewer health outcomes available for black carbon and other alternative metrics. Risk assessments based on PM_{2.5} studies will be the most inclusive. Alternative metrics such as black carbon may be used in sensitivity analyses. One need to keep in mind that the impact derived for different PM metrics should not be summed up given that the effects and sources are not fully independent.

Details of the HIA methods are further discussed in the HRAPIE project (question D5). We highlight only the following general issues:

- There are many recently conducted and published HIAs for different PM metrics and averaging times which can serve as a basis for the quantification, including the recent
update of the Global Burden of Disease. These HIAs draw from epidemiologic studies conducted in both Europe and North America;

- In selecting pollutant-outcome pairs for HIA, availability of related health data needs to be taken into account in framing the HIA as the lack of data may be a limiting factor;

- Mortality data for all natural causes tend to be more reliable than cause-specific mortalities. On the other side, air pollution is not related to all causes of death, thus, cause-specific assessments are more defensible. In light of such methodological conflicts, both analyses may be done to elucidate the sensitivity of results in the application to the EU population.

- For morbidity, baseline data are not necessarily available for every member country and therefore, may need to be estimated or derived from local studies or from other countries.

- Given the breadth of the existing evidence and the uncertainty inherent in HIAs, sensitivity of results due to making different assumptions need to be communicated.
B. Health effects of ozone

7. Question B1

What new evidence on health effects has emerged since the review work done for the WHO Air Quality Guidelines published in 2005, particularly with regards to the strength of the evidence on the health impacts associated with short-term and long-term exposure to ozone?

Answer:

The WHO 2005 review found support only for short-term effects of ozone on mortality and respiratory morbidity.

- Since 2005 several cohort analyses have been published on long-term ozone exposure and mortality. There is evidence from the most powerful study, the ACS, for an effect of long-term exposure to ozone on respiratory and cardiorespiratory mortality, which for the latter is less conclusive. Also there is some evidence from other cohorts for an effect on mortality among persons with potentially predisposing conditions (chronic obstructive pulmonary disease, diabetes, congestive heart failure, and myocardial infarction).

- Additionally, several new follow-up long-term exposure studies have reported adverse effects on asthma incidence, asthma severity, hospital care for asthma and lung function growth.

- New evidence published since 2005 on adverse effects from short-term exposure to ozone comes from large, multicentre time-series studies in Europe, the US and Asia. In Europe, adverse effects of short-term exposure to daily concentrations of ozone (maximum 1-hour or 8-hr mean) on all-cause, cardiovascular and respiratory mortality have been reported. Adverse effects of exposure to daily ozone concentrations on both respiratory and cardiovascular hospital admissions, after adjustment for the effects of particles (PM$_{10}$), have also been reported.

- In the 2005 review toxicological data from animal and human exposure studies already provided ample support for short-term effects of ozone on a range of pulmonary and vascular health-relevant endpoints. The evidence has strengthened in the intervening period. In addition, new findings from a range of experimental animal models, including primates, provides evidence of chronic injury and long-term structural changes of the airway in animals exposed to prolonged periods to ozone, and to ozone and allergens combined.

- New epidemiological and experimental data, both in humans and animal models, have also arisen suggesting an effect of ozone exposure on cognitive development and reproductive health, including preterm birth.
8. **Question B2**

<table>
<thead>
<tr>
<th>What new health evidence has been published in relation to the evidence or likeliness of a threshold below which impacts are not expected?</th>
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**Answer:**

Epidemiological studies reporting an effect of long-term exposure to ozone on mortality do not, in general, provide data to permit the firm identification of a threshold for the effects of long-term exposure to ozone.

