Chemical Information Profile

for

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

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

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National Institute of Environmental Health Sciences
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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
ADME				
Absorption	✓	✓	✓	
Distribution	✓		✓	
Metabolism				
Excretion	✓			
Acute Toxicity (up to 1 week)				
Dermal				✓
Inhalation/intratracheal instillation	✓		✓	
Injection				
Ocular				
Oral				
Subchronic Toxicity (1 to <26 weeks)				
Dermal				
Inhalation			✓	
Injection				
Oral				
Chronic Toxicity (≥26 weeks)				
Dermal				
Inhalation	✓		✓	
Injection				
Oral				
Synergism/Antagonism				
Synergistic effects			✓	
Antagonistic effects			✓	
Cytotoxicity				
Cytotoxic effects			✓	
Reproductive Toxicity				
Fertility effects				
Maternal effects				
Paternal effects				

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

*using $^{144}CeO_2$

Ceric Oxide Nomination Summary

Chemical Name: Ceric Oxide **CAS RN:** 1306-38-3

Formula: CeO_2 **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^3) in areas of high traffic to levels of >1µg/m^3.

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^3. Using data from this study and an uncertainty factor of 3000, a human equivalent Reference Concentration (RfC) of 0.3 µg Ce/m^3 was developed (TERA, 1999). Intratracheal instillation of fine particles of CeO_2 (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^3 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

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_2 are available in the Registry record and at http://www.reliabletechniques.fsnet.co.uk/CERIUM4.html.
Hill Formula: O2Ce **Line Formula:** O=Ce=O **Smiles Notation:** CeO2
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_2. Cerium-rich bastnasite (bastnaesite; bastnäsite) concentrate (CAS RN 68909-13-7) contains ~46% CeO_2 and other light lanthanide oxides (Molycorp, Inc., 1992); pure CeO_2 (99 – 99.999%) is also sold (Metall Rare Earth Ltd., 2004). Commercial rare earth (RE) oxide polishing powders may have considerably lower CeO_2 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_2 (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^3 (Molycorp, Inc., 1992); Bulk density 1500-2500 kg/m^3 (IUCLID, 2000)
Boiling Point: Not available (melts at 2500-2600 ºC)
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_{ow}: 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^{3+} and La^{3+}) [values not given in abstract] (Moermond et al., 2001; PMID:11521817). Uptake decreased with increased alkalinity but was independent of pH and salinity.

- 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

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_2), which may be further processed by extraction, oxidation, reduction, and precipitation to give pure CeO_2 (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_2 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_2 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).

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^3 time weighted average (TWA) inhalable particulate containing no asbestos and <1% crystalline silica
3 mg/m^3 TWA (respirable particulate)

NIOSH REL: None

OSHA PEL: 15 mg/m^3 TWA (total dust)
5 mg/m^3 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^3; 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, $(Ce,La)(CO_3)F$; cerite; euxenite; fergusonite; loparite; monazite, $(Ce,La,Nd,Th)PO_4$; and xenotime. The lanthanide oxides contain 30% CeO_2 (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

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_2 nanoparticles may raise ambient air concentrations of CeO_2, sulfate, or phosphate in heavily trafficked "street canyons" to ~1.25 µg/m^3 at a height of 1 m.

- Cerium emissions estimated from operation of a diesel engine burning 50 ppm CeO_2 in the fuel for one hour was 1.74 ng Ce/m^3 in non-filtered samples (particulate trap) and 0.4 ng/m^3 in filtered samples (HEI, 2001). Escape from the trap during a 15-min regeneration period was 4.7 ng Ce/m^3.
- Emission factors for fuel containing 100 ppm CeO_2 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^3 (HEI, 2001)
- Pasadena, California: 0.43 ng Ce/m^3 in fine particles (<1.8 µm in diameter) and 0.19 ng Ce/m^3 in ultrafine particles (<0.097 µm) (HEI, 2001)
- Osaka, Japan: Semi-rural area, 4.3 ng Ce/m^3; urban residential area, 5.6 ng Ce/m^3; and "metropolitan" area, 11 ng Ce/m^3 (HEI, 2001)
- Russia: Vicinity of a phosphate fertilizer plant, 10.2 ng/m^3 at 200 m from the source, 3.8 ng/m^3 at 2000 m, and 3.6 ng/m^3 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

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^3 at 200 m to 3.6 ng/m^3 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_2, 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_2 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 $^{144}CeO_2$ 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_{50}/LD_{50} Values: inhalation LC_{50} >50 mg/m^3 (rats) [HEI, 2001]
oral LD_{50} = 622 mg/kg bw (female mice) [HEI, 2001]
oral LD_{50} >5000 mg/kg bw (rat) [RTECS, 2003]
i.p. LD_{50} = 465 mg/kg (mice) [RTECS, 2003]

i.p. LD_{50} >1000 mg/kg bw (rats) [IUCLID, 2000]
dermal LD_{50} >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_2O_3 and Y_2O_3
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_2O_3 and Y_2O_3
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)

