

# **Chemical Information Profile**

**for**

## **Ceric Oxide [CAS No. 1306-38-3]**

**Supporting Nomination for Toxicological Evaluation by the  
National Toxicology Program**

**February 2006**

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*Prepared for*  
National Toxicology Program  
National Institute of Environmental Health Sciences  
National Institutes of Health  
U.S. Department of Health and Human Services  
Research Triangle Park, NC  
<http://ntp.niehs.nih.gov/>

## Data Availability Checklist for Ceric Oxide [1306-38-3]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat

Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

ENDPOINT	H	M	R	L
<b>ADME</b>				
Absorption	✓	✓	✓	
Distribution	✓		✓	
Metabolism				
Excretion	✓			
<b>Acute Toxicity (up to 1 week)</b>				
Dermal				✓
Inhalation/intratracheal instillation	✓		✓	
Injection				
Ocular				
Oral				
<b>Subchronic Toxicity (1 to &lt;26 weeks)</b>				
Dermal				
Inhalation			✓	
Injection				
Oral				
<b>Chronic Toxicity (≥26 weeks)</b>				
Dermal				
Inhalation	✓		✓	
Injection				
Oral				
<b>Synergism/Antagonism</b>				
Synergistic effects			✓	
Antagonistic effects			✓	
<b>Cytotoxicity</b>				
Cytotoxic effects			✓	
<b>Reproductive Toxicity</b>				
Fertility effects				
Maternal effects				
Paternal effects				

ENDPOINT	H	M	R	L
<b>Developmental Toxicity</b>				
Developmental abnormalities				
Embryonic/fetal effects				
Newborn effects				
<b>Carcinogenicity*</b>				
Dermal				
Inhalation		✓	✓	
Oral				
<b>Anticarcinogenicity</b>				
Anticarcinogenic effects				
<b>Genotoxicity</b>				
Cytogenetic effects			✓	
Microbial gene mutation			✓	
Gene mutation <i>in vitro</i>				
Gene mutation <i>in vivo</i>				
Germ cell effects				
<b>Neurotoxicity</b>				
Behavioral activity				
Motor activity	✓		✓	
<b>Immunotoxicity</b>				
Immunotoxicity			✓	
<b>Mechanistic Data</b>				
Target Organs/Tissues	✓	✓	✓	
Endocrine modulation				
Effect on enzymes				
Modes of action			✓	
Effect on metabolic pathways				
<b>Structure-Activity Relationships</b>				
		✓	✓	

\*using <sup>144</sup>CeO<sub>2</sub>

## Ceric Oxide Nomination Summary

**Chemical Name:** Ceric Oxide

**CAS RN:** 1306-38-3

**Formula:** CeO<sub>2</sub>

**Molecular Wt.:** 172.12



**Basis for Nomination:** Ceric oxide (microscale and nanoscale forms) is nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicological characterization due to widespread and expanding industrial uses, limited toxicity data, and a lack of toxicological studies for nanoscale ceric oxide. Ceric oxide is used in petroleum refining (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 ceric oxide has been used as a fuel additive for diesel powered vehicles to increase fuel efficiency. Potential exposure from nanoscale ceric oxide used in diesel fuels has been reviewed by the Health Effects Institute (HEI, 2001). These data suggest there may be an increase in ambient ceric 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 subchronic inhalation toxicity study of microscale ceric oxide, there were significant increases in lung weights, concentration-related metaplasia of the larynx, and alveolar epithelial hyperplasia for mid- and high-dose male and female rats. The human equivalent Lowest Observable Effect Level (LOEL) derived from this study was 1 mg Ce/m<sup>3</sup>. Using data from this study and an uncertainty factor of 3000, a human equivalent Reference Concentration (RfC) of 0.3 μg Ce/m<sup>3</sup> was developed (TERA, 1999). Intratracheal instillation of fine particles of CeO<sub>2</sub> (size not given) induce primary lung lesions (i.e., pulmonary fibrosis and alveolar proteinosis and granulomas) but coarse particles did not.

No toxicological studies of nanoscale ceric oxide are available, and there are no adequate studies in mice for evaluating the potential inhalation hazard of either nanoscale or microscale ceric oxide. Given the concern that nanoscale metal oxides may be more toxic per unit mass than microscale metal oxides (due to the larger surface area per unit mass), the toxicological potency of nanoscale ceric oxide may be greater per unit mass. Consequently a human equivalent RfC for nanoscale ceric oxide may be considerably lower than 0.3 μg Ce/m<sup>3</sup> and far lower than that predicted to occur from the use of nanoscale ceric oxide as a diesel additive.

Ceric oxide is recommended for inhalation toxicity studies, together with evaluations of chemical disposition and toxicokinetics. Studies of both the microscale and nanoscale forms are recommended to test the hypothesis that nanoscale ceric oxide may be more potent than microscale ceric oxide.

### A. Chemical Information

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#### *Molecular Identification*

**Chemical Name:** Ceric oxide

**CAS RN:** 1306-38-3

**Synonyms:** Cerium oxide (9CI); Cerium dioxide; Cerium(IV) oxide; Cerium oxide; Ceria

**Trade Names:** Opaline, Platinum Trent, Polishing Opaline, Regipol 1100, Trent Std./SSSS, and Ultratrent. Other trade names for products containing <90% CeO<sub>2</sub> are available in the Registry record and at <http://www.reliabletechniques.fsnet.co.uk/CERIUM4.html>.

**Hill Formula:** O<sub>2</sub>Ce

**Line Formula:** O=Ce=O

**Smiles Notation:** CeO<sub>2</sub>

**Molecular Weight:** 172.12

**PubChem CID:** [73963](#)

**InChI:** 1/Ce.2O/rCeO2/c2-1-3

**Salts:** Dissolution as Ce(III) salts of mineral acids requires the presence of a reducing agent. There are a number of cerium(III) salts.

**Purity of Commercial Products:** Specific products listed above contain >90% CeO<sub>2</sub>. Cerium-rich bastnasite (bastnaesite; bastnäsite) concentrate (CAS RN 68909-13-7) contains ~46% CeO<sub>2</sub> and other light lanthanide oxides ([Molycorp, Inc., 1992](#)); pure CeO<sub>2</sub> (99 – 99.999%) is also sold ([Metall Rare Earth Ltd., 2004](#)). Commercial rare earth (RE) oxide polishing powders may have considerably lower CeO<sub>2</sub> contents.

**Additives in Commercial Products:** Not available

**Impurities in Commercial Products:** Other lanthanides

**Mammalian Metabolites:** Not available

**Biodegradation Products:** Not available

**Environmental Transformation:** Diesel emissions may contain CeO<sub>2</sub> (major), Ce sulfate, or Ce phosphate. Cerium is expected to persist in soil and sediments ([HEI, 2001](#)) due to its ion-exchange positions or associated with carbonates, organic matter, and iron and manganese oxides/hydroxides (preference for the latter two forms at pH ≥7) (Pang et al., 2002; [PMID:12008295](#)). Plant root uptake is correlated with the fraction in ion-exchange positions (Zhang and Shan, 2001; [PMID:11291446](#)).

