Summary of Elvira Vaclavik Bräuners PhD thesis "Mechanisms of health effects of particulate matter in healthy non-smokers" defended 28.4.2008

Evaluation committee:

1. Professor Henrik E. Poulsen, M.D. dr.med. Dept of Clinical Pharmacology, Rigshospitalet, Blegdamsvej 9 (chairman)
2. Professor Benoit Nemery M.D. Ph.D., Chair Department of Public Health, Faculty of Medicine, Research Unit of Toxicology, Lab of Pneumology, Belgium
3. Professor Lennard Möller, Dept of Biosciences and Nutrition at Novum, Karolinska Institute, Huddinge, Sweden

Supervisors Professor Steffen Loft, Institute of Public Health, University of Copenhagen, and Ole Raaschou-Nielsen, Institute of Epidemiological Cancer Research, Danish Cancer Society.

There is presently consistent epidemiological evidence, indicating that increased levels of particulate air pollution (PM) leads to increased incidence of respiratory and cardiovascular morbidity and premature mortality, as well as cancer. Experimental research in humans and animals also point to the importance of adverse respiratory effects from short term particulate air exposures and long term exposure has been linked with increased risks of cancer, as well as cardiovascular and/or pulmonary disease, however mechanisms behind the translocation of PM through the lung epithelium to the systemic circulation and effects in target organs are still not fully elucidated.

The aim of this thesis was to investigate the mechanisms involved in PM induced oxidative DNA damage and systemic oxidative stress as well as effects on endothelial and lung function function, as well as alveoli integrity. Controlled exposure of healthy human volunteers at realistic concentrations was used and the fractions of air with particular significance were identified. The thesis reviews the relevant research on air pollution and the associated health effects and each chapter contains descriptions of the practical work performed and puts results obtained in this PhD in perspective with the literature. Areas covered in this PhD thesis include: 1) Characterisation, sources and exposure assessment of PM in relation to health effects assessment; 2) The epidemiological evidence of health effects; 3) The importance of the respiratory airways and potential mechanisms of translocation to other organs; and 4) The mechanisms involved in oxidative stress, inflammation, oxidative DNA damage and endothelial dysfunction.

PM is typically classified according to aerodynamic diameter and the smallest of these, ultrafine (UFP) PM, with a diameter less than 100 nm are now believed to be the most important in relation to adverse health effects. Particularly, traffic-related UFP seems relevant as indicated by both acute and long-term effect studies. The reason for UFP importance lies in their composition, size and surface area. Additionally, UFP seems to possess the ability to translocate through the epithelium of terminal bronchioles more effectively than larger particles via mechanisms that involve particle overload, inflammation and oxidative stress. Translocation of UFP has been documented using radio-labelled carbon, but this has been debated. In paper IV, we investigated the effect of ambient levels of UFP on alveoli integrity using labelled diethylenetriaminepentaacetic acid (DPTA) and plasma and urine CC16 levels. We found no evidence of altered alveoli integrity associated with the exposure to PM, this may have been due to the relatively low levels of exposure but may also reflect the general high lung integrity of the young non-smokers used.

DNA damage is considered to be an important initial event in carcinogenesis and can be caused by direct reaction with DNA forming adducts or as a consequence of oxidative stress and inflammation pathways. In paper I we investigated oxidized DNA in peripheral blood mononuclear cells (PBMC) which was central in this PhD and considered an indicator of systemic oxidative stress relevant for all outcomes studied. We found significant increases in oxidative DNA damage measured as FPG-sites in the comet assay, which are related to the oxidative guanine lesion 8-oxo-7,8-dihydro-2'deoxyguanosine (8-oxodG). This result confirms earlier results regarding exposure and oxidative DNA damage, but no previous studies have correlated damage with a particular fraction of PM. In paper I we were able to directly link these effects in DNA with sources of traffic emissions. We found highest correlations with fractions of PM having diameters of 23 (NC23)and 57 nm (NC57). The NC57 size mode mainly represents carbonaceous soot from diesel engine exhaust and represents the largest fraction of surface area, whereas the NC23 size mode represents condensed semi-volatile organic compounds from diesel vehicles. These size modes have a high deposition fraction in airways, which for hydrophobic UFP with diameter 12-64 nm was found to be above 50% in our participants and are also believed to have a high translocation.

PM has consistently been shown to have adverse effects on endothelial function in both panel and controlled chamber studies. A role of PM in reduced endogenous NO bioavailability in mediating adverse vascular effects is suggested, which may be due to either increased consumption or reduced production of NO. Risk factors including obesity, increasing age, cigarette smoke, and diabetes may enhance the effects of PM on endpoints related to CVD. In papers II and III we investigate the effects of PM exposure on endothelial function (EF) within two age groups representing different risk in light of age. All volunteers were healthy non-smokers with no family or personal history of CVD. We found significant effects of PM on endothelial function in the elderly but no effect on the young volunteers, reflecting the general consensus that age enhances the effects of PM and increases risk.

Collectively, the results of this thesis provide evidence that PM does induce effects on endothelial function in a vulnerable group (the elderly). We also find that PM induce oxidative DNA damage among young volunteers but with no apparent upregulation of defence and repair mechanisms. We found no evidence of increased biomarkers of inflammation or systemic oxidative stress possibly reflecting a lower sensitivity of the biomarkers to measure small changes, nor did we observe changes in lung blood gas barrier permeability

The PhD is based on 4 articles published in peer reviewed journals:

Bräuner EV, Forchhammer L, Møller P, Simonsen J, Glasius M, Wåhlin M, Raaschou-Nielsen O, Loft S. Exposure to ultrafine particles from ambient air and oxidative stress-induced DNA damage. Environ Health Perspect 115: 1177-1182, 2007

Bräuner EV, Møller P. Forchhammer L. Barregard L. Gunnarsen L, Afshari A, Wåhlin P, Glasius M, Dragsted LO, Basu S, Raaschou-Nielsen O, Loft S. Indoor Particles Affect Vascular Function in the Aged: An Air Filtration-based Intervention Study. Am J Resp Critical Care Med 177: 419-25, 2008

Brauner EV. Mortensen J, Møller P, Bernard A, Vinzents P, Wåhlin P, Glasius M, Loft S. Effects of Ambient Air Particulate Exposure on Blood-gas Barrier Permeability and Lung-function. Inhalation Toxicol, doi

Bräuner EV, Møller P, Barregard L, Glasius M, Wåhlin P, Vinzents P, Raaschou-Nielsen O, Loft S. No Effect of Ambient Air Fine and Ultrafine Particles on Vascular Function and Biomarkers. Particle Fibre Toxicol