Subchronic Toxicity

Route:	inhalation
Species:	rat
Dose/Duration:	not provided (aerosols)
Observation Time:	not provided
Effects:	TC_{LO} = 100 mg/m^3 at 2 hours intermittently for 30 days TC_{LO} = 50 mg/m^3 at 6 hours intermittently for 30 days
Source(s):	RTECS (2003)

Route:	inhalation
Species:	rat
Dose/Duration:	10-50 mg/m^3 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_{LO} = 50 mg/m^3 (RTECS, 2003)

Route:	inhalation (nose-only)
Species:	rat
Dose/Duration:	5, 50, or 500 mg/m^3 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_2 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^3 was determined for alveolar epithelial hyperplasia and of 0.55 mg Ce/m^3 for increased lung weight. The LOAEL for minimal bronchial lymph node metaplasia was 0.85 mg/m^3 in males and 0.82 mg Ce/m^3 in females (equivalent to ~1.0 mg CeO_2/m^3). Using an uncertainty factor of 3000, an inhalation reference concentration (RfC) of 0.3 µg/m^3 was derived for CeO_2 (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^{3+} (1.01 Å) and Ca^{2+} (1.00 Å) allows Ce^{3+} (and other light Ln^{3+} ions) to replace Ca^{2+} 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).
- Ln^{3+} ions are well known inhibitors of 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 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 Mg^{2+} (Shivakumar and Nair, 1991; PMID:2051999).

Synergistic/Additive Effects

Clear synergistic effects of Ce^{3+} have not been reported; however, 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, Ce^{3+} "mediated intracellular responses to Ca^{2+} ion fluxes in a cooperative manner."
- Substitutes for 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 (LC_{50} = 4740 µM) compared to $CeCl_3$ (LC_{50} = 29 µM), $CdCl_2$ (LC_{50} = 28 µM), $LaCl_3$ (LC_{50} = 52 µM), and La_2O_3 (LC_{50} = 980 µM)
- increasing concentrations eliminated cell surface features
- 1000 µM 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 $^{144}CeO_2$ produced lung tumors in mice while only one mouse in the control group (exposed to stable 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 $^{144}CeO_2$ 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 mg/m^3 of stable CeO_2 (mass median aerodynamic diameter 0.9-2.2 µm). [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_2/m^3 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_2 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^{2+}/Mg^{2+}-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

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 µM, 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 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; PMIID: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 Gd_2O_3 of 2 µg/m^3, higher than that for CeO_2 (0.3 µg/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 (ZrO_2) may be more similar to CeO_2 than titanium dioxide (titania) based on its crystal structure (Sobukawa, 2002). Studies reviewed by Smith and Carson (1978) indicated that ZrO_2 distribution in rats, mice, and guinea pigs after endotracheal injection and inhalation is similar to that observed with CeO_2. Rats that inhaled 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 CeO_2. Ultrafine particles of TiO_2 instilled into the lungs of rats were more harmful than fine 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 TiO_2 particles, animals showed species differences in lung responses. Hamsters were able to clear the highest dose, 10 mg/m^3, while mice and rats showed particle overload (Bermudez et al., 2004; PMID:14600271). Pigmentary TiO_2 inhalation by rats, mice, and guinea pigs of 10-250 mg/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-

year inhalation experiment, rats showed increasing severity of lung responses at doses from 10 to 250 mg TiO_2/m^3. 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

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_2 nanoparticles (cubic nanocrystals) that have an average size of 11 nm, a specific surface area (SSA) of 55 - 95 m^2/g, and a bulk density of 0.25 g/cm^3.
- NanoScale Materials, Inc. (undated) produces CeO_2 nanocrystallites up to 7 nm in size, with a SSA >50 m^2/g, an average pore diameter of 70 Å, and total pore volume of at least 1 cm^3/g.
- Combining nanoparticulates of CeO_2 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_2 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_2 doped with 20 mole percent of zinc or calcium cations and prepared by a "soft solution chemical route" at 40 ºC was dependent on pH during oxidation of precipitated cerium (III) hydroxide to CeO_2. 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_2 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)

- 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_2. Solution methods for producing pure CeO_2 or CeO_2 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_2 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_2 and other RE metal oxides by a plasma arc synthesis process.
- Nanoparticulate CeO_2 was also formed by a microemulsion method at annealing temperatures above 623 ºK; 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_2 (Envirox^{TM}) 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_2 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^{TM}, 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^{TM} catalytic converter has a surface area of 20-60 m^2/g (Rhodia Electronics and Catalysis, undated).
- Other uses for nanoparticulate CeO_2 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_2 for electro-optical devices (Kambe et al., 2003 pat. appl.). AMR Technologies Inc. (2005) is developing nanosized CeO_2 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_2 in developing cleaner burning, lower carbon monoxide-emitting cigarettes. Cerium dioxide/zirconium oxide fibers have been incorporated in the cigarette