#### *Physical-Chemical Properties*

**Physical State:** Solid; cubic, face-centered crystals. Sold as white, yellow (usually), or tan powders; may also be sold as nanoparticles ([Molycorp, Inc., 1992](#); [Reade Advanced Materials, 1997a,b](#))

**Specific Gravity or Density Value:** 7.28 g/cm<sup>3</sup> ([Molycorp, Inc., 1992](#)); Bulk density 1500-2500 kg/m<sup>3</sup> ([IUCLID, 2000](#))

**Boiling Point:** Not available (melts at 2500-2600 °C)

**Vapor Pressure:** Not available

**Solubility:** Not soluble in water or organic solvents ([IUCLID, 2000](#))

**Particle size:** Ambient air cerium is associated with the fine and ultrafine particles (<2 μm). The particle sizes of ceric oxide polishing powders are in the low-micrometer range (e.g., 0.45 to 6 μm) ([Trent Mann Products, Ltd., 2005](#); [Metall Rare Earth Ltd., 2005](#)).

**Log P = Log K<sub>ow</sub>:** Not available

**Bioconcentration Factor(s) (species):** 0.0009 (plants from soil with high rare earth element [REE] content) (ICRP, 1979; cited by Bulman, 2003); <5.5 (from plants to snails); 10,000-100,000/kg dry matter (plants and snails relative to surface water) (Weltje et al., 2002; [PMID:11887873](#)). The [IUCLID \(2000\)](#) dataset did not include information about bioaccumulation.

– Lanthanide biota-sediment accumulation factors in the Rhine-Meuse Estuary in the Netherlands were higher for larger ions (e.g., Ce<sup>3+</sup> and La<sup>3+</sup>) [values not given in abstract] (Moermond et al., 2001; [PMID:11521817](#)). Uptake decreased with increased alkalinity but was independent of pH and salinity.

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- REEs added to agricultural soil at <10 kg/ha did not significantly accumulate in the grain of maize plants (Xu et al., 2002; PMID:12109484). REEs are currently added to agricultural soils in China at a rate of <0.23 kg/ha/year.

### **B. Exposure Potential**

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#### ***U.S. Annual Production***

1986: 10,000-500,000 pounds (U.S. EPA, 2005 [[U.S. EPA IUR database](#); search by chemname for cerium\*])

2002: [Exempt from IUR reporting ([ChemIDplus, 2004](#))]

Bastnaesite:

>1-10 million pounds – cerium rich, acid-insoluble fraction [CAS RN 68909-12-6]

>10-50 million pounds – calcined concentrate [CAS RN 68909-13-7]

(U.S. EPA, 2005 [[U.S. EPA IUR database](#); search by chemname for bastnaesite\*])

#### ***Worldwide Annual Production***

~35,000 tons produced as part of the overall lanthanide oxide production, but only a small fraction is actually separated as a pure derivative ([Molycorp, Inc., 1992](#)). About 95% of all REE use is in mixed forms such as mischmetal and the cerium-rich bastnasite concentrate.

#### ***Production Processes***

Lanthanide ore is crushed, ground in a ball mill, and subjected to froth flotation without or with a hydrochloric acid leach to give a concentrate with 60 or 70% lanthanum oxides, respectively. Selective leaching gives the cerium-rich, acid-insoluble bastnasite concentrate (62% CeO<sub>2</sub>), which may be further processed by extraction, oxidation, reduction, and precipitation to give pure CeO<sub>2</sub> ([Molycorp, Inc., 1992](#); [Weese, 2004](#)).

#### ***Uses***

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 ([Hedrick \[USGS\], 2002](#); [HEI, 2001](#); [HEI, 2003](#); [Metall Rare Earth Ltd., 2004](#); [nGimat, 2005](#); [Rhodia Electronics and Catalysis, undated](#)). Recent patents on CeO<sub>2</sub> use in cosmetics include coatings of particle size 10 to 500 nm for metal pigments (Kaupp et al., 2004 pat. [German]); UV-scattering agent with average particle size <0.1 µm for nonirritating lipsticks (Kawamoto and Tanabe, 2005 pat. [Japanese]); and as the matrix for antibacterial or bacteriostatic compositions (example particle size 4 µm) for silver, copper, or zinc particles as the active ingredient for cosmetics or hygiene products (Baret, 2005 pat. [French]).

#### ***Occupational Exposure***

25,130 workers (13,436 females) were potentially exposed to CeO<sub>2</sub> in three industrial categories and 11 job categories including electrical and electronic technicians (17,417 [8,599 females]); grinding, abrading, buffing, and polishing machine operators (2,946 [2,448 females]); and optical goods workers (2,188 [2,448 females]) ([NIOSH National Occupational Exposure Survey 1981-1983](#)).

Exposure was confirmed by autopsy of workers with and without pneumoconiosis and workers who used carbon arc lamps or lens grinders. One subject who worked for 46 years in the engraving industry and was diagnosed with interstitial pneumoconiosis had cerium concentrations in the lungs and lymph nodes that were 2000- and 50-fold higher, respectively, than those of persons not exposed to cerium ([HEI, 2001](#)). Ce, La, and Nd concentrations in the lungs of a printer exposed to carbon arc lamp emissions were higher than those in the lungs of 41 workers who had died of cancer (Dufresne et al., 1994; PMID:8085148).

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### Exposure Limits (Standards and Criteria)

There are no standards or criteria specifically for cerium or ceric oxide. The values given here, (TLV) or regulated (OSHA PEL), are for particulates not otherwise classified.

ACGIH TLV: 10 mg/m<sup>3</sup> time weighted average (TWA) inhalable particulate containing no asbestos and <1% crystalline silica  
3 mg/m<sup>3</sup> TWA (respirable particulate)

NIOSH REL: None

OSHA PEL: 15 mg/m<sup>3</sup> TWA (total dust)  
5 mg/m<sup>3</sup> TWA (respirable fraction)

### General Population Exposure

#### Foods and Beverages, Cosmetics, etc.

Food Tolerance Levels: Not available

Drinking Water Limits: Not available

Other Exposure Limits: Not available

Average Daily Intake: 7.9 µg/day based on 2.9 mg/yr (calculated based on fecal ash concentration of 11 New Yorkers) (Linsalata et al., 1986; [PMID:3943969](#))

Dietary Intake Estimates: 0.006-0.24 mg/day (adult human diet in Sweden [country with REE deposits] (Wester, 1971; cited by Bowen, 1982)

Cosmetics: Ceric oxide is mentioned in nearly 300 U.S. cosmetics patent applications since 2001 (<http://www.uspto.gov>)—e.g., L'Oreal, Maybelline, and Anna Sui ([EWG, 2005](#) [product IDs = 907044, 907801, and 904395, respectively]).

#### Ambient Environment

Air Limit: [0.3 µg/m<sup>3</sup>; RfC from [TERA \(1999\)](#)]

Water Limit(s): Not available

Soil Limit: Not available

Environmental Exposure Estimates (U.S.): Hazard quotients (HQs) indicated a potential for respiratory effects due to lanthanide metals (chiefly cerium and lanthanum) for residents living in the area of a bastnasite ore mining and processing operation in San Bernardino County, California. For example, the noncancer HQ for lanthanide exposure of a school-age resident in the baseline scenario was 1.1 and the total of all respiratory HQs was 1.6 (Tetra Tech, Inc., 2001).