Recent experimental exposures of healthy human volunteers to ozone at concentrations of 60 ppb (120 µg/m$^3$) have reported impaired lung function and inflammation, relative to clean air controls, but thus far only in healthy young adults exposed for prolonged periods (6.6 hours) with exercise. These conditions are unlikely to reflect fully the range of exposures experienced in the general population and the real world combinations of susceptibility and exposure. Effects of ozone on lung function and inflammation have been reported under real world situations, most notably in summer camp studies at lower concentrations, less than 55 ppb (110 µg/m$^3$) as an 8-hour average. It has been argued that the responses at these lower levels may be due to subpopulations with greater susceptibilities or to additional effects of other stressors, such as other pollutants. The evidence for a threshold from epidemiological studies of short-term exposure is inconsistent with some large, multicity studies reporting little evidence for a threshold down to near background ozone concentrations, whereas other short-term studies suggest a threshold between 10 and 45 ppb (20 and 90 µg/m$^3$) (daily maximum 1-hour). In summary, the evidence for a threshold for short term exposure is not consistent, but where a threshold is observed, it is likely to lie below 45 ppb (90 µg/m$^3$) (maximum 1-hour).

9. **Question B3**

<table>
<thead>
<tr>
<th>Based on currently available health evidence, what ozone metrics, health outcomes and concentration-response functions can be used for health impact assessment?</th>
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</table>

**Answer:**

It is mainly adverse health outcomes with known baseline rates that are suited for HIA, typically mortality and hospital admissions. Evidence from time-series studies of short-term exposure to ozone suggests HIA calculations can be undertaken for a range of endpoints including all-age all-cause, cardiovascular and respiratory mortality and, for the 65+ age group, respiratory and cardiovascular hospital admissions. The epidemiological evidence supports calculations using all-year coefficients for daily maximum 8-hour ozone (scaled from the 1-hour measures reported in the literature) and including adjustment for PM$_{10}$. 
For the reasons stated in the answer to question B2 we recommend that health impact calculations for short-term exposures assume linear concentration-response relationships for the outcomes recommended. Since the epidemiological evidence regarding linearity does not extend down to zero, appropriate cut off points for HIA are therefore recommended; one at 10 ppb (20 µg/m³) for daily maximum 8-hr ozone and also, for consistency with previous work using SOMO35 data, 35ppb (70 µg/m³).

Because of the uncertainties regarding the effects of long-term exposure to ozone reported in the answer to question B1, we suggest that HIA for respiratory and cardiopulmonary mortality are undertaken as a sensitivity scenario. We recommend using coefficients from single pollutant models taken from the ACS cohort assuming the association to exist within the studied range of ozone concentrations.

### 10. Question B4

Is there evidence that other photochemical-oxidants (individually or in mixtures) are of public health concern e.g. does the impact of outdoor ozone on reaction products indoors explain the outdoor ozone associations, and links to the secondary organic aerosol?

**Answer:**

To date, the number of studies addressing the toxicity of the products of the reaction of ozone with VOCs, particles and indoor surfaces is limited. It is clear however that ozone is involved in the formation of secondary inorganic and organic PM in the outdoor environment and that the reaction of ozone with common indoor VOCs generates a plethora of compounds, many of which have been proposed to be respiratory irritants. The field is currently positioning itself to perform whole animal and human exposures studies to address whether the formation of these species, at relevant concentrations, constitutes a public health concern over and above that of ozone alone. At this time however there is insufficient information to make a definitive statement on the questions B4.
C. Proximity to roads, NO₂, other air pollutants and their mixtures

11. Question C1

There is evidence of increased health effects linked to proximity to roads. What evidence is available that specific air pollutants or mixtures are responsible for such increases, taking into account co-exposures such as noise?

Answer:

Motor vehicles are a significant source of urban air pollution. Health effects of proximity to roads were observed after adjusting for socioeconomic status, and after adjusting for noise. Elevated health risks associated with living in close proximity to roads is unlikely to be explained by PM₂.₅ mass since this is only slightly elevated near roads. In contrast, levels of pollutants such as ultrafine particles, CO, NO₂, black carbon, PAHs and some metals are also more elevated near roads. Individually or in combination, these are likely to be responsible for the observed health effects. Current available evidence does not allow discernment of the pollutants or pollutant combinations that are related to different health outcomes although association with tail pipe primary PM is increasingly identified.

Exhaust emissions are an important source of traffic related pollution and several epidemiological and toxicological studies have linked such emissions to adverse health effects. Road abrasion, tire wear and brake wear are non-exhaust traffic emissions which become relatively more important with progressive reductions in exhaust emissions. Toxicological research increasingly indicates that such non-exhaust pollutants could be responsible for some of the observed health effects.

