

Prior to initiating the testing of a substance, an NIEHS/NTP staff scientist develops a research concept document. This research concept outlines the general elements for a program of study of the substance to address specific research needs raised in its nomination to the testing program.

Additional information about the nomination, review, and selection of substances for study by the NTP is provided from *Nominations to the NTP Testing Program* (<http://ntp.niehs.nih.gov/go/nom>).

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### **NTP Concept Document: Nanoscale Cerium Oxide**

The National Toxicology Program (NTP) is developing a broad-based research program to address potential human health hazards associated with the manufacture and use of nanoscale materials. This initiative is driven by the intense current and anticipated future research and development focus on nanotechnology.

Cerium oxide is used in the petroleum refining industry (catalytic cracking catalysts), glass products, polishing powder, ceramics, crystals (e.g., for lasers and garnets), phosphors, automotive catalytic converters, as an additive to promote combustion of diesel fuels, as a pigment in dermatological preparations, and in nanoparticulate form as a carrier for otic and ophthalmic compositions. More recently nanoscale cerium oxide has been proposed as a fuel additive for diesel power vehicles to increase fuel efficiency. Potential exposure from nanoscale cerium oxide used in diesel fuels has been reviewed by the Health Effects Institute. These data suggest there may be an increase in ambient cerium oxide particles in air (currently approximately 1 ng/m<sup>3</sup>) in areas of high traffic to levels of >1 µg/m<sup>3</sup>.

In a 13 week nose only inhalation study of cerium oxide (MMAD 2.0±1.9 µm) conducted by Bio-Research Laboratories for Rhone-Poulenc Inc (CD rats, male/female, n=15 per group, 5/50/500 mg/m<sup>3</sup>, 6 hrs/day, 5 days/week) in both sexes there were statistically significant lung weight increases, concentration-related metaplasia of the larynx, and alveolar epithelial hyperplasia for mid- and high-dose; pigment accumulated in lungs at all doses; and significant increase in lymphoid hyperplasia in bronchial lymph nodes that correlated with pigment volume. The human equivalent LOEL derived from this study was 1 mg Ce/m<sup>3</sup>. Using uncertainty factors of 3000, TERA developed a human equivalent RfC for ambient air concentrations of 0.3 µg Ce/m<sup>3</sup> using data from this study.

There have been no toxicological evaluation of nanoscale cerium oxide and no adequate studies in mice for evaluating inhalation hazard. Given the concern that nanoscale metal oxides, may be more toxic per unit mass than microscale metal oxides (due to the increase surface area per unit mass), the potency of toxicity of nanoscale CeO<sub>2</sub> may be greater per unit mass. Consequently a human equivalent RfC for nanoscale cerium oxide may be considerably lower than seen in the BRL study and far lower than that predicted to occur from use of nanoscale cerium oxide as a diesel additive.

As part of the NTP's Nanomaterial Safety evaluation, the project leader presented a concept to evaluate the comparative pulmonary and systemic toxicity associated with exposure to microscale and nanoscale cerium oxide (CAS 1306-38-3). It was proposed to develop a broad based research project to evaluate the comparative inhalation toxicity of nanoscale and microscale cerium oxide, together with evaluations of in vivo kinetics and tissue disposition. These studies should provide sufficient dose response information to conduct an effective comparative quantitative risk assessment for inhalation exposure to nanoscale cerium oxide. In addition it was

proposed to include evaluations of effects on the immune, neurological, and cardio-pulmonary systems.

Some key issues were discussed during the review:

- Concern that a comparative study may be ceric oxide specific and not provide any generalizable information applicable to other nanoscale materials and /or other lanthanide class metals.
- Concern about the uncertainties about the types and form of nanoscale and microscale ceric oxides in use or in the environment after combustion and that for commercial application, industry should develop the safety data.
- Uncertainties about what is known and unknown about current and potential exposures in occupational settings, around mining and manufacturing sites, in cosmetics and as a proposed diesel additive
- Debate over the relative importance of studying nanoscale cerium oxide alone vs a more complete series of studies on both nanoscale and microscale cerium oxide as a representative under the same study design

Based on the discussion, the Concept Review Group made the following recommendations:

1. Approval of development of a limited series of prechronic pulmonary inhalation studies with nanoscale ceric oxide, including standard measures of histopathology, analysis of biomarkers of inflammation in bronchioalveolar lavage fluid, and analysis of ceric oxide lung burden and clearance.
2. That proposed immunological studies, evaluation of immunohistochemical markers of neurotoxicity, cardiovascular endpoints, and pulmonary function studies should be discussed by the study design team for possible inclusion and may be valuable endpoints to include.
3. Not to conduct studies of microscale ceric oxide even though it was recognized that this would provide a valuable publicly available comparison of well-characterized micro and nanoscale materials. It was noted that comparisons could still be made to the already published study of microscale ceric oxide.

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