#### Levels in Tissues, Body Fluids, and Excreta

Tissue (e.g., heart, lung, liver, kidney, testis, ovary), hair, and nail values were <1 ppm. Lymph node concentrations and cerebrospinal fluid may be an order of magnitude higher. Blood concentrations were reported in the parts-per-billion range. Urinary excretion was estimated to be up to 36 µg/day (Bulman, 2003; Inagaki and Haraguchi, 2000 [[PMID:10885074](#)]; Iyengar et al., 1978; Linsalata et al., 1986 [[PMID:3943969](#)]; Rodushkin and Axelsson, 2000 [[PMID:11059839](#)]; Volokh et al., 1990 [[PMID:2169646](#)]).

### Environmental Occurrence

**Natural Occurrence**: Cerium (60 ppm) is more abundant in the earth's crust than other lanthanides. Soils and roots of plants in the vicinity of monazite deposits may be enriched with cerium and other lanthanides. Cerium-containing minerals include allanite; bastnasite, (Ce,La)(CO<sub>3</sub>)F; cerite; euxenite; fergusonite; loparite; monazite, (Ce,La,Nd,Th)PO<sub>4</sub>; and xenotime. The lanthanide oxides contain 30% CeO<sub>2</sub> ([HEI, 2001](#); [Christie et al. \[USGS\], 1998](#); [Molycorp, Inc., 1992](#); Ure and Berrow, 1982).

#### U.S. Environmental Releases

##### Toxics Release Inventory

- Air: Not available
- Water: Not available
- Land: Not available
- Other (specify): Not available

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Industries Represented: Not available

Number of Facilities: Not available

*Hazardous Waste Sites:* Yes \_\_\_ No X No. of Facilities \_\_\_

*Industrial Releases (non-TRI substance):* Average cerium concentrations estimated in waste streams at the Mountain Pass, CA mine and mill site were 2-5% with maximums up to ~26% ([California Regional Water Quality Control Board, Lahonton Region, 2004](#)).

*Mobile Sources:* Fuel containing CeO<sub>2</sub> nanoparticles may raise ambient air concentrations of CeO<sub>2</sub>, sulfate, or phosphate in heavily trafficked "street canyons" to ~1.25 µg/m<sup>3</sup> at a height of 1 m.

- Cerium emissions estimated from operation of a diesel engine burning 50 ppm CeO<sub>2</sub> in the fuel for one hour was 1.74 ng Ce/m<sup>3</sup> in non-filtered samples (particulate trap) and 0.4 ng/m<sup>3</sup> in filtered samples ([HEI, 2001](#)). Escape from the trap during a 15-min regeneration period was 4.7 ng Ce/m<sup>3</sup>.
- Emission factors for fuel containing 100 ppm CeO<sub>2</sub> have been calculated to be 0.3 to 3.3 mg/km, depending on vehicle type ([HEI, 2001](#)).
- In tests with a Pt/Ce catalyst (0.5 ppm Pt and 7.5 ppm Ce in the diesel fuel), filtered emissions had 4.7 µg Ce/bhp-hr and 1.1 µg Pt/bhp-hr (brake-horsepower hour) (Clean Diesel Technologies, Inc., [2001](#), [2002](#) slides).
- It is estimated that by 2010 cerium emissions from use of diesel fuel in the European Union could total 1.3 million pounds annually (worst-case scenario: 22 million pounds) ([HEI, 2001](#)).
- Cerium concentrations to a depth of 10 cm in soil within 10 m of a roadway may be increased by 5-30 µg/g within 40 years ([Rauch et al., 2000](#)).

*Municipal and Hospital Waste Incineration:* The mean cerium concentration found in bottom ash from incineration of various wastes was: food scrap – 8.57 ppm, animal waste – 23.5 ppm, horticultural wastes – 27.3 ppm, sewage sludge – 35.4 ppm, and municipal waste – 24.6 ppm (Zhang et al., 2001a; [PMID:11757853](#)).

### Concentrations in Environmental Media

*Surface Water:* Individual REE concentrations in surface waters and sea water are at or below the low parts-per-trillion (pg/mL, ng/L) level [no concentrations given] (Rao and Biju, 2002).

*Groundwater:* Pore wastewater collected between 1967 and 2002 leaked from a closed landfill unit at the Molycorp Mountain Pass Mine and Mill site and contaminated the groundwater. The mean cerium concentration in the wastewater (~67 million gallons) was 0.935 mg/L (0.024-1.700 mg/L) ([California Regional Water Quality Control Board, Lahonton Region, 2004](#)).

*Industrial Wastewater:* See groundwater above.

*Municipal Waste/Sewage:* Cerium was never detected in class D municipal and nonmunicipal landfill leachate or wastewaters in a U.S. survey ([U.S. EPA, 1998](#)). Mean cerium concentration in sewage sludge ash in Japan was 35.4 ppm (Zhang et al., 2001a; [PMID:11757853](#)).

*Ambient Air:*

- San Francisco Bay Area: 1.3-5.5 ng Ce/m<sup>3</sup> ([HEI, 2001](#))
- Pasadena, California: 0.43 ng Ce/m<sup>3</sup> in fine particles (<1.8 µm in diameter) and 0.19 ng Ce/m<sup>3</sup> in ultrafine particles (<0.097 µm) ([HEI, 2001](#))
- Osaka, Japan: Semi-rural area, 4.3 ng Ce/m<sup>3</sup>; urban residential area, 5.6 ng Ce/m<sup>3</sup>; and "metropolitan" area, 11 ng Ce/m<sup>3</sup> ([HEI, 2001](#))
- Russia: Vicinity of a phosphate fertilizer plant, 10.2 ng/m<sup>3</sup> at 200 m from the source, 3.8 ng/m<sup>3</sup> at 2000 m, and 3.6 ng/m<sup>3</sup> at 2500 m. Forty-five percent of the particles were 0.03 to 2 µm, 43% were 2 to 8 µm, and 12% were >8 µm in diameter (Volokh et al., 1990; [PMID:2169646](#)).

*Soils:* Mean concentration for 924 soils: 84.2 ppm lanthanides (range: 9.8-300 ppm). Soils near a heavily trafficked roadway in Great Britain contained 47-136 ppm Ce and soils in a rural area contained 38 ppm ([HEI, 2001](#)).

### C. Toxicological Information

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#### *General Toxicity*

**Human Toxicity:** RE pneumoconiosis has been reported in several case studies of workers exposed to ceric and other RE oxides via inhalation. [Note: Many of the workers were also exposed to silicates or carbon black ([HEI, 2001](#)).]

- At least 20 cases of pneumoconiosis in photoengravers and projectionists exposed to RE oxide fumes from carbon arc lamps (Knight, 1994).
- Endomyocardial fibrosis in a population in southern India may be linked to high cerium (from monazite deposits) and low magnesium in the diet ([HEI, 2001](#)).
- Children near a phosphate fertilizer plant in Russia, who were exposed to cerium concentrations decreasing from 10.2 ng/m<sup>3</sup> at 200 m to 3.6 ng/m<sup>3</sup> at 2500 m were 1.5 times more likely to have respiratory diseases, chronic inflammation of the tonsils, etc. (Volokh et al., 1990; [PMID:2169646](#)).