12. Question C2

Is there any new evidence on the health effects of nitrogen dioxide (NO₂) that impact upon the current limit values? Are long-term or short-term limit values justified on the grounds that NO₂ affects human health directly, or is it linked to other co-emitted pollutants for which NO₂ is an indicator substance?

Answer:

Many studies, not previously considered, or published since 2004, have documented associations between day-to-day variations in NO₂ and variations in mortality, hospital admissions, and respiratory symptoms. Also, more studies have now been published showing associations between long-term exposure to NO₂ and mortality and morbidity. Both short- and long-term studies have found these adverse associations at concentrations that were at or below the current EU limit values, which for NO₂ are equivalent to the WHO Air Quality Guidelines. Chamber and toxicological evidence provides some
mechanistic support for a causal interpretation of the respiratory effects. Hence, the results of these new studies provide support for updating the current WHO Air Quality Guidelines for NO\textsubscript{2} to give: (i) an epidemiologically based short-term guideline and (ii) an annual average guideline based on the newly accumulated evidence. In both instances, this could result in lower guidelines.

There is evidence of small effects on inflammation and increased airway hyperresponsiveness with NO\textsubscript{2} \textit{per se} in the range 0.2 to 1 ppm (380 to 1880 \(\mu\text{g/m}^3\)) from chamber studies (under a broad range of exposure conditions, with exposure durations of 15 minutes to 6 hours, with some inconsistency in results), with more marked, consistent, responses observed from 1 ppm (1880 \(\mu\text{g/m}^3\)). New review reports suggest weak to moderate lung cell changes in animal studies at one-hour concentrations of 0.2 to 0.8 ppm (380–1500 \(\mu\text{g/m}^3\)). These concentration ranges are not far from concentrations that occur at the roadside or in traffic for multiple hours. The chamber studies examined small numbers of healthy or mild asthmatic subjects whereas the general population will include subjects who are more sensitive and may therefore experience more pronounced effects at lower concentrations.

The associations between NO\textsubscript{2} and short-term health effects in many studies remain after adjustment for other pollutants. The pollutants used in the adjustments include PM\textsubscript{10}, PM\textsubscript{2.5}, and occasionally black smoke. This does not prove that these associations are completely attributable to NO\textsubscript{2} \textit{per se}, as NO\textsubscript{2} in these studies may also represent other constituents (which have adverse health effects) not represented by currently regulated PM metrics. 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\textsubscript{2} has some direct effects.

It is much harder to judge the independent effects of NO\textsubscript{2} in the long-term studies because, in those investigations, the correlations between concentrations of NO\textsubscript{2} and other pollutants are often high so that NO\textsubscript{2} might be representing a mixture. In this case, chamber studies do not apply and toxicological evidence is limited. However, some epidemiological studies do suggest associations of long term NO\textsubscript{2} exposures with respiratory and cardiovascular mortality, and with children’s respiratory symptoms and lung function, that were independent of PM mass metrics. As with the short-term effects, NO\textsubscript{2} in these studies may represent other constituents. Despite this, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations is suggestive of a causal relationship.

13. Question C3

Based on existing health evidence, what would be the most relevant exposure period for a short-term limit value for NO\textsubscript{2}?  

Answer:
The most relevant exposure period based on existing evidence is one hour because 1-hour peak exposures in chamber studies have been shown to produce acute respiratory health effects. Toxicological studies also support the plausibility of responses to peak concentrations. Time-series and panel studies have examined associations using both 24-hour average and 1-hour average NO2 concentrations with similar results. Evidence from these studies would support the development of a 24-hour WHO guideline or a 1 hour guideline but, as there is chamber study and toxicological evidence on, or close to, a 1 hour basis and much less evidence on a 24 hour basis, a 1 hour exposure period is preferred. In urban areas, 1-hour peak concentrations and 24-hour averages were so highly correlated that it should be possible for a 1-hour peak guideline to be derived from studies using 24-hour average NO2 following expert analysis of how these metrics are related in Europe. There is, therefore, no need to develop a 24-hour limit value in addition to a 1-hour guideline based on epidemiological studies.

