

NTP Research Concept: Nanoscale Silver

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Nomination Background and Rationale

The U.S. Food and Drug Administration nominated nanoscale silver (n-Ag) for study by the National Toxicology Program (NTP) based on (a) increasing widespread use in drug, food and cosmetic products, and (b) the general lack of data on the toxicology and pharmacokinetics of these materials (<http://ntp.niehs.nih.gov/go/29287>). In addition, the U.S. EPA recently requested manufacturers of n-Ag containing devices to provide information regarding environmental fate and environmental impact.

The potential for human exposure may be through manufacturing, use of home sanitizing kits, or use of consumer products containing n-Ag (clothing, textiles). In addition, intentional exposure may occur through ingestion of colloidal silver or use of n-Ag in wound dressings. n-Ag is being included in these products because of the well-known activity of ionic silver as an antibacterial and antifungal agent. Nanoscale elemental silver (Ag^0) can be ionized to ionic silver (Ag^+). The ionized form Ag^+ has been used as an antimicrobial for many years; e.g. silver nitrate used for treatment of eyes of newborns, and silver sulfadiazine used in wound dressings. n-Ag has a higher surface than non-nanoscale Ag^0 and it is being used as an alternate source of Ag^+ since it is able to produce a more sustained release of Ag^+ .

There are several forms of silver to which individuals may be exposed. These include silver salts, e.g. silver nitrate, silver chloride; silver sulfadiazine; colloidal silver protein complexes (formed by mixing silver nitrate, sodium hydroxide and gelatin); metallic silver; and colloidal silver, which may contain both nanoscale Ag^0 and/or dissolved ionic Ag^+ .

Most toxicological information is available for silver salts, and is based on studies of silver nitrate, silver chloride, and silver acetate. Little information is available for well-characterized n-Ag. In general, silver (as silver salts) exhibits low acute toxicity. The most sensitive human response to silver is the “cosmetic” condition argyria, an irreversible blue-grey discoloration of the skin and mucous membranes associated with application or ingestion of silver-containing compounds, that results from precipitation of elemental silver in the skin as result of UV photoreduction of ionic silver. Current guidelines for permissible levels of Ag in water (0.1 mg/L) are based on argyria in humans. Case reports note that ingestion of colloidal silver preparations over long periods results in argyria in humans. “Colloidal” silver may be primarily n-Ag, whereas in other cases it may be primarily Ag^+ , depending upon how it is made. For the case reports of argyria induced by “colloidal silver”, it is not known if these colloidal preparations were primarily n-Ag or contained significant quantities of ionized Ag^+ .

The relationship between particle sizes, ionization to Ag^+ and comparative absorption, distribution, metabolism and elimination (ADME) of n-Ag and Ag^+ *in vivo* is not known.

While silver nitrate and other silver salts may be useful surrogates for the potential toxicity of Ag^+ formed from ionization of n-Ag, there is insufficient data to evaluate whether the potential toxicity of n-Ag is due solely to the production of Ag^+ or if there are effects of n-Ag itself. With regard to longer term exposure to well-characterized n-Ag, there are no adequate data on carcinogenicity, immunotoxicity, neurotoxicity, reproductive toxicity, developmental toxicity, or the potential role of particle size on the development of any adverse response.

Key Issues

For nanoscale materials the dose metric related to observed effects is a key issue. Some studies have shown that surface area-based metrics may be more appropriate for the comparison of potency of pulmonary toxicity of some metal oxides. While this may not be applicable to all nanoscale materials or all routes of exposure, it indicates that other dose metrics that scale with physicochemical properties, rather than the mass of nanoscale material, should be considered in the interpretation of dose-response data. Consequently, experimental approaches may require the comparative analysis of multiple forms of a given nanoscale material of similar composition but with varying in particle size, coatings, shape, or other physicochemical parameters.

Proposed Approach

Hypotheses to evaluate:

- The toxicity profile of n-Ag is the same as that of Ag^+ .
- The pharmacokinetics of n-Ag is the same as for silver salts such as silver nitrate.
- Differences in potency of different sized particles of n-Ag are due to the relative differences in ionization to Ag^+ .

Specific Aims:

Phase 1

- Use Ag^0 of at least three sizes spanning from <10 nm to > 100 nm and thoroughly characterize the relationship between primary particle size and ionization to Ag^+ *in vitro* and in biological media.
- Conduct comparative pharmacokinetic and tissue disposition studies of at least two sizes of Ag^0 (including <10 nm to > 100 nm) and one Ag^+ species (e.g. silver nitrate as a highly ionized silver salt) in rodents (rats and mice) after multiple routes (i.e. oral, intravenous and dermal) of administration. Tissue analyses should include quantitative evaluation of Ag^0 and Ag^+ , and, if feasible, localization of Ag^0 and Ag^+ within tissues.

Phase 2

- Evaluate the comparative effects after repeated exposures in rodents (rats and mice) using two particle sizes of nanoscale Ag^0 and one Ag^+ species, under similar exposure concentrations of expected Ag^+ *in vivo*. Studies should include an evaluation of potential systemic toxicity and organ specific toxicity and potential toxicity to the immune and nervous systems.

Phase 3

- Evaluate the comparative effects of chronic oral exposure to two nanoscale Ag^0 particle sizes including *in utero*/perinatal exposure under conditions of similar mass dose and expected internal Ag^+ dose.

Significance and Expected Outcome

While the extent of human exposure to nanoscale silver has not been quantified, the increasing use of nanoscale silver in consumer products increases the probability that a larger number of individuals will be exposed. Additionally, there are known exposures where individuals intentionally ingest nanoscale silver dietary supplements or receive treatment with medical devices containing nanoscale silver. The intent of the NTP Nanotechnology Safety Initiative (<http://ntp.niehs.nih.gov/go/nanotech>) is to understand the potential adverse effects of nanoscale materials before widespread exposure has occurred, and thus provides further justification for this research program. Information from these studies may be used by regulatory agencies such as the FDA, U.S. EPA and CPSC in their interpretation of the potential adverse biological and toxicological events associated with exposure to nanoscale silver or products containing nanoscale silver.