#### *Chemical Disposition, Metabolism, and Toxicokinetics*

**Absorption and Clearance:** Skin absorption is negligible (poorly soluble in water and body fluids). When inhaled as CeO<sub>2</sub>, cerium precipitates in the lysosomes of alveolar macrophages as insoluble phosphates in fine needles or granules. Lung clearance rate is measured in years. Mucociliary movement clears insoluble particles in the alveolar region to the gastrointestinal (GI) tract, the lymph nodes, or systemic circulation. Clearance is ~99% from the nasopharyngeal and tracheobronchial regions and 80% from the lungs. Residual insoluble materials are primarily cleared to the tracheobronchial lymph nodes.

- Approximately 90% of insoluble cerium in lymph nodes is cleared to the blood; only 1-5% is absorbed from the deposition sites.
- Approximately 10% of absorbed cerium is excreted in the feces and urine with retention of 45% in the liver, 35% in the skeleton, and 10% in other organs (primarily, the spleen and kidneys).
- In the blood, cerium complexes with proteins or forms phosphate, hydroxide, and carbonate compounds in colloids. If the binding capacity of the protein transport system is not overwhelmed, cerium is transported to the liver and bones. If the system is overwhelmed, such as with i.p. dosing, colloidal aggregates form at the delivery site and are then distributed to the liver and spleen.
- Excretion mechanisms have not been elucidated ([HEI, 2001](#)).

**Human Studies:** The less-soluble forms of inhaled cerium (e.g., ceric oxide) may remain in the lung and lymph nodes for years. Cerium deposits were found in the alveoli and interstitial tissue of an optical lens grinder 20 years after exposure to CeO<sub>2</sub> powder particulates (<1 - 10 μm); some cerium deposits were also found inside the cells. REs were also found in granules in the tracheobronchial lymph node macrophages and liver Kupffer cells of a movie projectionist exposed to RE oxides from a carbon arc lamp ([HEI, 2001](#)).

**Animal Studies:** Several inhalation experiments with <sup>144</sup>CeO<sub>2</sub> have shown similar pulmonary clearance rates in rats, hamsters, and mice while in dogs the rate was slower. Absorption of moderately soluble cerium compounds was <0.1% in adult rodents but higher in newborn rodents. Repeated doses increased retention half-times ([HEI, 2001](#)). Specific studies of absorption by the GI tract were not available. REEs in the bloodstream partition preferentially in the microsomes of liver cells. Ce, La, and Gd primarily partitioned into the nuclear fraction then the cell membrane of liver cells treated *in vitro* with REEs. At least three cerium-binding proteins have been identified in liver cells of rats given cerium intravenously (Chai et al., 2004).

#### *Acute Toxicity*

LC<sub>50</sub>/LD<sub>50</sub> Values: inhalation LC<sub>50</sub> >50 mg/m<sup>3</sup> (rats) [[HEI, 2001](#)]  
oral LD<sub>50</sub> = 622 mg/kg bw (female mice) [[HEI, 2001](#)]  
oral LD<sub>50</sub> >5000 mg/kg bw (rat) [RTECS, 2003]  
i.p. LD<sub>50</sub> = 465 mg/kg (mice) [RTECS, 2003]



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i.p. LD<sub>50</sub> >1000 mg/kg bw (rats) [[IUCLID, 2000](#)]  
dermal LD<sub>50</sub> >2000 mg/kg bw (rats) [[IUCLID, 2000](#)]

Route: intratracheal instillation  
Species: rat  
Dose/Duration: not provided/single dose  
Observation Time: 180 days  
Effects: no acute or subchronic pulmonary effects observed compared to those of Nd<sub>2</sub>O<sub>3</sub> and Y<sub>2</sub>O<sub>3</sub>  
Source(s): Otaki et al. (2003; CA 140:1737 [Japanese]); Toya et al. (2003; CA140:1736 [Japanese])

Route: intratracheal instillation  
Species: rat  
Dose/Duration: 50 mg/single dose  
Observation Time: 8 months  
Effects: granulomatosis nodules, giant cells, fibrosis, and pneumoconiosis; lower degree of fibrotic changes compared to those of Nd<sub>2</sub>O<sub>3</sub> and Y<sub>2</sub>O<sub>3</sub>  
Source(s): Mogilevskaya and Raiklin (1963 [CA 60:12564] or 1967 [the English translation]); more details in Haley (1991; [PMID:1955325](#)) and [IUCLID \(2000\)](#)

Route: dermal application  
Species: rabbit (New Zealand albino, male)  
Dose/Duration: 0.5 g powder in water (paste)  
Observation Time: 24, 48, and 72 hours  
Effects: not irritating  
Source(s): [IUCLID \(2000\)](#)

Route: dermal application  
Species: rabbit (New Zealand albino)  
Dose/Duration: 0.5 g/once to one abraded and one intact site under occlusion  
Observation Time: 24 and 72 hours  
Effects: not irritating  
Source(s): [IUCLID \(2000\)](#)

Route: eye instillation  
Species: rabbit  
Dose/Duration: 0.1 g  
Observation Time: ≥24 hours  
Effects: not irritating  
Source(s): [IUCLID \(2000\)](#)

Route: eye instillation  
Species: rabbit (New Zealand albino)  
Dose/Duration: 0.1 g/ one of treated eyes followed with a 30-second rinse  
Observation Time: 24, 48, and 72 hours  
Effects: slightly irritating  
Source(s): [IUCLID \(2000\)](#)

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### ***Subchronic Toxicity***

Route: inhalation  
Species: rat  
Dose/Duration: not provided (aerosols)  
Observation Time: not provided  
Effects: TC<sub>LO</sub> = 100 mg/m<sup>3</sup> at 2 hours intermittently for 30 days  
TC<sub>LO</sub> = 50 mg/m<sup>3</sup> at 6 hours intermittently for 30 days  
Source(s): RTECS (2003)

Route: inhalation  
Species: rat  
Dose/Duration: 10-50 mg/m<sup>3</sup> intermittently for 17 weeks  
Observation Time: not provided  
Effects: changes in liver and respiratory organ function and gas exchange  
Source(s): Tarasenko et al. (1974; CA 82:150059 [Russian])  
Note: TC<sub>LO</sub> = 50 mg/m<sup>3</sup> (RTECS, 2003)

Route: inhalation (nose-only)  
Species: rat  
Dose/Duration: 5, 50, or 500 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks  
Observation Time: not provided  
Effects: Males - statistically significant increase in relative spleen weight (food consumption and body weight gain lagged slightly)  
Both sexes - 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  
Source(s): [Rhône-Poulenc Inc. \(aka Rhodia\) \(1995\)](#) [details from [TERA \(1999\)](#) and TSCA test submission OTS0556219 abstract from the U.S. EPA web site; [IUCLID \(2000\)](#); and [HEI \(2001\)](#)]

Intratracheal instillation of coarse particles of CeO<sub>2</sub> in rat lung did not induce primary lung lesions but finer particles did (sizes not given in CAPLUS abstract). Pulmonary fibrosis and alveolar proteinosis and granulomas were the typical lesions. The persistent effects were described as subchronic (Takaya et al., 2005). Based on Ce content described by Bio-Research Laboratories for inhalation experiments, a NOAEL of 0.41-0.43 mg Ce/m<sup>3</sup> was determined for alveolar epithelial hyperplasia and of 0.55 mg Ce/m<sup>3</sup> for increased lung weight. The LOAEL for minimal bronchial lymph node metaplasia was 0.85 mg/m<sup>3</sup> in males and 0.82 mg Ce/m<sup>3</sup> in females (equivalent to ~1.0 mg CeO<sub>2</sub>/m<sup>3</sup>). Using an uncertainty factor of 3000, an inhalation reference concentration (RfC) of 0.3 µg/m<sup>3</sup> was derived for CeO<sub>2</sub> ([TERA, 1999](#)).