14. Question C4

Based on currently available health evidence, what NO2 metrics, health outcomes and concentration-response functions can be used for health impact assessment?

Answer:

This answer assumes application in health impact assessment for NO2 itself, given that impacts of other pollutants – notably PM mass - are also being quantified. The use of NO2 as an indicator for health impact assessment of local traffic measures is discussed in the rationale. The evidence base supports quantification of effects of short-term exposure using the averaging time as in the relevant studies. The strongest evidence is for respiratory hospital admissions with some support also for all-cause mortality – these are recommended outcomes for use in the core analysis. Cardiovascular hospital admissions can be included as a sensitivity analysis (the evidence is more uncertain than for respiratory admissions). It is recommended to derive concentration-response functions from time-series studies which have provided effect estimates for NO2 adjusted for at least PM mass.

For a core HIA of effects of long-term exposure to NO2, the recommended health outcome is bronchitic symptoms in asthmatic children with the coefficient, adjusted for a PM metric, based on the Southern California Children’s Health Study. HIA using asthma prevalence could also be performed. However, as only estimates from single pollutant models are currently available for asthma prevalence, this health outcome should only be used in sensitivity analyses comparing results to those of HIA for PM mass. Cohort studies also show relationships between long-term exposure to NO2 and mortality but not all are sufficiently robust for use in a core HIA. Therefore, the effect of long-term exposure to NO2 on all-cause mortality is recommended for sensitivity analysis only. Concentration-response functions from cohort studies with effect estimates for NO2 which were adjusted for at least PM mass should be used. In the same way, cardiovascular mortality could also be included in sensitivity analysis – this would be
subject to the same uncertainty regarding mechanistic understanding of cardiovascular effects.

15. **Question C5**

<table>
<thead>
<tr>
<th>Is there any new evidence on the health effects of air emissions of As, Cd, Hg, Pb and Ni (and their compounds), that would impact upon current target values?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Answer:</strong></td>
</tr>
</tbody>
</table>

*Arsenic (As):* Yes, there is some new evidence on the cancer risk of air emissions of As, but it is contradictory in terms of the direction of risk. This new evidence is insufficient to impact upon the current EU target value.

*Cadmium (Cd):* Yes, there is new evidence on the health effects of air emissions of Cd. Reaching the present AQG and EU target values does not prevent increasing Cd levels in agricultural soil by air deposition, and thereby adverse health effects in the general population. If the AQG are reviewed, this new evidence should be considered.

*Mercury (Hg):* No, there is no new evidence on the health effects of air emissions of Hg that would impact upon the current policy.

*Lead (Pb):* Yes, there is definitely new evidence on the health effects of air emissions of Pb that would impact upon the current limit value. This evidence shows that effects on the central nervous system in children and on the cardiovascular system in adults occur at, or below, the present standards in the AQG and EU.

*Nickel (Ni):* Yes, there is some new evidence on the health effects of air emissions of Ni, but this would probably not have any significant impact upon the risk estimate and the present target value.

16. **Question C6**

<table>
<thead>
<tr>
<th>Is there any new evidence on health effects due to air emissions of PAHs that would impact upon current target values?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Answer:</strong></td>
</tr>
</tbody>
</table>

Some PAHs are potent carcinogens, and are often attached to airborne particles, which may also play a role in their carcinogenicity. As PAHs are carcinogenic by a genotoxic mode of action, their levels in air should be kept as low as possible. There is new evidence linking PAH exposure to cardiovascular endpoints but at present these effects of PAH exposure cannot be separated from the effects of particles and therefore cannot impact on the target values. Studies on early biological effects of PAH exposure based on
biomarkers, including PAH-DNA adducts, in general populations of children and adults also suggest a range of potential non-carcinogenic effects. Overall there is not new evidence from which to propose a new target value. However, it should be noted that, based on previous literature, the existing target value of 1 ng/m$^3$ BaP is associated with the lifetime cancer risk of approximately $1 \times 10^{-4}$.

