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Toxicity of metal containing micro- and nanoparticles

- Studies from an inhalation perspective

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ABSTRACT

Particles in urban environments have for a long time been associated with different health problems and diseases, such as worsening of asthma and chronic obstructive pulmonary disease as well as cancer and cardiovascular diseases. In addition, metal containing particles present in occupational settings and industries, particularly particles produced during welding, have been linked to several adverse health effects. In recent years it has also become obvious that humans get exposed to metal containing particles in subway systems although possible health effects of such exposure is unknown. Furthermore, engineered nanoparticles (often containing metals) are increasingly being used within various applications including consumer products, thus constituting a risk for human exposure. In all, this means that the exposure to metal containing particles is present in society and may increase in the future due to the increased use of nanoparticles in various products.

There is thus today a great need for more knowledge concerning toxicity of these particles. The main aim of this thesis was to investigate the toxicity and underlying biological mechanisms following exposure to different metal containing micro- and nanoparticles from an inhalation perspective.

In studies I-IV (paper I-IV), the toxicity and underlying mechanisms were investigated for a wide range of metal and metal oxide containing micro- and nanoparticles following exposure of cultured human lung cells (A549). In particular, the importance of material composition, size and ion release for induction of toxicity in terms of cytotoxicity, DNA damage, oxidative DNA damage, mitochondrial depolarisation, generation of intracellular ROS and haemolysis of red blood cells was explored. In general, there was a high variation in the toxic potential of the investigated particles and the high and size-dependent toxicity of CuO was especially highlighted in study I-II. One suggested reason for this is the release of toxic ions inside cells, facilitated by a Trojan horse like mechanism where the particles transport the ions in to the cell. The investigations of industrially relevant iron and chromium based particles revealed that ion release from these particles, in an acidic and complexing fluid, were dependent on particle size and most likely the surface oxide of the particles. Further, investigations of stainless steel (316L) in several other artificial biological fluids, with neutral and weakly alkaline pH, revealed that the ion release was only increased in the acidic and complexing fluid. The toxicity of the iron and chromium based microparticles was in general low but increased DNA damage potential of 316L and NiO nanoparticles was observed, and the latter was also confirmed in study III.

In study III (paper III), several metal containing particles were observed to have an oxidative capacity. Despite this, no considerable oxidative DNA damage was detected using the FPG comet assay. The results suggest that this may be due to interference of some of the nanoparticles with the FPG enzyme that is supposed to find the oxidative damage within the assay. Ag nanoparticles particularly inhibited the enzyme, mainly due to Ag ions.

In study V (paper V), immunological effects in healthy humans were studied during 24 hours after a 2 hour exposure to the PM rich environment of a subway station. The results indicated a small, but transient, direct inflammatory response seen as a decrease in the level of lymphocytes in blood as well as small changes in the lymphocyte subpopulation in the end of the follow-up time. In addition, an increase in DNA damage in mononuclear cells of the blood was detected in some of the subjects.

In conclusion, the results from these studies indicate that the chemical composition of metal containing particles is crucial for the toxicity of the tested particles. This thesis especially highlights toxic effects of CuO and NiO nanoparticles. Release of ions from particles may be one important factor for toxicity and this thesis shows that the release of metals ions from stainless steel particles increased in acidic pH. Additionally, interference of nanoparticles and toxicity assays may be important to consider and this thesis highlights possible interactions with FPG in the comet assay especially with Ag nanoparticles. Exposure to the air at a subway station, rich in metal containing particles, did not cause any large acute toxic effects in humans. Still, some parameters indicated that the immune system reacted to the exposure.

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