### ***Chronic Toxicity***

Not available

### ***Synergistic/Antagonistic Effects***

In the review of cerium pharmacology, Jakupec et al. (2005; PMID:[15674649](#)) noted that Ce(IV) salts are not biologically stable in aqueous media at pH above 3. Therefore cerium species that circulate in the blood as colloidal compounds or protein complexes likely contain Ce(III). The close similarity of the ionic radii of Ce<sup>3+</sup> (1.01 Å) and Ca<sup>2+</sup> (1.00 Å) allows Ce<sup>3+</sup> (and other light Ln<sup>3+</sup> ions) to replace Ca<sup>2+</sup> ions in biomolecules.

### Antagonistic/Inhibitory Activities

- The hepatotoxicity induced by trivalent cerium compounds is inhibited by compounds such as phenobarbital that induce drug-metabolizing enzymes. Trivalent cerium protected the liver from carbon tetrachloride-induced hepatotoxicity (Evans, 1990).
- $\text{Ln}^{3+}$  ions are well known inhibitors of  $\text{Ca}^{2+}$ -dependent physiological processes such as those involved in blood clotting (e.g., prothrombin activation) and neuronal and muscular functions. Trivalent cerium compounds inhibit active transport of  $\text{Ca}^{2+}$  through mitochondrial membranes, calcium and potassium channels, calcium-dependent hemolysis in burn patients, calcium-dependent enzymes, and contractility in cardiac, skeletal, and smooth muscle (e.g., intestinal) (Jakupec et al., 2005; PMID:[15674649](#)).
- Possible connection between cerium toxicity/magnesium deficiency and endomyocardial fibrosis (Brown et al., 2004; PMID:[15275858](#); Eapen et al., 1996; PMID:[8720088](#)). The combination has promoted fibrogenesis in rat heart (Kumar et al., 1996; PMID:[8694866](#)). Cerium had an inhibitory effect on protein synthesis in cultured cardiac myocytes and lung fibroblasts exposed to normal- and low-levels of  $\text{Mg}^{2+}$  (Shivakumar and Nair, 1991; PMID:[2051999](#)).

### Synergistic/Additive Effects

Clear synergistic effects of  $\text{Ce}^{3+}$  have not been reported; however,  $\text{Ce}^{3+}$  compounds have the following activities (Jakupec et al., 2005; PMID:[15674649](#)):

- Enhanced currents through type A gamma-aminobutyric acid-activated chloride channels of rat dorsal root ganglion neurons.
- When bound to calmodulin,  $\text{Ce}^{3+}$  "mediated intracellular responses to  $\text{Ca}^{2+}$  ion fluxes in a cooperative manner."
- Substitutes for  $\text{Ca}^{2+}$  ions in calcium/calmodulin-dependent enzymes such as phosphorylase kinase.
- Enhances epinephrine and norepinephrine release from the adrenal medulla in the presence of calcium ions (Evans, 1990).

### Cytotoxicity

Rat alveolar macrophages *in vitro*:

- least cytotoxic lanthanide tested ( $\text{LC}_{50} = 4740 \mu\text{M}$ ) compared to  $\text{CeCl}_3$  ( $\text{LC}_{50} = 29 \mu\text{M}$ ),  $\text{CdCl}_2$  ( $\text{LC}_{50} = 28 \mu\text{M}$ ),  $\text{LaCl}_3$  ( $\text{LC}_{50} = 52 \mu\text{M}$ ), and  $\text{La}_2\text{O}_3$  ( $\text{LC}_{50} = 980 \mu\text{M}$ )
- increasing concentrations eliminated cell surface features
- 1000  $\mu\text{M}$   $\text{CeO}_2$  altered cell morphology in 15% of the macrophages ([HEI, 2001](#)).

Guinea pig macrophages *in vitro*: low cytotoxicity (Zou et al., 1992; CA 118:53788 [Chinese])

### Reproductive and Developmental Toxicity

**Human Studies:** Not available

**Animal Studies:** Not available

### Carcinogenicity

**Human Studies:** Not available

**Animal Studies**

- Single or repeated inhalation exposures to  $^{144}\text{CeO}_2$  produced lung tumors in mice while only one mouse in the control group (exposed to stable  $\text{CeO}_2$ ) developed a pulmonary neoplasm (Lundgren et al., 1975; TOXLINE NIOSH/0015530).
- 83 rats exposed by inhalation once every 60 days for 1 year (7 exposures) to  $^{144}\text{CeO}_2$  developed 101 lung tumors compared to a tumor incidence of 4.0% in sham-exposed controls and 7.5% of the controls exposed to 11 and 22  $\text{mg}/\text{m}^3$  of stable  $\text{CeO}_2$  (mass median aerodynamic diameter 0.9-2.2  $\mu\text{m}$ ). [This was not significantly different from the incidence in unexposed controls ([HEI, 2001](#)).]

### Anticarcinogenicity

Trivalent cerium compounds have antiproliferative effects in tumor cells *in vitro* and tumors *in vivo* (Jakupec et al., 2005; PMID:[15674649](#)).

### **Genetic Toxicity**

**Microbial Gene Mutation:** Negative in Ames test (*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP2uvrA) at 1-5,000 µg/plate ([CCRIS, 1993](#) [search Record No. 2288]; [IUCLID, 2000](#); Shimizu et al., 1985 [CA 105:1998])

**Human Studies (*in vitro* and *in vivo*):** Not available

**Animal Studies (*in vitro* and *in vivo*)**

**Gene Mutation:** Not available

**Cytogenetic Effects:** Negative in murine bone marrow micronucleus test at 2000 mg/kg bw [Note: The dose may have been inadequate to elicit a response due to low absorption] ([HEI, 2001](#); [IUCLID, 2000](#)).

**Germ Cell Effects:** Not available

### **Neurotoxicity**

**Human Studies:** Zhu et al. (1997; [PMID:9258470](#)) reported subclinical nervous system damage in Chinese subjects living in an RE area measured by somatosensory evoked potential but not by auditory brainstem response (cerium was not specifically mentioned).

**Animal Studies:** Female rats exposed to 500 mg CeO<sub>2</sub>/m<sup>3</sup> in the Rhodia 13-week subchronic study showed reduced forelimb grip strength, but no other clear behavioral effects were noted (e.g., changes in motor-activity count or in functional observations) ([HEI, 2001](#)).

### **Immunotoxicity**

**Human Studies:** Not available

**Animal Studies:** CeO<sub>2</sub> was negative in the rat popliteal lymph node proliferation assay when injected s.c. into the foot pad at doses of 0.35, 3.5, and 35 mg/kg bw. When 300 mg/kg bw was injected intradermally into the abdominal skin and 150 mg/kg bw was injected s.c. into a foot pad, IgE levels did not increase and no lymph node histopathology was noted other than accumulation of fine granulated material and discoloration ([HEI, 2001](#)). The bronchial and mediastinal lymphoid hyperplasia observed in the Rhodia 13-week inhalation study ([HEI, 2001](#); [Rhône-Poulenc, Inc., 1995](#)) may have been a nonspecific response to the high particle loading rather than an antigenic response ([HEI, 2001](#)). Ceric oxide (50% dilution in an intradermal injection) was not sensitizing in the guinea pig maximization test ([IUCLID, 2000](#)).