17. **Question C7**

| Is there any new evidence on the health effects of short term (less than 1 day) exposures to SO2 that would lead to changes of the WHO air quality guidelines based on 10 minute and daily averaging periods or the EU’s air quality limit values based on hourly and daily averaging periods? |

**Answer:**

There are no new respiratory chamber studies that would change the 10 minute guideline of 500 $\mu$g/m$^3$, previously based on these types of studies. However, a reanalysis of the previous literature has found a small difference between responders and non-responders at 0.2 ppm (572 $\mu$g/m$^3$) (not statistically significant after control for multiple comparisons), the starting point for deriving the previous guideline. Thus, while the currently available statistical analysis suggests that the starting point does not need to be changed, a small increase in the safety factor from the current value of 1.15 might be justified when the time comes to reconsider the guideline, as the small though non-significant, difference between responders and non-responders at this concentration increases the uncertainty as to whether this is a no effect level or a minimal effect level. Should further evidence confirm this difference, then the starting point may need to be changed in future.

The 24-hour average guideline was based on the low end of the concentration ranges used in the time-series studies and the Hong Kong intervention study. The time-series evidence continues to accumulate and continues to be inconsistent when adjusted for other pollutants for many but not all outcomes (e.g. it is consistent for asthma admissions). The results of the original Hong Kong intervention study remain as a reduction in mortality for a reduction in pre- and post-intervention exposure to SO$_2$ independent of PM$_{10}$, although a more recent report suggests more difficulty in disentangling the effects of the reductions in SO$_2$ from reductions in other constituents, such as nickel or vanadium. The new studies are at a similar range of concentrations to the previous studies, so the 24-hour average guideline does not need to be changed if the same method (using a concentration at the low end of the range of concentrations) to set the guideline were to be followed.

18. **Question C8**

| Are there important interactions amongst air pollutants in the induction of adverse health effects that should be considered in developing air quality policy? |
Answer

(Note: This answer does not consider interactions with host susceptibility behaviour or other factors with the exception of temperature)

There are interactions amongst air pollutants that change the toxicity of the mixture. These occur at the level of physicochemical interactions in air as well at the biological level. In developing air quality policies the following issues can be considered:

- There is very little evidence from health studies that the mixture of air pollutants results in significant more health effects (synergy) than would be expected based on the information for the single pollutants. However, this is largely due to a lack of data and methodological limitations.
- Very few epidemiologic studies have examined the potential for interaction amongst pollutants. This is likely due to their moderate to high correlations. The existence of such pollutant mixtures makes it often difficult, in an uncontrolled setting, to determine either independent or synergistic effects of ambient air pollutants.
- Synergistic effects at the biological level between ultrafine particles and transition metals, and between particles and VOCs have been shown indicating larger combined impact on human health than would be expected for the separate entities.
- A reduction of NOx emissions without an accompanying abatement of VOCs may result in no change, or even in an increase of ozone concentrations close to the source.
- Airborne particles of any kind can carry aero-allergens or toxic condensed vapours such that their impact can be substantially larger than without particles. There is a trend that the smaller the particles the stronger the adjuvant effect are. Limited evidence has been published suggesting that the nitrogen dioxide can enhance allergic responses.
- In general, reduction of one component will not result in a significant increase in the health risks associated with other components. The implications for reducing PM on (semi)VOCs formation are not evident.
- There is some evidence of potential interactions amongst pollutants and high temperature.
- Changing the air pollution mixture due to changing fuels may under certain conditions lead to more harmful emissions.

19. Question C10

What is the contribution of exposure to ambient air pollution to the total exposure of air pollutants covered by the regulations, considering exposures from indoor environments, commuting and workplaces?

Answer:

- Tobacco smoke, where permitted indoors, dominates the exposure of the exposed individuals to at least PM$_{2.5}$, [BC, ultrafine particles,] CO, benzene, BaP and naphthalene, and contributes also to the NO$_2$ exposure. Tobacco smoke exposures and
risks, however, are targeted in specific policies and not in ambient air policies, and therefore the other answers below refer to tobacco smoke free conditions.