paper/wrapper, tobacco, and/or filter (Snaidr, 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_2 into the environment are anticipated to be similar to larger scale CeO_2 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_2 in cosmetics, such as sunscreens, would lead to more widespread exposure to the general population. The nanoparticulate form of a material (e.g., TiO_2) 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_2 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_2 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_2 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_2 nanoparticles have a strong electrostatic attraction for the negatively charged surface of bacteria up to a concentration of 8 mg Ce/m^2. In suspensions of 8-nm CeO_2 nanoparticles, *E. coli* covered with 1 mg Ce/m^2 lost 50% of their ability to divide; with 13 mg Ce/m^2, >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_2 (2-10 nm), even when exposed to ultraviolet light. The protective effect was hypothesized as being due to regenerative free radical scavenging.

References

Altair Nanomaterials, Inc. 2002. Development Products. Internet address: http://www.altairnano.com/main_content/DevProducts.html. Last accessed on February 23, 2005.

AMR Technologies. 2004. AZoNanotechnology new product: Cerium oxide nanoparticles. Posted on February 9, 2004. Internet address: http://www.azonano.com/details.asp?ArticleID=509. Last accessed on March 21, 2005.

AMR Technologies Inc. 2005. Annual Information Form. March 2, 2005. Internet address: http://www.amr-ltd.com/pdfs/AMR2004AIF.pdf.

Applied NanoWorks. 2004. Pinnacle cerium dioxide. Internet address: http://www.appliednanoworks.com/products/pinnacleaf_cerium_dioxide.html. Last accessed on March 25, 2005.

Bailey, D., Chow, L., Merchant, S., Kuiry, S.C., Patil, S., Seal, S., and Rzigalinski, B. 2005 abstr. Cerium oxide nanoparticles extend cell longevity and act as free radical scavengers. Internet address: http://www.med.miami.edu/MNBWS/Rzigalinski112.html. Last accessed on February 23, 2005.

Baret, G. [assignee: Strand Cosmetics Europe]. 2005 pat. Cosmetic products containing metal and metal oxide particles (Fr.). French Patent No. 2869537 A1. Issue date: November 4, 2005. Fr. Demande, 15 pp. Abstract from TOXCENTER 2005:300749.

Bermudez, E., Mangum, J.B., Asgharian, B., Wong, B.A., Reverdy, E.E., Janszen, D.B., Hext, P.M., Warheit, D.B., and Everitt, J.L. 2002. Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles. Toxicol Sci, 70(1):86-97.

Bermudez, E., Mangum, J.B., Wong, B.A., Asgharian, B., Hext, P.M., Warheit, D.B., and Everitt, J.I. 2004. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. Toxicol Sci, 77(2):347-357.

Borm, P.J., and Kreyling, W. 2004. Toxicological hazards of inhaled nanoparticles--potential implications for drug delivery. J Nanosci Nanotechnol, 4(5):521-531.

Bowen, H.J.M. 1982. The elemental content of human diets and excreta. In: Environmental Chemistry: A Specialist Periodical Report, Vol. 2. The Royal Society of Chemistry, London, pp. 70-93.

Brookhaven National Laboratory. 2005. Ceria nanoparticles catalyze reactions for cleaner-fuel future. Internet address: http://www.bnl.gov/bnlweb/pubaf/pr/PR_display.asp?prID=05-19. Last accessed on March 25, 2005.

Brown, C.J., Chenery, S.R., Smith, B., Mason, C., Tomkins, A., Roberts, G.J., Sserunjogi, L., and Tiberindwa, J.V. 2004. Environmental influences on the trace element content of teeth--implications for disease and nutritional status. Arch Oral Biol, 49(9):705-717.

Bulman, R.A. 2003. Metabolism and toxicity of the lanthanides. In: Sigel, A., and Sigel, H., Eds. Metal Ions in Biological Systems, Vol. 40. Marcel Dekker, Inc., New York, NY, pp. 683-706.

California Regional Water Quality Control Board, Lahontan Region. 2004. Board Order No. R6V-2004-(Tentative). WDID No. 6B360009001. Revised Waste Discharge Requirements for Molycorp, Inc., Mountain Pass Mine and Mill Site, North Tailings Pond (P-16) Closure and Post-Closure Maintenance. Internet address: http://www.waterboards.ca.gov/lahontan/docs/Molycorp_P16_Tentative.pdf.

CCRIS (Chemical Carcinogenesis Research Information System). 1993. [Search by record number] Cerium(IV) Dioxide. CCRIS Record No. 2288. Internet address: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. Last updated on July 22, 1993. Last accessed on March 24, 2005.

Cerulean International, Division of Oxonica. 2004. Envirox™ - The economy of scale… About Cerulean International. Internet address: http://www.cerulean-international.com/about.htm. (For more product information, see Environ Fuel Additive, Internet address: http://www.oxonica.com/environ-print.htm.) Last accessed on February 23, 2005.