### **Immunomodulatory Effects**

Trivalent cerium protects against the systemic inflammatory response in burn patients, inhibits the edematous inflammatory response induced by inflammatory agents, interferes with functions of epidermal Langerhans cells (inhibits Ca<sup>2+</sup>/Mg<sup>2+</sup>-dependent ATPase), inhibits functions of the reticuloendothelial system such as phagocytic activity of hepatic Kupffer cells, and inhibits histamine release from basophil granulocytes (Jakupec et al., 2005; [PMID:15674649](#)).

## **D. Mechanistic Data**

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An in-depth review of the mechanisms of action of the lanthanides (generally based on activities of the salts and chelates) is available in *Biochemistry of the Lanthanides* by Evans (1990). [Note: Cerium is not listed in the index, and only the chapter on clinical applications was retrieved and examined.]

### **Target Organs/Tissues**

**Human:** Lungs, lymph nodes

**Animal:** Lungs, lymph nodes, liver, skeleton, spleen, and kidney (sites of accumulation)

### **Endocrine Modulation**

**Human:** Not available

**Animal:** Not available

### **Effect on Enzymes**

Information on effects of lanthanides on enzymes is available from Evans (1990).

**Human:** Not available

**Animal:** Not available

### *Modes of Action*

**Human:** Not available

**Animal:** In the lungs, cerium may induce replacement fibrosis after tissue damage. Alternatively, other cell types that release inflammatory factors may be involved. In some cases, particulate overload may be involved. Cerium (0.5  $\mu\text{M}$ , species not identified) was associated with intracellular production of reactive oxygen species in rat cardiac but not pulmonary fibroblasts *in vitro* (Nair et al., 2003; PMID:12972691). Long-term effects from inhalation of stable lanthanides compared to those of radioactive species could not be interpreted as a benign pneumoconiosis in animals or humans (Haley, 1991; PMID:1955325).

**Effect on Metabolic Pathways:** Information on effects of lanthanides on cellular metabolism is available from Evans (1990), but  $\text{CeO}_2$  was not specifically identified.

**Activation:** Not available

**Perturbation:** Not available

### *Structure-Activity Relationships*

**Isomers:** Not available

**Congeners:** Not available

#### **Oxides of Other Lanthanides**

- All of the lanthanides with a valence of 3 have similar chemistry and low acute toxicity. However, their atomic and cationic radii decrease with increasing atomic number, leading to some dissimilarity (Haley, 1965 [TOXLINE NIOSH/00066547]; Hirano and Suzuki, 1996 [PMID:8722113]). Taylor and Leggett (2003; PMID:14526955) constructed a generic biokinetic model to derive parameters for each of the lanthanides.
- Lanthanum(III) ions (ionic radius 1.061 Å) are well known as participating in calcium-ion-mediated physiological reactions because of similar size (calcium ion radius 0.99 Å) (Hirano and Suzuki, 1996 [PMID:8722113]; Knight, 1994). The ionic radii of cerium(III) (1.034 Å), neodymium (0.995 Å), and praseodymium (1.013 Å) (EnvironmentalChemistry.com, 2005) are closer than that of La(III) and might be expected to replace calcium ions in the body as well.
- TERA (1999) developed an inhalation RfC for  $\text{Gd}_2\text{O}_3$  of 2  $\mu\text{g}/\text{m}^3$ , higher than that for  $\text{CeO}_2$  (0.3  $\mu\text{g}/\text{m}^3$ ). Toxicities of the lanthanides are often compared to those of yttrium compounds, with the latter being more toxic. Because of differences in oxidation state, toxicities of other lanthanide oxides and yttrium oxide are not considered here.

**Oxides of Other Tetravalent Metals:** Ceric compounds are chemically more similar to compounds of zirconium, titanium, and thorium. Because of radiological issues, thorium dioxide (thoria), a known human carcinogen, is not included in this discussion.

**Zirconium Dioxide:** Zirconium oxide ( $\text{ZrO}_2$ ) may be more similar to  $\text{CeO}_2$  than titanium dioxide (titania) based on its crystal structure (Sobukawa, 2002). Studies reviewed by Smith and Carson (1978) indicated that  $\text{ZrO}_2$  distribution in rats, mice, and guinea pigs after endotracheal injection and inhalation is similar to that observed with  $\text{CeO}_2$ . Rats that inhaled  $\text{ZrO}_2$  showed no clinical signs of toxicity; histological examination showed plethora of the lungs, perivascular edema, and insignificant plethora of the internal organs. Four months after a single endotracheal exposure, rats showed a mild fibrotic reaction; at 8 months fibrosis was more pronounced and regions of moderate emphysema were observed.

**Titanium Dioxide:** Titanium dioxide has three crystal structures (Wikipedia, 2006), none of which resembles that of  $\text{CeO}_2$ . Ultrafine particles of  $\text{TiO}_2$  instilled into the lungs of rats were more harmful than fine  $\text{TiO}_2$  particles, inducing more epithelial injury, polymorphonuclear leukocyte recruitment, and cytotoxicity (Renwick et al., 2004; PMID:15090666). In 13-week inhalation studies with ultrafine  $\text{TiO}_2$  particles, animals showed species differences in lung responses. Hamsters were able to clear the highest dose, 10  $\text{mg}/\text{m}^3$ , while mice and rats showed particle overload (Bermudez et al., 2004; PMID:14600271). Pigmentary  $\text{TiO}_2$  inhalation by rats, mice, and guinea pigs of 10-250  $\text{mg}/\text{m}^3$  for 90 days caused the most severe reactions in rats with progressive alveolar metaplasia and fibroproliferative responses at the highest dose (Bermudez et al., 2002; PMID:12388838). In a two-

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year inhalation experiment, rats showed increasing severity of lung responses at doses from 10 to 250 mg TiO<sub>2</sub>/m<sup>3</sup>. Alveolar cell hyperplasia and cholesterol granulomas were pronounced at the highest dose (Lee et al., 1985; TOXLINE NIOSH/0015098). Cystic keratinizing squamous cell carcinomas developed from metaplastic squamous epithelium, an effect presumed to be unique to rats (Lee et al., 1986; TOXLINE NIOSH/00164417). Lung tumors were found only in rats exposed to the highest concentration (Trochimowicz et al., 1988; TOXLINE NIOSH/00184490).

