BSC Nomination Review

Meeting of the National Toxicology Program
Board of Scientific Counselors

National Institute of Environmental Health Sciences
Rall Building, Rodbell Conference Center
Research Triangle Park, NC

June 22, 2007

NTP Study Nomination: Nanoscale Silver

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BSC Reviewer: Drs. Jim Riviere and Martin Philbert

1. Does the NTP research concept address the needs of the nomination?

Yes. This is a well-reasoned and sound nomination based on the increasingly common and widespread use of nanometer-sized Ag^0 (hereinafter, nano-Ag^0) in consumer and healthcare products. Uses of nano-Ag^0 include fashion textiles and fabrics (reducing odor and permitting multiple uses of the article of clothing prior to laundering), microbiocidial water filtration units, hydrosols and hydrogels for application to fabrics and food preparation surfaces, refrigerators and washing machines, cleansing applications, sterilization and wound-healing applications, electronics and communications, pigments and paints, agriculture, cosmetics, soft drinks, footwear, coatings and films, packaging, and various military/defense applications. The major question needed to be answered is if the nanostructure of silver imparts different pharmacokinetic and/or toxicological properties compared to soluble forms of silver (salts) to which humans have been exposed for centuries. Since it is the form of the Ag that is primarily being assessed, the *in vitro* characterizations suggested in Phase I are excellent. The reviewers assume that results of the pharmacokinetic and tissue disposition studies in the second part of Phase I (rats, mice after oral, dermal and IV administration) will provide the information needed to design rational toxicological studies in Phases II and III. It is important to quantify and localize Ag^0 and Ag^+ in tissue. It would also be important to assess agglomeration state of absorbed nano-Ag^0 and Ag^+ in plasma and tissues using electron microscopy. Pending the knowledge gained from these ADME studies, the systemic toxicology studies proposed are excellent. It is important to select an appropriate soluble form of silver as a control against purely nanostructure effects. The results of these studies should allow a proper experimental design for the Phase III studies. The reviewers urge the NTP to assess the results obtained from the proposed Phase I studies in the context of data collected on carbon nanotubes, C_{60} Fullerenes, carbon black and other nanometer scale materials to optimize the experimental design for subsequent studies.

2. Is the proposed study approach as outlined in the research concept document appropriate in scope given the merit of the nomination? Are there other studies that should be considered for this substance?

Yes. The proposed study covers most of the considerations of dose, route and anticipated outcome. The following are offered for consideration:

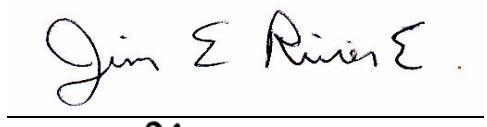
i. The document does not address the respiratory route of exposure which is likely to be the most common occupational encounter with nano-Ag^0.
ii. Attention should be paid to the mucosae, especially those that subtend commensals and potentially pathogenic microflora.
iii. It is suggested that there be the inclusion of a nanoparticle control, or at the very least, comparison to existing NTP data on the ADME and toxicology of other well-characterized nanomaterials with similar and/or dissimilar properties.
iv. Since one of the major applications for nano-Ag^0 is in the formulation of dressings and bandages, it is suggested that special attention should be paid to the application of this material to damaged skin.
v. Maintenance of the strong historical focus on physical characterization of the nanomaterial to be used and, to the extent possible, the description of aggregation, agglomeration or other flocculation of the nanoparticle in dosing solutions, cells, tissues and organs.
vi. Since Ag, Au and other nanomaterials exhibit strong plasmonic behaviors, there should be consideration of the effects of sunlight/radiation on exposed dermal surfaces following systemic exposure to nano-Ag^0.

3. Does the proposed research program address an important area of biomedical research (e.g. children's health, genetic susceptibility, specific environmental disease) and/or advance the field of environmental health sciences?

Yes. The field of nanotoxicology is in its infancy and it is crucial that we understand the rate limiting properties of nanomaterias that make their ADME and/or toxicity different than their non-nanoscale traditional chemical counterparts.

4. Do the nomination and proposed research program merit NTP evaluation and if so, what priority (low, moderate, or high) should it be given?

HIGH

Reviewer's Signature: 

Date: July 12, 2007