Chai, Z.F., Zhang, Z.Y., Feng, W.Y., Chen, C.Y., Xu, D.D., and Hou, X.L. 2004. Study of chemical speciation of trace elements by molecular activation analysis and other nuclear techniques. J Anal At Spectrom, 19(1):26-33.

ChemIDplus. 2004. Ceric oxide. Provided by the U.S. National Library of Medicine, Bethesda, MD. Internet address: http://chem.sis.nlm.nih.gov/chemidplus/jsp/chemidheavy/ChemFull.jsp?MW=172.118. Last updated on September 9, 2004. Last accessed on December 20, 2004.

Chen, J., Seal, S., Sezate, S.A., Ramsey, M., Elias, R., Wong, L., Cao, W., and McGinnis, J.F. 2005 abstr. Nanoceria particles confer neuroprotection in retinal cells *in vitro*. IOVS, 46(Suppl. S):186. Meeting information; Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology, Ft. Lauderdale, FL, May 1-5, 2005. Abstract from BIOSIS 2006:42854.

Christie, T., Brathwaite, B., and Tulloch, A. [U.S. Geological Survey (USGS)]. 1998. Mineral Commodity Report 17 – Rare Earths and Related Elements. Internet address: http://crownminerals.med.govt.nz/minerals/docs/comreports/report17_rareearths.pdf.

Chu, D., Lee, I.C., Pati, R.K., and Ehrman, S.H. 2004. Ceria based nano-scale catalysts for water-gas shift (WGS) reaction. Internet address: http://www.asc2004.com/Manuscripts/sessionM/MP-03.pdf.

Clean Diesel Technologies, Inc. 2001 slides. PPT Slide. Presentation to the Corning Incorporated Diesel Emission Control Retrofit Users Conference, February 2001, Pasadena, CA, 25 slides. Internet address: http://www.corning.com/environmentaltechnologies/products__services/diesel_whitepapers/Valentine/sld001.htm. Last accessed on January 3, 2005.

Clean Diesel Technologies, Inc. 2002 slides. CARB – International Diesel Retrofit Advisory Committee. Part II – Use of Metal Additives; What Are the Issues? Internet address: http://www.arb.ca.gov/diesel/presentations/020602/CDTMetalAdditiv.pdf.

Degussa Advanced Nanomaterials. 2003. Degussa investing EUR 25 million in "advanced nanomaterials." Press release – February 27, 2003. Internet address: http://www.advanced-nano.com/webapps/adnano.nsf/hauptpunkte_en/1656A94A956D271EC1256D030042D9E8?opendocument. Last accessed on February 23, 2005.

Dufresne, A., Krier, G., Muller, J.F., Case, B., and Perrault, G. 1994. Lanthanide particles in the lung of a printer. Sci Total Environ, 151(3):249-252.

Eapen, J.T., Kartha, C.C., Rathinam, K., and Valiathan, M.S. 1996. Levels of cerium in the tissues of rats fed a magnesium-restricted and cerium-adulterated diet. Bull Environ Contam Toxicol, 56(2):178-182.

EnvironmentalChemistry.com. 2005. Periodic table of elements; sorted by ionic radius. Internet address: http://environmentalchemistry.com/yogi/periodic/ionicradius.html. Last accessed on January 20, 2005.

Evans, C.H. 1990. Biochemistry of the Lanthanides. Plenum Press, New York, NY, 460 pp.

EWG (Environmental Working Group). 2005. Skin deep: A safety assessment of ingredients in personal care products. [Search by product IDs = 907044, 907801, and 904395]. Internet address: http://www.ewg.org/reports/skindeep/browse_products.php. Last accessed on January 31, 2005.

Fox, B. 2004. AZoNanotechnology article: Efficiency trials for Oxonica nano fuel additive, Envirox. Internet address: http://www.azonano.com/details.asp?ArticleID=31. Last accessed on March 21, 2005.

Haley, P.J. 1991. Pulmonary toxicity of stable and radioactive lanthanides. Health Phys, 61(6):809-820.

Haley, T.J. 1965. Pharmacology and toxicology of the rare earth elements. J Pharm Sci, 54(5):663-670.

Hedrick, J.B. 2002. Rare earths. U.S. Geological Survey Minerals Yearbook—2002. Internet address: http://minerals.usgs.gov/minerals/pubs/commodity/rare_earths/rareemyb02.pdf.

HEI (Health Effects Institute). 2001. Evaluation of human health risk from cerium added to diesel fuel. HEI Communication 9. Internet address: http://www.healtheffects.org/Pubs/Cerium.pdf.

HEI. 2003. HEI Special Committee on Emerging Technologies. Chart 1. Emerging technologies for diesel and diesel-like engines: Potential emissions of health concern. Draft. June 9, 2003. Internet address: http://www.healtheffects.org/Scet/SCET-chart1.pdf.

Hirano, S., and Suzuki, K.T. 1996. Exposure, metabolism, and toxicity of rare earths and related compounds. Environ Health Perspect, 104(Suppl. 1):85-95.

