Report of a toxicology forum symposium on air quality and cardiovascular health effects: what's the impact - October 24, 2007

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ABSTRACT

CONCAWE sponsored a special session at the ToxForum meeting (October 2007) on Air Quality and Cardiovascular health effects. The session provided an opportunity to bring together leading scientists and have a debate on the state of knowledge in this field. The discussion amongst participants resulted in a series of recommendations for future research.

KEYWORDS

Air quality, health effects, cardiovascular disease

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SUMMARY

Population studies on health effects of air pollution have suggested that the largest burden of disease by specific cause is due to cardiovascular effects, in particular from long-term exposures. The possible acceleration of atherosclerosis by air pollution is currently a prominent research theme in the EU and the USA. Appropriate exposure assessment is a critical aspect of population studies. A special ToxForum session (at the Brussels meeting October 2007) on Air Quality and Cardiovascular health effects was convened to debate the latest research in this area. Leading scientists presented the state of knowledge in this field. The discussion amongst participants resulted in a series of recommendations for future research. Presentations covered vascular toxicity of complex emissions; mechanistical studies; exposure assessment; cardiovascular effects of diesel exhaust and chronic effects.

Identified priorities for future studies included:

- Expand focus of future cardiovascular disease research to other pollutants than $PM_{2.5}$;
- Epidemiological studies require more emphasis on exposure assessment of targeted populations;
- Biological pathways which play an important role in atherogenesis (the process of plaque formation in the inner lining of arteries) should be studied such as inflammatory pathways in particular;
- High priority should be given to toxicological characterisation of emissions from new fuels.

1. INTRODUCTION

1.1. PURPOSE

Population studies on health effects of air pollution have suggested that the largest burden of disease by specific cause is due to cardiovascular effects, in particular from long-term exposures. The possible acceleration of atherosclerosis by air pollution is currently a prominent research theme in the EU and the USA. Appropriate exposure assessment is a critical aspect of population studies.

The identification of key pollutants and host factors is important for efficient air quality management. Mechanistic studies have provided indications of the role that specific pollutants may play, as well as of interactions of multiple pollutants and of host factors. Internationally, a number of research groups are active in this area, postulating modes of action and applying novel technologies.

This session aimed to bring together representatives of several research groups active in this area of significant public health concern in order to provide delegates with an update of the state of the science.

Additionally, the session aimed to provide insight to new research regarding the relationship of air quality to cardiovascular health effects. This included both animal and human data as well as relevant exposure research. The presentations, comments, questions and responses were recorded by the ToxForum and will be published on their website, available to members only. The purpose of this report is to give a brief overview of the presentations.

2. PROGRAMME OUTLINE

Introduction: Chair: Peter Pärt – DG Joint Research Centre, European Commission

Presentation 1: The Comparative Toxicity Test Programme of the National Environmental Respiratory Centre – Matt Campen, Lovelace Respiratory Research Institute, USA

Presentation 2: Recent Clinical Studies – Anthony Seaton, Aberdeen University, UK

Presentation 3: Integrated Exposure Assessment: Which Pollutants to Measure, Including Recommended Metrics and Averaging Periods – Matti Jantunen, Finnish Public Health Institute, Finland

Presentation 4: Neurological and Cardiovascular Effects in Rats Exposed to Diesel Exhaust – Miriam Gerlofs-Nijland, National Institute for Public Health and the Environment, The Netherlands

Presentation 5: Chronic Effects of Air Pollution: Where to Focus Research Resources – Nino Kuenzli, Centre for Research in Environmental Epidemiology, Spain

3. PRESENTED MATERIALS

3.1. INTRODUCTION – PETER PÄRT

P. Pärt began by highlighting recent assessments such as the CAFE assessment on health impacts of $PM_{2.5}$ in EU25 (2000). This assessment attributes 347,900 premature deaths and 3,618,700 life years lost as examples of the significance of the issue. The EEA Belgrade Report of 2007 shows that while many EU countries meet or are close to the EU limit value of 40 $\mu g/m^3$ for PM_{10}, most fail to meet the WHO guideline of 20 $\mu g/m^3$. Given that a majority of the European population is impacted by air pollution (assuming the numbers are accurate) the cost for actions to improve air quality is justified by the perceived benefits of improved health.