- In general, all air pollution exposures of indoor and occupational origin as well as the commuting exposures vary between the individuals much more than exposure to air pollution of ambient origin, and depend strongly on the microenvironments and behaviour of the individual.
- Specifically, commuting can increase exposures to particulate matter, NO₂, CO and benzene, and is a major contributor to the exposure to ultrafine particles, black carbon and some metals, most importantly Fe, Ni and Cu in underground rail transport systems.
- Individual industrial workday exposure levels may be orders of magnitude higher than the average population exposure levels, but as they affect only quite specific and controlled population subgroups and are controlled by occupational and not by ambient air pollution policies, they are not covered in this chapter.
- Population exposures to NO₂ (where gas appliances are infrequent), PM_{2.5}, BC, O₃, CO and SO₂ (with more limited evidence also concerning inhaled exposures to BaP, As, Cd, Ni and Pb) originate dominantly from ambient air and outdoor sources.
- Ambient air, indoor sources and commuting are all important for population exposures to NO₂ (where gas appliances are frequent), benzene and naphthalene.
- The high end of the individual exposures to PM_{10-2.5} and naphthalene originate from indoor sources and commuting.
- Solid fuel fired indoor fireplaces and stoves, where used in suboptimal conditions, dominate the high end of the exposures to PM_{2.5}, BC, UFP, CO, benzene and BaP of the affected individuals.
D. General questions

20. Question D1

What new information from epidemiological, toxicological and other relevant research on health impacts of air pollution has become available that may require a revision of the EU air quality policy and/or WHO air quality guidelines notably for particulate matter, ozone, nitrogen dioxide and sulphur dioxide?

Answer

Introduction

Since the publication of the WHO Air Quality Guidelines, Global Update 2005, a considerable amount of new scientific information has appeared on all four pollutants discussed here. In many cases these have shown associations with adverse health outcomes at levels of the pollutants lower than those in the studies on which the 2005 WHO Guidelines were based. This is particularly true for PM, Ozone and NO₂. In the light of this, we would recommend that WHO begins the process of developing revisions to the earlier Guidelines, with a view to completing the review by 2015. We would further recommend that the European Commission ensures that the evidence on the health effects of air pollutants and the implications for air quality policy are regularly reviewed.

PARTICULATE MATTER

- There is a need to revise the current WHO Air Quality Guidelines (AQG) for PM₁₀ (20 μg/m³, annual average and 50 μg/m³, 24h average, 99th percentile) and PM₂.₅ (10μg/m³, annual average and 25 μg/m³, 24h average, 99th percentile).
  The current state of scientific knowledge, supported by a huge body of new studies, shows a wide range of adverse health effects associated with exposure to PM₂.₅ (see answers to question A1) and PM₁₀ (see answers to question A4). The data strongly suggest that these effects have no threshold within the ambient range studied, follow a mostly linear concentration-response (C-R) function and are likely to occur at fairly low levels, close to PM₂.₅ background concentrations. The scientific basis for the AQG for PM₂.₅ and PM₁₀ and the corresponding interim targets (all set in 2005, Global update) is therefore now even stronger than seven years ago. The AQG values set in 2005 include no margin of safety. In 2005 the AQG values were set to reflect levels close to the lower end of the available C-R functions at this time; there now exists more recent information at lower PM levels than previously.
- In the same light, there is a strong need to re-evaluate and lower at least the limit value stage 2 for PM₂.₅ of 20 μg/m³ (annual average, to be met by 2020) set in section D, annex XIV of the of the ambient air quality Directive 2008/50/EC.
  At the moment there is a considerable gap between the WHO AQG for PM₂.₅ (10 μg/m³, annual average), the PM₂.₅ US standard set in 2012 (12 μg/m³, annual
average), the EU limit value to be met in 2015 (25 μg/m³, annual average) and the EU Stage 2 indicative limit value (20 μg/m³). The need of an additional PM₂.₅ short-term (24h) limit value (as suggested in answer to question A3) and a re-evaluation of the PM₁₀ limit values should be discussed by the EC too.