ICRP (International Commission on Radiological Protection). 1979. Limits of intakes of radionuclides by workers. Ann ICRP, 2, pages not given. Cited by Bulman (2003).

Inagaki, K., and Haraguchi, H. 2000. Determination of rare earth elements in human blood serum by inductively coupled plasma mass spectrometry after chelating resin preconcentration. Analyst, 125(1):191-196.

IUCLID (International Uniform ChemicaL Information Database). 2000. IUCLID dataset: Cerium dioxide [CAS No. 1306-38-3]. European Commission—European Chemicals Bureau. Internet address: http://ecb.jrc.it/IUCLID-Data-Sheet/1306383.pdf.

Iyengar, G.V., Kollmer, W.E., and Bowen, H.J.M. 1978. The Elemental Composition of Human Tissues and Body Fluids: A Compilation of Values for Adults. Verlag Chemie, New York, NY.

Jakupec, M.A., Unfried, P., and Keppler, B.K. 2005. Pharmacological properties of cerium compounds. Rev Physiol Biochem Pharmacol, 153:101-111.

Jani, P., Halbert, G.W., Langridge, J., and Florence, A.T. 1990. Nanoparticle uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency. J Pharm Pharmacol, 42(12):821-826.

Kambe, N., Blum, Y.D., Chaloner-Gill, B., Chiruvolua, S., Kumar, S., and MacQueen, D.B. [assignee: NanoGram Corporation]. 2003 pat. appl. Polymer-inorganic particle composites. U.S. Patent Application No. 20030207129 A1. November 6, 2003. Internet address: http://appft1.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PG01&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.html&r=1&f=G&l=50&s1=%2220030207129%22.PGNR.&OS=DN/20030207129&RS=DN/20030207129. Last accessed on March 24, 2005.

Kaupp, G., Schuster, T., Kremitzl, H.-J., and Sommer, G. [assignee: Eckart G.m.b.H. and Co., K.-G.]. 2004 pat. Coated metal pigments for use in cosmetic formulations (Ger.). German (DE) Patent No. 10238090 A1. Issue date: March 4, 2004. Ger. Offen., 3 pp. Abstract from TOXCENTER 2004:66191.

Kawamoto, Y., and Tanabe, Y. [assignee: Nippon Shikizai Inc.]. 2005 pat. Lip stick composition having minimized skin irritation (Jpn.). Japanese Patent No. 2005220099 A2. Issue date: August 18, 2005. Japan Kokai Tokkyo Koho, 8 pp. Abstract from TOXCENTER 2005:232470.

KIA (Kemco International Associates), Inc. 2000a. Cerium oxide. Internet address: http://www.kemcointernational.com/CeriumOxide.htm. Last accessed on February 23, 2005.

KIA, Inc. 2000b. Nano material applications. Internet address: http://www.kemcointernational.com/NANOPHASEAPPLICATIONS.htm. Last accessed on February 23, 2005.

Knight, A.L. 1994. The rare earths. In: Zenz, C., Dickerson, O.B., and Horvath, E.P., Eds. Occupational Medicine, 3rd ed. Mosby—Year Book, Inc., St. Louis, MO, pp. 572-576.

Kumar, B.P., Shivakumar, K., Kartha, C.C., and Rathinam, K. 1996. Magnesium deficiency and cerium promote fibrogenesis in rat heart. Bull Environ Contam Toxicol, 57(4):517-524.

Lee, K.P., Trochimowicz, H.J., and Reinhardt, C.F. 1985. Pulmonary response of rats exposed to titanium dioxide (TiO_2) by inhalation for two years. Toxicol Appl Pharmacol, 79(2):179-192.

Lee, K.P., Henry, N.W., Trochimowicz, H.J., and Reinhardt, C.F. 1986. Pulmonary response to impaired lung clearance in rats following excessive TiO2 dust deposition. Environ Res, 41(1):144-167.

Limbach, L.K., Li, Y., Grass, R.N., Brunner, T.J., Hintermann, M.A., Muller, M., Gunther, D., and Stark, W.J. 2005. Oxide nanoparticle uptake in human lung fibroblasts: Effects of particle size, agglomeration, and diffusion at low concentrations. Environ Sci Technol, 39(23):9370-9376.

Linsalata, P., Eisenbud, M., and Franca, E.P. 1986. Ingestion estimates of Th and the light rare earth elements based on measurements of human feces. Health Phys, 50(1):163-167.

Lundgren, D.L., McClellan, R.O., and Hahn, F.F. 1975. Biological effects of repeated inhalation exposure of mice and Syrian hamsters to aerosols of $^{144}CeO_2$. III. In: Boecker, B.B., and Rupprecht, F.C., Eds. Annual Report of the Inhalation Toxicology Research Institute, Lovelace Foundation for Medical Education and Research. Report No. LF-52, pp. 230-235.

MarkeTech International, Inc. 2005. Nanophase powders. Internet address: http://www.mkt-intl.com/powders/nanophas.htm. Last accessed on March 21, 2005.