Concerning particles, P. Pärt remarked that of current $PM_{2.5}$, 34% is attributed to mobile sources, 25% to domestic wood stoves and 20% to industrial processes. Scenarios for the future (ca 2020) indicate that this situation will change and the contribution of domestic wood stoves and industrial processes will increase while emissions from transport will decrease. A strong driver for this development will be climate change policies aiming at reducing CO_2 emissions. Fossil fuels are replaced by wood and other biological fuels which are CO_2 neutral. Meanwhile, refined engine technology in combination with particle filters will reduce particle emissions from transport.

P. Pärt pointed on a couple of challenges. The growing use of alternative fuels in transport – what do we know about the potential health impacts of emissions from ethanol fuels or from bio-diesel? Toxicological analysis of tail-pipe emissions is important and we should not only focus on particles but also on the gaseous components.

3.2. THE COMPARATIVE TOXICITY TEST PROGRAMME OF THE NATIONAL ENVIRONMENTAL RESPIRATORY CENTRE: VASCULAR TOXICITY OF COMPLEX EMISSIONS – MATT CAMPEN

The focus of the National Environmental Respiratory Centre (NERC) is on understanding aggregate risks and the proportion of health burden caused by multiple air pollutants rather than single pollutants (e.g. $PM_{2.5}$). The NERC research strategy addresses two fundamental information gaps:

- A detailed exposure composition-concentration-response database amenable to multivariate analysis;
- Contemporary, detailed, head-to-head comparisons of the health effects of anthropogenic source emissions.

The research programme is looking at several exposure sources: diesel, gasoline, wood, coal, road dust, and residual oil. In addition, the health-related endpoints include respiratory and cardiovascular markers.

For gasoline emissions exposures, the NERC studies have found vascular effects in the absence of pulmonary effects using a series of analyses and animal models such as the ApoE knockout mouse which is genetically prone to atherosclerosis. For mice exposed to diesel emissions, there was no difference in effect for filtered vs.

unfiltered emissions. This suggests that something other than PM (e.g. nitrogen compounds) contributed to the cardiovascular response.

The current focus of the research is on comparing diesel, gasoline, wood smoke and coal emissions. Further epidemiological and clinical research is required to understand the overall health burden and identification of any susceptible populations.

3.3. AIR POLLUTION AND CARDIAC DISEASE: SOME RECENT STUDIES OF MECHANISMS - ANTHONY SEATON

Professor Seaton reported on a few clinical studies in which he had been involved. One included 112 healthy subjects and another 100 non-smoking cardiac disease patients.

For the study with the healthy subjects, estimates of personal exposure were based on the concentrations of PM_{10} in the surrounding area. Changes in micro circulation and in the behaviour of red blood cells were observed. Activation of endothelial factors was a likely explanation. Supportive evidence for this was provided from a recent study which suggested that human endothelial cells respond to PM_{10} by specifically stimulating clotting processes.

The second study involved 100 non-smoking patients with documented cardiac disease. Personal NO_2 exposure was measured and $PM_{2.5}$ exposure was estimated. Twenty-four hour ECG was conducted as well as blood analysis for haematological factors and biochemical changes. A number of statistically significant changes were observed. However, there were no consistent positive associations between these and PM exposure. The author concluded that the absence of clear association was probably related to the excellent care that the subjects received for their prior cardiac condition.

The presenter's conclusions were:

- Particulate air pollution is "known" to be associated with heart attacks;
- Mechanism may be inflammation, effects on endothelium and clotting;
- Modern cardiac therapy probably reduces risks of short term adverse effects.

3.4. EXPOSURE ASSESSMENT: WHICH POLLUTANTS TO MEASURE – MATTI JANTUNEN

The presenter stated that the "final truth" about which particle characteristics and which sources cause the highest risks "is still uncertain". The leading contenders, based on epidemiological and toxicological evidence, are particles from combustion processes including traffic and particles with high surface area and contents of transition metals. Traffic is, therefore, a particularly interesting exposure environment, which is poorly depicted by ambient monitoring. Information was presented regarding the average contributions of sources to ambient and microenvironment $PM_{2.5}$ concentrations and personal exposures.

The overall characteristics of exposures were discussed. For a Helsinki EXPOLIS study, individual $PM_{2.5}$ exposure samples revealed the full distributions of exposure

from various sources. There was an exceptionally high proportion from workday exposure (includes commuting), in particular, of Zn, Si, and Na.

M. Jantunen discussed a study regarding exposure to PM for schoolchildren on their way to and from school in Leicester. It is difficult to draw any conclusion from this work related to air quality and mortality from cardiovascular effects.