**Reactive Moieties:** Not available

### E. Nanoscale Ceric Oxide

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#### *Properties*

##### **Relative to larger particles of the same substance**

- Surface area-to-volume ratio increases with decreasing size
- Higher chemical reactivity and interactions in intermixed nanomaterials in composites, resulting in higher strength and resistance to heat and chemicals
- Lower temperatures needed to produce coatings
- Transparency if particle size is below the critical wavelength of light

##### **Variations**

- Properties vary depending on the manufacturer, method of preparation, and particle size (a narrow range of particle size is preferred).
- KIA, Inc. ([2000a,b](#)) sells CeO<sub>2</sub> nanoparticles (cubic nanocrystals) that have an average size of 11 nm, a specific surface area (SSA) of 55 - 95 m<sup>2</sup>/g, and a bulk density of 0.25 g/cm<sup>3</sup>.
- [NanoScale Materials, Inc. \(undated\)](#) produces CeO<sub>2</sub> nanocrystallites up to 7 nm in size, with a SSA >50 m<sup>2</sup>/g, an average pore diameter of 70 Å, and total pore volume of at least 1 cm<sup>3</sup>/g.
- Combining nanoparticulates of CeO<sub>2</sub> with those of zirconium dioxide (zirconia) and/or oxides of samarium, lanthanum, or praseodymium and doping them with other metals improves the overall properties. For example, zirconia increases thermal stability (NTC, 2003a-f); doping CeO<sub>2</sub> with zirconium or copper improves its ability to store and release oxygen ([Brookhaven National Laboratory, 2005](#); [Cerulean International, Division of Oxonica, 2004](#); [Fox, 2004](#)).
- Particle shape (rod-like or spherical) of nanoscale CeO<sub>2</sub> doped with 20 mole percent of zinc or calcium cations and prepared by a "soft solution chemical route" at 40 °C was dependent on pH during oxidation of precipitated cerium (III) hydroxide to CeO<sub>2</sub>. The product had smaller particle size (2-4 nm) and lower catalytic activity for oxidation of castor oil (a common sunscreen and lip balm ingredient) than ultrafine zirconium dioxide or titanium dioxide (also widely used in sunscreens) (Yabe and Sato, 2003).
- Ceric oxide doped with calcium ions absorbed ultraviolet light and was transparent in visible light (Yabe and Sato, 2003).

#### *Producers/Suppliers*

The following are U.S. producers/suppliers of nanoscale CeO<sub>2</sub> products unless otherwise specified. The year of the source information and references to other sources of product information are given.

- [Altair Nanomaterials, Inc. \(2002\)](#)
- [AMR Technologies \(2004\)](#); [Oger \(2002\)](#) (Canadian with U.S. sales office)
- [Applied NanoWorks \(2004\)](#)
- [Cerulean International, Division of Oxonica \(2004\)](#); [Fox \(2004\)](#) (United Kingdom)
- Kemco International Associates, Inc. (KIA) ([2000a,b](#))
- [MarkeTech International, Inc. \(2005\)](#)
- [Meliorum Technologies, Inc. \(2004\)](#)
- [NanoGram Corporation \(2005\)](#)
- Nanophase Technologies Corporation (NTC) (2003a-e)
- [Nanoscale Materials, Inc. \(undated\)](#)

## Chemical Information Profile for Ceric Oxide

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- [QinetiQ Nanomaterials, Division of Tetronics Ltd. \(2004\)](#) (United Kingdom)
- [Reade Advanced Materials \(1997b\)](#)
- [Rohm and Haas Electronic Materials \(2004\)](#) (sells dispersions of products produced by NTC)

### **Production Processes**

**Ceric Oxide:** There are numerous production processes for nanoscale CeO<sub>2</sub>. Solution methods for producing pure CeO<sub>2</sub> or CeO<sub>2</sub> doped with transition metals, RE metals, or metal ions include coprecipitation, hydrothermal, microemulsion, sol-gel, solution-combustion, electrochemical, solid-state reaction, mechanochemical (e.g., precipitation followed by ball milling), chemical vapor deposition, sputtering, and "pyrolysis" of organic acid metal salt solutions in a methane-oxygen flame ([Chu et al., 2004](#)).

- [KIA, Inc. \(2000a\)](#) produces nanoscale CeO<sub>2</sub> by a Physical Vapor Synthesis process; cerium is vaporized from a composite and condensed by rapid cooling with oxygen. Weak agglomerates in the micrometer range are dispersed to give a typical-particle size distribution of "a few nanometers to a few hundred nanometers."
- [NanoGram Corporation \(2005\)](#) uses a laser pyrolysis technology (see also [Kambe et al., 2003 pat. appl.](#)) [NTC \(2004 press release\)](#) produces multi-ton quantities of nanoscale CeO<sub>2</sub> and other RE metal oxides by a plasma arc synthesis process.
- Nanoparticulate CeO<sub>2</sub> was also formed by a microemulsion method at annealing temperatures above 623 °K; trivalent cerium was present at lower temperatures (Zhang et al., 2001b; PMID:11512840).

### **Coated Nanoparticulates and Dispersions**

- Nanophase Technologies Corporation supplies a dry powder form of nanoparticulates entirely encapsulated with various substances using a proprietary process to make them completely compatible with hydrophobic to very polar systems. To produce aqueous dispersions, a high electrostatic charge is maintained by controlling conditions, with or without added dispersants, so that the nanoparticles repel each other. Nonionic stabilizers are added to organic dispersions (solvents and resins) ([NTC, 2003f](#)).
- Cerulean International coats its nanoparticulate (10 nm) CeO<sub>2</sub> (Envirox™) with dodecylsuccinic anhydride so it will immediately disperse when added to diesel fuel and remain dispersed during storage and pumping of fuel ([Fox, 2004](#)).

### **Uses**

- Nanoparticulate CeO<sub>2</sub> has been used in the semiconductor industry for years in chemical-mechanical polishing/planarization (CMP) and is on the market for use as a diesel fuel additive to reduce combustion particulates ([Willems & van den Wildenberg, 2004](#)). CMP is used to polish insulating layers and copper circuit paths in the newer microchips ([DeGussa Advanced Nanomaterials, 2003](#)).
- The Cerulean International diesel additive, Envirox™, will be used by the United Kingdom in a 7000-bus fleet starting in 2005 ([Stuart, 2005](#)). Some materials currently used in catalytic converters for gasoline-powered vehicles approach the nanoscale size range. For example, the cerium oxide/zirconium oxide used in the Actalys™ catalytic converter has a surface area of 20-60 m<sup>2</sup>/g ([Rhodia Electronics and Catalysis, undated](#)).
- Other uses for nanoparticulate CeO<sub>2</sub> that are being studied include catalysts for chemical scrubbers, nanoparticle coatings, electrodes and electrolytes in fuel cells, and reactive dopants for glass to improve photostability (NTC, 2003a-f; [NanoScale Materials, undated](#)). NanoGram researchers have patented polymer composites including nanoparticulate CeO<sub>2</sub> for electro-optical devices ([Kambe et al., 2003 pat. appl.](#)). [AMR Technologies Inc. \(2005\)](#) is developing nanosized CeO<sub>2</sub> material to be evaluated for use in cigarettes that emit low sidestream smoke. Several U.S. patent applications mention that inventors from Philip Morris USA, Inc. (e.g., Zhang, 2003 pat. appl.) are also using nanoparticulate CeO<sub>2</sub> in developing cleaner burning, lower carbon monoxide-emitting cigarettes. Cerium dioxide/zirconium oxide fibers have been incorporated in the cigarette

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paper/wrapper, tobacco, and/or filter (Snaird, 2004 pat. appl.). Use in sunscreen cosmetic preparations is also being considered (Yabe and Sato, 2003).