Meliorum Technologies, Inc. 2004. Ceria nanomaterial. Cerium oxide nanomaterial product overview. Internet address: http://www.meliorum.com/Meliorum-CeO2.pdf.

Metall Rare Earth Ltd. 2004. Cerium oxide, metal and compounds from Metall Rare Earth Limited. Shenzhen, China. Internet address: http://www.metall.com.cn/re/ce.htm. Last accessed on December 28, 2004.

Metall Rare Earth Ltd. 2005. Cerimax---Cerium oxide polishing powder. Internet address: http://www.metall.com.cn/cepp.htm. Last accessed on January 10, 2006.

Moermond, C.T., Tijink, J., van Wezel, A.P., and Koelmans, A.A. 2001. Distribution, speciation, and bioavailability of lanthanides in the Rhine-Meuse estuary, The Netherlands. Environ Toxicol Chem, 20(9):1916-1926.

Mogilevskaya, O.Ya., and Raikhlin, N.T. 1963. Biological effects of rare, dispersed, and other metals and their compounds used in industry: Rare earth elements (Russ.). In: Z.I. Izraelson, Ed., Toksikologiya Redkikh Metallov, pp. 195-208. [An English translation of the book *Toxicology of Rare Metals* was published by the Israel Program for Scientific Translation in 1967.]

Molycorp, Inc. 1992. Cerium. A Guide to Its Role in Chemical Technology. Molycorp, Inc., Mountain Pass, CA. Internet address: http://www.molycorp.com/cerium_book.pdf.

Nair, R.R., Preeta, R., Smitha, G., and Adiga, I. 2003. Variation in mitogenic response of cardiac and pulmonary fibroblasts to cerium. Biol Trace Elem Res, 94(3):237-246.

NanoGram Corporation. 2005. Product concepts: Catalysts and carriers. Internet address: http://www.nanogram.com/concepts/cc.htm. Last accessed on March 21, 2005.

NanoScale Materials, Inc. Undated. NanoActive™ Cerium Oxide. Internet address: http://nanoactive.interkan.net/Literature/NA%20106v2%20-%20NanoActive%20CeO2.pdf.

nGimat. 2005. Electronics. Internet address: http://www.microcoating.com/nanotech/electronics.html. Last accessed on March 28, 2005.

NIOSH (National Institute for Occupational Safety and Health) National Occupational Exposure Survey (1981-1983). Ceric Oxide. Internet addresses: http://www.cdc.gov/noes/noes2/11740occ.html (occupation) and http://www.cdc.gov/noes/noes1/11740sic.html (standard industrial classification). Last accessed on January 20, 2005.

NTC (Nanophase Technologies Corporation). 2003a. Nanoparticles, NanoTek® Cerium Oxide. Internet address: http://www.nanophase.com/catalog/item.asp?DEPARTMENT_ID=38&ITEM_ID=47. Last accessed on March 18, 2005.

NTC. 2003b. Nanoparticle dispersions, dispersion polishing products. Internet address: http://www.nanophase.com/catalog/index.asp?DEPARTMENT_ID=47. Last accessed on March 21, 1005.

NTC. 2003c. AZoNanotechnology new product: Commercial availability of nanocrystalline rare earth oxides. Posted on April 10, 2003. Internet address: http://www.azonano.com/details.asp?ArticleID=315. Last accessed on March 21, 2005.

NTC. 2003d. AZoNanotechnology new product: Nanosized rare earth metal oxides catalysts as an alternative to precious metals. Posted on October 22, 2003. Internet address: http://www.azonano.com/details.asp?ArticleID=336. Last accessed on March 21, 2005.

NTC. 2003e. AZoNanotechnology new product: Nanotechnology in fuel cells. Posted on October 22, 2003. Internet address: http://www.azonano.com/details.asp?ArticleID=337. Last accessed on March 21, 2005.

NTC. 2003f. Nanocrystalline materials: Technologies and capabilities. Internet address: http://www.nanophase.com/technology/capabilities.asp. Last accessed on March 21, 2005.

NTC. 2004 press release. Nanophase announced commercial availability of novel new nanomaterials. Posted on January 9, 2004. Internet address: http://nanophase.com/investor_relations/press.asp?PRESS_RELEASES_ID=78. Last accessed on March 25, 2005.

Oger, G. 2002. Materials firm AMR Technologies turns to nano for new products. Small Times, September 23, 2002. Internet address: http://www.smalltimes.com/document_display.cfm?document_id=4666. Last accessed on March 24, 2005.

Otaki, N., Toya, T., Takata, A., Takaya, M., Serita, F., Shinohara, Y., Ono-Ogasawara, M., Omae, K., and Kohyama, N. 2003. Acute and subchronic pulmonary effects of rare metal oxides on rats. 2. Analysis of bronchoalveolar lavage fluids (Jpn.). Kidorui, 42:176-177.