M. Jantunen presented his view of relevant metrics and averaging times for exposure monitoring related to air quality:

- Particle size: the exposure data and risk evidence is still strongest for $PM_{2.5}$;
- Particle characteristics: surface area, contents of transition metals, elemental carbon and organic carbon and reactive oxygen species generation capacity are all important characteristics;
- Particle sources: small scale solid fuel combustion, traffic PM (diesel exhaust particles in particular), metals smelting and probably also metro/subway particles are important;
- Urban cohort studies and tobacco studies point out that exposures acquired over long times, 1 to 10 years, are far more important than e.g. 24 hour peak exposures;
- Short averaging times are still needed in exposure sampling, when focusing on specific sources.

The presenter concluded with some information related to exposures in microenvironments. He observed that focusing on these areas could yield better exposure information for correlation to the anticipated health effects.

3.5. NEUROLOGICAL AND CARDIOVASCULAR EFFECT IN RATS AND HUMANS EXPOSED TO DIESEL EXHAUST – MIRIAM GERLOFS-NIJLAND

The paper presented results from controlled diesel engine exhaust exposure studies in rats as well as human volunteers. In rats, prolonged exposure (4 weeks, 150 $\mu g/m^3$) to diesel engine exhaust resulted in an oxidative stress response and impaired fibrinolysis and coagulation response. Inflammation was not observed and there were no changes in vascular function. The author concluded that diesel engine exhaust may aggravate neurological impairment. However, the evidence for this was weak.

Acute exposure (2 hours, 1.9 mg/m^3) at a very high level resulted in a time-dependent oxidative stress reaction, followed by an inflammatory response. Oxidative stress was preceded by a procoagulant reaction.

Human volunteers received acute exposure (1 hour, 300 $\mu g/m^3$) to diesel exhaust under controlled conditions. Brain activity was measured. Changes in brain activity were observed and the conclusion was that exposure impacted information processing in the brain. There was no basis for judging if this change was adverse. Changes in systemic blood flow were also observed.

The presenter concluded that the changes observed may not only be caused by the particles themselves, but could be associated with chemicals on the surface of particles as well.

3.6. CHRONIC (CARDIOVASCULAR) EFFECTS OF AIR POLLUTION - NINO KUENZLI

The presenter reviewed the complexity of cardiovascular disease and multiple factors that lead to it. The distinction between acute events, triggered by acute exposures to pollution or other causes (e.g. an opulent meal, stress, or sex), and the long-term development of the underlying cardiovascular pathologies is crucial in the interpretation and planning of studies. Evidence has strongly increased suggesting a causal role of air pollution in triggering myocardial infarction, strokes or arrhythmia, i.e. acute events. The role of air pollution in the development of atherosclerosis as the primary underlying pathology of cardiovascular diseases is, however, far less understood. There is a need for well designed epidemiological studies on that issue. Animal studies strongly suggest air pollutants to be atherogenic (the ability to form plaques in the inner lining of arteries). Given the important public health role of atherosclerosis and the ubiquitous exposure to air pollution human studies are now needed.

N. Kuenzli identified a number of research needs in order to better understand the impact of ambient air pollution from traffic and other sources on the chronic pathologic processes that ultimately lead to cardiovascular diseases:

1. Refine exposure assessment, including source specific approaches and methods to disentangle effects of pollution and noise;

2. Investigate various complementary markers of pre-clinical atherosclerosis;

3. Investigate chronic cardiovascular effects in both new cross-sectional and in particular cohort studies to investigate the progression of atherogenesis (the process of forming plaques in the inner lining of arteries);

4. Investigate susceptibility factors of effects of air pollution on atherogenesis;

5. Investigate biologic mechanisms to understand the epidemiological observations and develop targeted preventive strategies.

4. SUMMARY AND CONCLUSIONS

- Estimates of the cardiovascular effects of $PM_{2.5}$ alone may underestimate the public health impact of the total air pollution mixture - gaseous components of air pollution, including ground level ozone, might be a larger contributor than hitherto assumed;

- Research on health effects of particles has very much been centred on number and size. Future research should focus on particle quality (composition) and source;

- Because of the many 'confounding' factors associated with increased mortality from cardiovascular disease – focussed research is needed on exposure from air pollution in targeted populations;

- Studies investigating effects of multiple pollutants may be more informative than singling out components;

- Studies should be undertaken to clarify whether long-term residential exposure to urban air pollution stimulate the inflammatory pathways which play a significant role on the development and progression of atherogenesis;

- It is important to toxicologically characterise the emissions from "new fuels" notably biofuels (automotive and power generation) as an indication of potential long-term health effects. The research should not be limited to particles but expand to other components in (gaseous) in the emission.