The scientific support for the exposure-reduction approach to managing PM air quality incorporated in Directive 2008/50 has strengthened, and this approach provides in principle, a preferable way to reduce health impacts of PM₂.₅. The National exposure reduction target, set in section B, annex XIV of the Directive, should be set as mandatory legislation by 2020. Irrespective of the actual concentration or a specific limit or target value, the health of populations benefits from lower PM average exposure.

- WHO should consider developing an additional AQG to capture the effects of road vehicle PM emissions that are not well captured by PM2.5, building on the work on BC/EC (Health effects of Black Carbon, WHO 2012) and evidence on other pollutants in vehicle emissions.

- Besides the public health/air quality concerns, BC it is also an important short-lived climate forcer, which contributes to warming of the Earth’s atmosphere. Reducing BC emissions and concentrations is beneficial for population health and, for sources with high BC/OC ratios, helps to mitigate short-term climate change.

- Although there is considerable evidence that ultrafine particles can contribute to the health effects of particulate matter, for ultrafine particles, measured by the number of particles, the data on concentration-effect functions are too scarce to evaluate and recommend an AQG. The same evaluation applies for organic carbon (OC). Current efforts to reduce the numbers of ultrafine particles in engine emissions should continue, and their effectiveness assessed, given potential health effects.

- Given the significant short and long term health effects identified as being caused by exposure to PM₂.₅, the National Emissions Ceiling Directive (NECD) should be revised to include a ceiling for PM₂.₅. Member States should be required to give priority to reducing emissions from vehicles and from combustion of liquid and solid fuels, including non-road mobile-machinery and biomass burning, in achieving the ceilings in a revised NECD and also in achieving limits for PM in the ambient air quality Directive.

- The EU should consider appropriate actions to reduce non-tailpipe emissions from road traffic, given the increasing relative contribution of non-tailpipe emissions when vehicle exhaust emissions are reduced.

2. OZONE

- The most important policy-related issues with regard to ozone are the recent emergence of evidence for effects of long-term (months to years) exposures, and the existence (or otherwise) and concentration level of a threshold below which effects
are unlikely in the general population. Long-term ozone concentrations are determined by hemispheric or global emissions of precursor pollutants. If a no-effects threshold concentration does not exist, or is very low, and hypothetically assuming a linear dose-response function through the origin, total annual health impacts will be proportional to annual mean ozone concentrations and will be much larger than otherwise, with similar policy implications for regional versus global hemispheric controls.

- In the light of the Answers to the B1-B4 questions, WHO should consider developing guidelines for long-term average ozone concentrations.

- The EU should analyse the extent to which current or foreseen policies within the EU, or the CLRTAP Gothenburg Protocol (which covers a wider geographical area) are sufficient to reduce long-term average ozone concentrations. Depending on the outcome of this analysis the EU should then consider engaging with other major emitters in the northern hemisphere to consider possible actions to reduce these longer-term ozone concentrations, possibly using the CLRTAP Task Force on Hemispheric Transport of Air Pollution (co-chaired by the EU and the USA) to guide the discussions. Reductions of methane within and outside the EU would be beneficial in reducing long-term average ozone concentrations.

- Answer to question B2 concluded that evidence for a short-term threshold is not consistent but where a threshold is observed it is likely to lie below 90 µg/m³ (maximum 1-hour mean). In performing Health Impact Assessments the use of SOMO35 and SOM010 has been recommended for short-term effects. For long-term effects, the answer to question B2 has recommended a HIA as a sensitivity scenario.

- Given the emerging evidence discussed in the answers to questions B, and pending the outcome of the health impact assessment the EU should consider setting a long-term Target Value, possibly as a summer (April to September inclusive) mean for which evidence is stronger than for an annual mean.

3. NITROGEN DIOXIDE

- Since the 2005 WHO Guidelines release new epidemiological studies have emerged reporting associations with both short-term and long-term exposures to NO₂. Some of these, notably the short term studies, report associations which are robust to inclusion of other pollutants.

- Many of these studies were in areas where concentrations were at or below the current EU Limit Values.

