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Published in:

Book of extended abstracts: 7th Intl Aerosol Conf, St. Paul, Mn, USA (2006)

2006

[Link to publication](#)

Citation for published version (APA):

Bohgard, M., Nielsen, J., Tinnerberg, H., Hagerman, I., Berglund, M., Swietlicki, E., Gudmundsson, A., Pagels, J., Löndahl, J., Nilsson, E., & Deppert, K. (2006). Methodology for studies on respiratory and cardiovascular effects of humans at occupational exposure to airborne nanoparticles. In *Book of extended abstracts: 7th Intl Aerosol Conf, St. Paul, Mn, USA (2006)*

Total number of authors:

11

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Methodology for Studies on Respiratory and Cardiovascular Effects of Humans at Occupational Exposure to Airborne Nanoparticles

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INTRODUCTION

In production environments, airborne particles have been a threat to workers' health for several hundred years. In 1713 the Italian physician Ramazzini published *De Morbis Artificum* with descriptions of health hazards in a number of different occupations. He observed, for example, that many workers who were exposed to airborne mineral particles (e.g. stone-cutters and quarrymen) got the disease we today know as *silicosis*.

Today the effects on health and environment of the increasing industrial applications of nanotechnology are addressed (Oberdorster et al., 2005). Exploitation of nanotechnology can increase emissions of nano-sized particles into the air in production, manufacturing treatment, handling, usage, waste disposal and recycling of various materials and as the result of accidents such as fires.

Awareness of the health impact of airborne nanoparticles particles is also increasing. Studies on health effects of air pollution show that airborne particles can cause a variety of diseases and are responsible for increased morbidity and mortality (e.g. respiratory and cardiovascular diseases) in polluted areas (Ezzati et al., 2002; Brook et al., 2004; WHO, 2002).

Most of the knowledge about occupational health hazards has been achieved by observations of effects on humans. The aim of this work was to develop and recommend methodology based on direct observations and measurements of effects on humans for dose-response and dose-effect determination at occupational exposures to nanoparticles. The methodology combines competence and techniques from Aerosol physics and technology, Occupational Hygiene, Occupational Medicine, Nanotechnology and Cardiology.

METHODS

The methodology includes measurements and examinations of humans in two model environments 1) Work places where significant exposures are expected to occur and 2) A controlled chamber environment for

exposure provocations. The exposure levels in the chamber are not exceeding the levels found in the subjects' places of work.

Workplace studies

Characterisation of the workplace concerning exposure to nanoparticles: The aerosol characterisation techniques include: dry particle size distributions (3-10 000 nm) measured with differential mobility analyser – condensation particle counter (DMA/CPC) and time-of-flight technique (Aerodynamic Particle Sizer, APS), hygroscopic properties with a Tandem DMA-system (20-500 nm), and filter sampling with subsequent elemental analysis and electron microscopy. An instrument RESPI (Löndahl et al. 2006) will be used to measure, on-line and in-situ, the particle dose for particle diameters 10-1000 nm, to the airways

Examination:

A) Basal examination: Volunteers of the exposed workers are asked to complete a questionnaire about symptoms from airways, the cardiovascular system, smoking habits, atopy, medical and work history. A general physical examination including pulmonary auscultation is performed. A skin prick-test with 13 common allergens is carried out. Each subject performs spirometry and those who complain of asthmatic symptoms will also be tested with methacholine.

B) Diary study: For 3 weeks after having been off work for holiday, the workers record in a diary symptoms from their eyes, airways and cardiovascular systems and results from peak-flow measurements. Before and after the diary study, the workers' are sampled blood for fibrinogen and C-reactive protein analysis. In a subgroup nasal lavage is performed and analysed for mediators and inflammatory markers (Nielsen et al., 1992).

The exposure is assessed for each individual worker based on the aerosol measurements performed and on information about work tasks during the period. The individual exposure assessment will be performed for

several variables regarding particle characteristics as well as peak and number of peak exposures.

Chamber studies

A specially designed stainless steel aerosol chamber (Pagels, 2005) with a floor area of 3x3 m² and height 2.4 m is used for controlled human provocation studies (each individual is exposed for 8 hours). Particles to be used (from work place) are generated into the chamber. Particle concentrations can be controlled as well as ventilation rate, temperature and relative humidity. Aerosol measurement systems (DMA/CPC and tandem-DMA) are connected to the chamber and are used to determine size distribution, number concentration hygroscopicity determination. Filter sampling devices are used for obtaining samples for electron microscopy and elemental analysis. The RESPI instrument is used to determine particle deposition to the airways.

Medical examinations are carried out before, after four hours, and after the provocation. Symptoms from eyes and airways are registered according to a symptom score model. Furthermore, spirometry, acoustic rhinometry, nasal lavage (Nielsen et al., 1994), induced sputum and breath condensate will be obtained. A venous blood sample is obtained before, after, and 24 hours after the provocation for analysis of fibrinogen, C-reactive protein, TNF- α and ICAM-1. From the nasal lavage and induced sputum, cells are separated for differential count and the supernatant is later analysed for markers of inflammation and mediators such as albumin, ECP, ICAM-1, Substance P, TNF- α , IL 1, and IL8. The breath condensate is also analysed for markers of inflammation.

ECG is recorded at rest. Influence of nanoparticles to affect the autonomic regulation of the heart will be studied by analysis of the heart rate variability (HRV) (Heart Rate Variability. Standards of Measurement, Physiological Interpretation and Clinical Use, 1996) Time series of ECG are collected and changes in the sympathetic and the parasympathetic nervous system are studied both in frequency and time domain. Frequency analysis of changes of HRV due to sympathetic tonus are shown in the low frequencies (0.04-0.15 Hz) and to parasympathetic tonus in the high frequencies (0.15- 0.4 Hz), where effects of respiratory frequency also can be observed.

RESULTS

Various parts of the methodology have been successfully applied for nanoparticles from combustion and thermal working processes. Preliminary results from a pilot study of HRV at exposure to an aerosol from burning candle (3-4 10⁴ particles/cm³, median diameter: 12 nm) showed changes in both low and high frequencies compared to low particle concentration.

Keywords: nanoparticles, occupational health

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The work was supported by the Swedish Council for Working Life and Social Research and the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning.