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Nanotoxicological studies in the Air-Liquid Interface using engineered metal NPs – Protein corona, gene analysis and dose response

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There is an ongoing discussion whether traditional toxicological methods are sufficient to evaluate the risk of inhalable nanoparticles. Since the use of manufactured nanoparticles is increasing, the need for toxicological data is great. There is also an increased interest in metal nanoparticles for targeted drug delivery. This has led to the emergence of Air-Liquid Interface toxicology. Here aerosol NPs are administered directly from air and deposited upon cellular cultures, or relevant media, providing a more realistic in vitro environment for toxicological studies, especially for lung deposition – one route of exposure that has been pinpointed as important in risk assessments.

This work takes on a holistic approach towards the toxicology of metal NPs. The NPs are characterized in aerosol phase with regards to both mass, size and morphology. The NPs are then deposited onto cellular cultures or into physiological media using a commercialised deposition chamber, *Nano Aerosol Chamber In Vitro Toxicity* (NACIVT), a chamber based on the work by Savi (2008). When deposited into cellular media, blood serum or into lung fluid the NPs characteristics in solution can be studied using several methods. By using UV-Vis spectroscopy the relative degree of agglomeration is determined and by using dynamic light scattering and particle tracking analysis the hydrodynamic size is determined. Upon deposition onto cellular cultures, both primary and standardized cell lines, endpoints of varying sensitivity is investigated to determine the NP effects. Cellular viability and cytotoxicity is determined using standard assays. Protein expression from the cells will be investigated in the surrounding media, cytokines, interleukins etc. In addition state of the art gene analysis techniques will be employed, both towards a whole genome perspective and single genes. The rationale is that as particles may not be directly terminal towards the cells, they still react in characteristic ways expressing various genes.

One type of NP that will be used is agglomerate and sintered silver (AgNP) generated by a spark discharge system, described by Mueller (2012). The system is capable of generating aerosols of a variety of different metal particles with different shapes properties. The aerosol is generated polydisperse as agglomerates, by using a sintering furnace the agglomerates can be compacted to varying degrees. This results in metal NP aerosols with the varying total surface areas, while retaining the same total mass.

In order to characterize a sintered AgNP aerosol it was connected to a laminar flow diluter (model 3302, TSI Inc.) and the NACIVT was coupled in parallel with a TEOM and an SMPS system. The dilution system allowed for a stable dilution up to 15 times. Also AgNP was deposited in the NACIVT on silicon surfaces for electron microscopy and determination of deposition efficiency, Figure 1A.

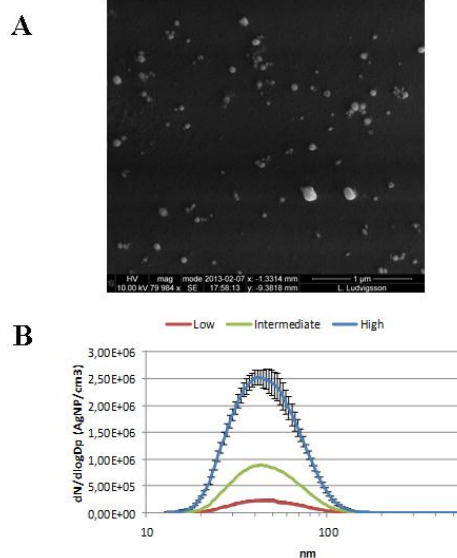


Figure 1. A) Sintered AgNPs deposited onto a SEM grid in the nacivt chamber. B) Average SMPS scan of sintered AgNP at three concentrations tested.

The cell exposures were performed at three concentration levels, exposing the cells placed in the NACIVT chamber during one hour. The SMPS system scanned the size distributions continuously, shown in Figure 1B, The AgNP aerosol was stable during the events and deposition efficiency approximately 15-20%. By TEOM the mass concentrations with std was 1520(180), 467(97) and 99(20) μg/m³.

In conclusion a stable aerosol of AgNP agglomerates was generated for exposure of cells during 1h duration, with endpoints including state of the art gene analysis and standard assays.

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