- The results of these new studies provide support for updating the current WHO Air Quality Guidelines for NO₂ to give: (i) an epidemiologically based short-term guideline and (ii) an annual average guideline based on the newly accumulated evidence from outdoor studies. In both instances, this could result in lower guidelines.
• There is consistent short-term epidemiological evidence and some mechanistic support for causality so that it is reasonable to infer that NO₂ has some direct effects. However, as with the short-term effects, NO₂ in the long-term epidemiological studies may represent other constituents. Despite this, the mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations is suggestive of a causal relationship.

• There is no health-based case for either increasing, or removing the NO₂ limit values in the EU Directive. Dependent on the outcome of any revision of the WHO Air Quality Guidelines for NO₂, there could then also be a case for the EU to consider revising the Directive limit values.

• There is no evidence to suggest changing the averaging time for the short-term EU limit value which is currently one hour.

4. SULPHUR DIOXIDE

• There is a need to revisit the evidence base for setting the WHO AQG for SO₂ (very short-term and short-term).

• Since the WHO air quality guidelines (AQG) were formulated in 2005 some new studies on toxicological and health effects of SO₂ have been published. A reanalysis of the previous chamber study literature suggests a need to consider whether to increase the safety factor for the 10 minute guideline. For the 24-hour average guideline, the new studies give similar results to the previous studies. The new studies are at a similar range of concentrations to the previous studies, so the 24-hour average guideline does not need to be changed if using the same method (using a concentration at the low end of the range of concentrations observed in the studies) to set the guideline (Answer to question C7). However, the evidence should be looked at again.

21. Question D2

What new information from epidemiological, toxicological and other relevant research on health impacts of air pollution has become available that may require a revision of the EU air quality policy and/or WHO air quality guidelines notably for particulate matter, ozone, nitrogen dioxide and sulphur dioxide?

Answer

There is reasonably consistent evidence from past and more recent studies that decreased air pollution levels following an intervention or unplanned decrement in pollution have
been associated with improvements in health. The assessed decrements in pollution were not exclusively associated with legislation, but may have been due to strikes, German reunification etc. In addition, there is significant and consistent evidence from around the world that workplace or public spaces smoking-bans have resulted in a reduction in the cardiovascular health burden of the general population in the regions, where they were introduced.

Those findings are supported by a large body of remarkably coherent evidence from studies of both long- and short-term exposure to air pollution, relying on naturally occurring exposure variability, that provide effect estimates quantifying health improvements that could be expected from long- or short-term reductions in air pollution exposures in a given population.

22. Question D4

<table>
<thead>
<tr>
<th>The 6th Environment Action Programme aims to “achieve levels of air quality that do not give rise to significant negative impacts on and risks to human health and the environment (Article 7 (1) of Decision No. 1600/2002/EC). Is there evidence of a threshold in the concentration/response curves for PM$_{2.5}$, ozone and NO$_2$?</th>
</tr>
</thead>
</table>

**Answer**

Existing studies do not provide evidence of a threshold in the concentration response curve between PM$_{2.5}$ and health outcomes, either for short or long term exposure at the commonly observed ambient levels. On the contrary, for long-term exposures, there is some evidence that the curve increases more rapidly at lower concentrations compared to higher exposures. Enhanced methodologies are proposed to better account for the uncertainty incorporated in epidemiological designs especially in the investigation of long term effects, outside exposure ranges observed in cohort studies. Similarly, there is lack of evidence of a threshold for NO$_2$ and O$_3$, although the evidence base for assessing the existence of a threshold or the shape of the concentration-response curve is weaker than for PM$_{2.5}$. 
List of invited experts participating in REVI HAAP

Scientific Advisory Committee

This Committee supervises the implementation of the project on evidence on health aspects of air pollution to review EU (REVIHAAP) and ensure the highest possible quality and relevance of its outputs. The following experts are the Committee members:

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- Bert Brunekreef, The Netherlands
- Aaron Cohen, United States
- Klea Katsouyanni, Greece
- Daniel Krewski, Canada
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The WHO Regional Office for Europe

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"Review of evidence on health aspects of air pollution – REVI HAAP"

First results