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Comment

Nanosilver: Safety, health and environmental effects and role in antimicrobial resistance

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European Commission, Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)

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Considering emerging and newly identified health risks

On request of the European Commission, the independent Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) was requested to assess whether the use of nanosilver, in particular in medical care or in consumer products, could result in additional risks compared to more traditional uses of silver and whether the use of nanosilver to control bacterial growth could result in resistance of micro-organisms. The full text of the SCENIHR Opinion is freely accessible [1]. This Comment looks at several unresolved problems that require the attention of the materials science community.

Silver (Ag) materials, including those at the nanoscale (nanosilver), are widely used today for their antibacterial activity. However, the usefulness of (nano)silver in various medical applications may be limited because of the increased resistance of micro-organisms against silver.

The various silver compounds have different physico-chemical properties, such as solubility and surface charge, which affect their fate and biological activity. There are a lot of methods for production and applications of nanosilver in food packaging materials, food supplements (currently these two applications are not allowed in the EU unless specifically authorized), dental materials, textiles, electronics, household appliances, cosmetics, medical devices, water disinfectants and room sprays.

Quantitative data on the life cycle of products containing nanomaterials is in general extremely scarce. All silver content in non-recycled waste will ultimately end up in the environment, either as solid waste in landfills; emission from wastewater treatment plants (in effluent water or in sludge); or as residual waste from incineration plants (e.g., fly ash, slag or bottom ash). No actual measurements of the incineration of nanosilver-containing products exist, but depending on the type of nanomaterial, models predict a release of 25–100% of air-borne NPs, which are effectively caught by the filter systems. In Europe, the main environmental exposure route of silver compounds in textiles and cosmetics will be through wastewater treatment plants. Measurements of nanomaterials in consumer products and their release into the environment are therefore urgently needed.

Nanosilver undergoes several transformations when it is released into the environment. After aggregation and agglomeration, the important ones are dissolution and subsequent speciation, such as formation of silver chloride and silver sulphide. Silver sulphide is particularly important because it is highly stable; sulphide is available in wastewater treatment plants and also in many freshwater bodies. The chemical species that are present determine the bioavailability and toxicity of silver in the environment. A large fraction of the silver released to freshwater bodies sorbs to suspended particulate matter and is transferred to the sediments, where it may be stored, accumulate, or undergo transformations or resuspension depending on physical, chemical, and biological conditions.

Two important points need to be taken into consideration. Firstly, not all conventional methods used to assess Ag-NP solubility are able to reflect Ag^+ availability and, secondly, assessing the dynamic interactions between Ag-NPs and biotic receptors, including the sustained delivery of Ag^+ is likely to be complex and has not yet been studied.

The main target organs for silver nano-particles (Ag-NPs) distribution after systemic availability are the spleen, liver and kidney.

1369-7021/ http://dx.doi.org/10.1016/j.mattod.2015.02.014

Recent data indicate that some persistence of Ag may occur in the brain and testes. For distribution of silver to the brain it is not clear whether the silver is present in the brain tissue or limited to the endothelium of the brain.

There is some evidence that ionic Ag may form silver structures at the nanoscale *in vivo*. Presence of Ag in feces after intravenous and subcutaneous administrations indicates biliary excretion of Ag originating from parentally administered Ag-NPs.

A limitation of toxicokinetic studies on nanosilver is that most of them used inductively coupled plasma mass spectrometer (ICP-MS) or Atomic absorption spectrometry (AAS) for detection of the Ag, so it cannot be definitively concluded that Ag-NPs are distributed to the organs, since all nanoparticles need to be completely dissolved to run the analytical assays. Nevertheless, more detailed studies suggest uptake in cells/organs through a combination of cellular uptake routes like ion transportation and endocytosis of particles. This would give rise to a delivery route for Ag-NPs that is different from what is known for dissolved species of silver and will thereby constitute a 'nano-specific' exposure.

In vitro studies show that cytokine production in macrophages can be induced by nanosilver. *In vivo* studies could not clearly show whether oral exposure to silver nanoparticles consistently results in alterations of the non-specific immune responses. *In vitro*, several of the studies reported genotoxic effects of nanosilver. The controversial results may be explained by differences in Ag-NP coating/shapes, cell type used, the cellular uptake, intracellular dissolution, genotoxicity endpoint, and the way the cells were exposed. As the studies available on the *in vivo* genotoxicity of Ag-NPs are few and concern Ag-NPs of variable characteristics, further studies are required to conclude whether Ag-NPs could be genotoxic *in vivo*. The possibility of secondary genotoxic effects associated with inflammation and oxidative stress induced by silver nanoparticles has not been studied.

The mode of action of silver is mainly attributed to the release of silver ions. Ionic silver has a broad spectrum of antimicrobial activity against planktonic and sessile bacteria and it is generally considered to interact with multiple microbial target sites – microbial proteins – with eventually structural and metabolic disruption. Ag-NP properties may also account for some bacterial toxicity effect.

There is evidence of an effect of Ag-NPs on the composition of bacterial flora and on the bacterial adaptation associated with certain conditions and uses. Similar to ionic silver, bacterial resistance has been demonstrated for Ag-NPs as well. However, evidence is often fragmentary and focused on a few specific cases. There is a paucity of information on the resistance mechanisms to Ag-NPs. Exposure to ionic silver and Ag-NPs produces a stress-response and affects gene expression.

More data is needed to better understand bacterial response to ionic silver and Ag-NPs exposure. Regarding the hazard associated with the dissemination of a resistance mechanism following the use of Ag-NPs, no documentation is currently available, representing a serious gap of knowledge.

Further reading

[1] http://ec.europa.eu/health/scientific_committees/emerging/opinions/index_en.htm.