Pang, X., Li, D., and Peng, A. 2002. Application of rare-earth elements in the agriculture of China and its environmental behavior in soil. Environ Sci Pollut Res Int, 9(2):143-148.

QinetiQ Nanomaterials, Division of Tetronics Ltd. 2004. AZoNanotechnology company profile: QinetiQ Nanomaterials. Internet address: http://www.azonano.com/details.asp?ArticleID=1034. Last accessed on March 21, 2005.

Rao, T.P., and Biju, V.M.N. 2002. Ultratrace analysis of individual rare earth elements in natural water samples. Rev Anal Chem, 21(3):233-243.

Rauch, S., Morrison, G.M., Motelica-Heino, M., Donard, O.F.X., and Muris, M. 2000. Elemental association and fingerprinting of traffic-related metals in road sediments. Environ Sci Technol, 34(15):3119-3123.

Reade Advanced Materials. 1997a. Cerium oxide powder. Internet address: http://www.reade.com/Products/Oxides/cerium_oxide.html. Last accessed on January 26, 2005.

Reade Advanced Materials. 1997b. Nanoparticles/nanopowders. Internet address: http://www.reade.com/Products/Nanomaterials/nanoparticles.html. Last accessed on February 23, 2005.

Renwick, L.C., Brown, D., Clouter, A., and Donaldson, K. 2004. Increased inflammation and altered macrophage chemotactic responses caused by two ultrafine particle types. Occup Environ Med, 61(5):442-447.

Rhodia Electronics and Catalysis. Undated. Catalysis. Automotive emissions control. Internet address: http://www.rhodia-ec.com/site_ec_us/catalysis/page_automotive.htm. Last accessed on January 13, 2005.

Rhône-Poulenc, Inc. (aka Rhodia). 1995. TSCATS Low Detail Report: Cerium dioxide. 8(e)/FYI ID No. 8EHQ-0295-13019B. Submission date: January 30, 1995. EPA Receive date: February 1, 1995. http://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearchView/6566F8D8D5ABA41B85256930004F2665. Last accessed on January 14, 2005.

Rodushkin, I., and Axelsson, M.D. 2000. Application of double focusing sector field ICP-MS for multielemental characterization of human hair and nails. Part II. A study of the inhabitants of northern Sweden. Sci Total Environ, 262(1-2):21-36.

Rohm and Haas Electronic Materials. 2004. Celexis™ Slurry for Direct STI. Internet address: http://www.eminess.com/documents/celexis.pdf.

Royal Society. 2004. Nanoscience and nanotechnologies: Opportunities and uncertainties. The Royal Society and The Royal Academy of Engineering. Internet address: http://www.nanotec.org.uk/report/summary.pdf.

RTECS (Registry of Toxic Effects of Chemical Substances). 2003. Cerium oxide. RTECS No. FK6310000. Profile last updated on February 2003. Provided by STN International, Bethesda, MD.

Shimizu, H., Suzuki, Y., Takemura, N., Goto, S., and Matsushita, H. 1985. Results of microbial mutation test for forty-three industrial chemicals. Sangyo Igaku, 27(6):400-419.

Shivakumar, K., and Nair, R.R. 1991. Cerium depresses protein synthesis in cultured cardiac myocytes and lung fibroblasts. Mol Cell Biochem, 100(1):91-96.

Smith, I.C., and Carson, B.L. 1978. Trace Elements in the Environment, Vol. 3—Zirconium. Ann Arbor Science Publishers, Inc., Ann Arbor, MI, 423 pp.

Snaidr, S.M. [assignee: Rothmans, Benson & Hedges Inc.]. 2004 pat. appl. Ceria/zirconia fibers for use in cigarettes. World Patent No. 2004023903 A2. Issue date: March 25, 2004. PCT Int. Appl., 16 pp. Abstract from TOXCENTER 2004:84692.

Sobukawa, H. 2002. Development of ceria-zirconia solid solutions and future trends. R&D Rev Toyota CRDL, 37(4):1-5.

Stuart, C. 2005. Oxonica's deal with bus fleet puts company on right road. Small Times, February 7, 2005. Internet address: http://www.smalltimes.com/print_doc.cfm?doc_id=8742. Last accessed on February 23, 2005.

Takaya, M., Toya, T., Takata, A., Otaki, N., Yoshida, K., and Kohyama, N. 2005. Biological effects of rare earth oxides to respiratory organs (Jpn.). Earozoru Kenkyu, 20(3):207-212. Abstract from TOXCENTER 2005:279214.

Tarasenko, N.Y., Spasskii, S.S., and Shubochkin, L.N. 1974. Hygienic standardization of cerium dioxide aerosol in the working zone atmosphere (Russ.). Gig Tr Prof Zabol, 0(10):29-32.

Tarnuzzer, R.W., Colon, J., Patil, S., and Seal, S. 2005. Vacancy engineered ceria nanostructures for protection from radiation-induced cellular damage. Nano Lett, 5(12):2573-2577. Abstract from MEDLINE 2005694694.