### **Potential Human Exposure and Health Effects**

Sources and pathways for entry of nanoscale CeO<sub>2</sub> into the environment are anticipated to be similar to larger scale CeO<sub>2</sub> and will depend on specific applications and waste disposal methods. In general, release of nanoparticles from products in which they have been fixed or embedded are expected to be low; recommendation that manufacturers assess this potential has been made ([Royal Society, 2004](#)). Workers producing and handling dry powders, dry aggregates that disperse in solution, and consolidated powders (granules) have greater potential for dermal and inhalation exposure than workers producing and handling dispersions. Potential exposure from use in diesel fuels has been reviewed ([HEI, 2003](#)). Future use of nanoparticulate CeO<sub>2</sub> in cosmetics, such as sunscreens, would lead to more widespread exposure to the general population. The nanoparticulate form of a material (e.g., TiO<sub>2</sub>) may be more toxic than larger particles of the same material due to the presence of transition metals on the surfaces of some nanoparticles, promoting release of free radicals in contact with body tissues, or the larger surface area and its ability to generate oxidative stress ([Royal Society, 2004](#)). Borm and Kreyling (2004; [PMID:15503438](#)) reviewed the toxicological hazards of inhaled nanoparticles (particles less than 100 nm in diameter) used as drug carrier systems (specific carriers not identified in the abstract). Nanoparticulate CeO<sub>2</sub> may be better absorbed from the GI tract as suggested by greater absorption (34%) of 50-nm polystyrene particles by rats compared to absorption of 100 nm particles (26%) (Jani et al., 1990; [PMID:1983142](#)).

### **Toxicity Studies**

Absorption, Distribution, Metabolism, and Excretion: Uptake of CeO<sub>2</sub> nanoparticles *in vitro* by human lung fibroblasts from the culture media was found to depend chiefly on particle size for particles in four size fractions (20-50 nm [size fraction I], 40-80 nm [II], 80-150 nm [III], and 250-500 nm [IV]) and was linear over time. Nanoparticle number density and total particle surface area had little effect on the outcome. The particles in size fraction I agglomerated in the cell culture; this fraction was taken up by the fibroblasts to a lesser extent and more slowly than the fractions containing larger particles. Uptake of the size fraction I particles was diffusion controlled, while transport of the largest fraction was limited by sedimentation. At the low, physiologically relevant CeO<sub>2</sub> concentrations used (100 ng/g to 100 µg/g [100 ppb to 100 ppm]), physical transport to the cell surface was slower than cellular uptake. In the biological fluids, surface charge distribution, which tends to keep nanosized particles dispersed, was dominated by protein adsorption (Limbach et al., 2005; [PMID:16382966](#)).

Antagonistic Effects: Ceric oxide nanoparticles protected almost 99% of normal human breast cell lines from radiation-induced cell death but had little effect in MCF-7 human breast tumor cells (Tarnuzzer et al., 2005; [PMID:16351218](#)). Pre-incubation with nanoceria particles protected rat pup retinal neurons from hydrogen peroxide-induced reactive oxygen species *in vitro* (Chen et al., 2005 abstr.).

Cytotoxicity: At physiological pH (6-8), CeO<sub>2</sub> nanoparticles have a strong electrostatic attraction for the negatively charged surface of bacteria up to a concentration of 8 mg Ce/m<sup>2</sup>. In suspensions of 8-nm CeO<sub>2</sub> nanoparticles, *E. coli* covered with 1 mg Ce/m<sup>2</sup> lost 50% of their ability to divide; with 13 mg Ce/m<sup>2</sup>, >95% of the ability was lost. During adsorption, Ce(IV) was reduced to Ce(III) (Thill et al., 2005).

Neurotoxicity: Bailey et al. (2005 abstr.; laboratory of B. Rzigalinski) reported increased longevity in cultured rat nerve cells when treated with nanoparticulate CeO<sub>2</sub> (2-10 nm), even when exposed to ultraviolet light. The protective effect was hypothesized as being due to regenerative free radical scavenging.



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### **Search Strategy**

Searches begun in November 2004 included Internet searches using the search engine Google and searches at specific government web sites (U.S. Geological Survey; U.S. EPA Substance Registry System, TSCA Test Submissions Database [TSCATS], and [TSCA] Inventory Update Registry database; U.S. FDA; and NIOSH). Other sites searched included the site [www.inchem.org](http://www.inchem.org), which indexes documents from many World Health Organization and European groups, and the web sites of U.S. producer Molycorp, Inc. and producers of polishing powders and nanoparticulate ceric oxide. Since toxicity reviews were located during these efforts, formal database searches were done only as the need arose to fill information gaps. Before focus was narrowed to ceric oxide, PubMed searches in early

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December 2004 sought information on the occurrence of lanthanides in environmental media and biota. By January 10, ceric oxide inhalation studies were sought in TOXLINE and toxicity studies on both cerium(IV) and cerium(III) oxides were sought in CAPLUS (cerium oxide studies are not always distinguishable unless CAS RNs are added to the indexing). Some PubMed (MEDLINE) searches to fill information gaps in late January 2005 combined the terms ((cerium OR ceric) AND oxide\*) OR (ceria NOT ceria [au]) with the following terms:

brain	magnes*	calcium OR calci*	coagula*	anticoagula*
enzym*	inhibit*	inactivat*	deactivate*	receptor*
synergis*	antagonis*	plaque	soluble	solubi*

Later searches in PubMed and TOXLINE looked for toxicity information for titanium dioxide to include in a discussion of structure-activity relationships. In March 2005, the focus was on nanoparticles, so the cerium oxide terms were combined in PubMed with (nanop\* OR nanom\* OR nanoc\* OR nano OR nm). In Google searches, "cerium oxide" OR ceric oxide were combined with nanoparticles OR nanoparticulate(s) OR nanomaterials OR nanophase OR nanospheres.

For the January 30, 2006 update, the databases MEDLINE, NIOSHTIC, CABA, AGRICOLA, EMBASE, ESBIODBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, PASCAL, and LIFESCI were searched simultaneously on STN International with the following strategy:

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L1      3167 S 1306-38-3
L2      3896 S CERIA
L3      4679 S (CERIC OR CERIUM) (4A) (OXIDE OR DIOXIDE)
L4      3234 S CEO2
L5      140 S CE2O3
L6      8527 S L1 OR L2 OR L3 OR L4
L7      8580 S L6 OR L5
L8      801 S L7 AND (2005-2006)/PY
L9      818 S L7 AND 2004/PY
L10     1619 S L8 OR L9
        SET DUPORDER FILE
L11     1441 DUP REM L10 (178 DUPLICATES REMOVED)
L12     1411 S L10 NOT SYNTH?
L13     461 S L12 NOT CATALY?
L14     950 S L12 AND CATALY?
L15     0 S L14 AND (RATS OR MICE OR HUMAN OR RABBIT? OR HAMSTER? OR SALMONELLA)
L16     9 S L14 AND (TOXIC? OR PHARMAC? OR GENOTOXIC? OR CARCINO? OR CYTOX?)
L17     89 S L14 AND (CELL? OR SUBCELL? OR BLOOD OR SERUM OR URIN?)
L18     96 S L16 OR L17
L19     557 S L13 OR L18
L20     525 DUP REM L19 (32 DUPLICATES REMOVED)
L21     210 SORT L20 1-210 TI
        SAVE L21 CERIAUPDATE/A
```