Taylor, D.M., and Leggett, R.W. 2003. A generic biokinetic model for predicting the behaviour of the lanthanide elements in the human body. Radiat Prot Dosimetry, 105(1-4):193-198.

TERA (Toxicology Excellence for Risk Assessment). 1999. Development of references doses and reference concentrations for lanthanides. Prepared for The Bureau of Land Management, National Applied Resource Sciences Center. Amended Stage 2 on November 11, 1999. Internet address: http://www.tera.org/pubs/Lanthanides.pdf.

Tetra Tech, Inc. 2001. Human Health and Ecological Risk Assessment for the Mountain Pass Mine. Final Report. Prepared for County of San Bernardino, Land Use Services Department, Planning Division, San Bernardino, CA, June 2001. Internet address: http://www.co.san-bernardino.ca.us/landuseservices/Public%20Notices/HHERA%20Final%20Report.pdf.

Thill, A., Spalla, O., Rose, J., and Auffan, M. 2005. Physicochemical and biological interactions between Ce(IV) oxides, nanoparticles, and *Escherichia coli*. Paper No. 49. Abstracts of Papers, 230th ACS National Meeting, Washington, DC, August 28-September 1, 2005, pp. 587-589.

Toya, T., Otaki, N., Takata, A., Takaya, M., Serita, F., Shinohara, Y., Ono-Ogasawara, M., Omae, K., and Kohyama, N. 2003. Acute and subchronic pulmonary effects of rare metal oxides on rats. 1. Histopathological examination (Jpn.). Kidorui, 42:174-175.

Trent Mann Products, Ltd. (formerly Reliable Technologies). 2005. Cerium oxide – Trent. Product Data Sheet. Internet address http://www.reliabletechniques.fsnet.co.uk/trent1.html and http://www.reliabletechniques.fsnet.co.uk/trent2.html. Last updated on July 22, 2005. Last accessed on January 10, 2006.

Trochimowicz, H.J., Lee, K.P., and Reinhardt, C.F. 1988. Chronic inhalation exposure of rats to titanium dioxide dust. J Appl Toxicol, 8(6):383-385.

Ure, A.M., and Berrow, M.L. 1982. The elemental constituents of soils. In: Environmental Chemistry: A Specialist Periodical Report, Vol. 2. The Royal Society of Chemistry, London, pp. 94-204.

U.S. EPA (Environmental Protection Agency). 1998. Identification and Description of Mineral Processing Sectors and Waste Streams. Final. Technical Background Document. Office of Solid Waste, U.S. EPA. Internet address: http://www.epa.gov/epaoswer/other/mineral/part1.pdf.

U.S. EPA. 2005. Inventory Update Rule. [Search by chemname for bastnaesite*.] Office of Pollution, Prevention and Toxics, U.S. EPA. Internet address: http://www.epa.gov/opptintr/iur/iur02/search03.htm. Last updated on January 26, 2005. Last accessed on January 26, 2005.

Volokh, A.A., Gorbunov, A.V., Gundorina, S.F., Revich, B.A., Frontasyeva, M.V., and Pal, C.S. 1990. Phosphorus fertilizer production as a source of rare-earth elements pollution of the environment. Sci Total Environ, 95:141-148.

Weese, W. 2004. Statement of the Legal and Factual Basis for the Terms of the Proposed Permit [MDAQMD Rule 1203(B)(1)(a)(i)]. Title V Federal Permit to operate Molycorp, Inc., Mountain Pass Mine, Mountain Pass, CA. Permit No. 000500364. Issue date: March 17, 2004. Internet address: http://www.arb.ca.gov/fcaa/tv/tvinfo/permits/moj/molyeval.pdf.

Weltje, L., Heidenreich, H., Zhu, W., Wolterbeek, H.T., Korhammer, S., de Goeij, J.J., and Markert, B. 2002. Lanthanide concentrations in freshwater plants and molluscs, related to those in surface water, pore water and sediment. A case study in The Netherlands. Sci Total Environ, 286(1-3):191-214.

Wester, P.O. 1971. Trace element balances in two cases of pancreatic insufficiency. Acta Med Scand, 190(3):155-161. Cited by Bowen (1982).

Wikipedia. 2006. Titanium dioxide. Internet address: http://en.wikipedia.org/wiki/Titanium_dioxide. Last updated on February 24, 2006. Last accessed on February 28, 2006.

Willems & van den Wildenberg. 2004. NRM NanoRoadMap (NRM) project: Work document on nanomaterials. Internet address: http://www.nanoroadmap.it/sectoral%20reports/sect%20report%20materials.pdf.

Xu, X., Zhu, W., Wang, Z., and Witkamp, G.J. 2002. Distributions of rare earths and heavy metals in field-grown maize after application of rare earth-containing fertilizer. Sci Total Environ, 293(1-3):97-105.

Yabe, S., and Sato, T. 2003. Cerium oxide for sunscreen cosmetics. J Solid State Chem, 171:7-11.

Zhang, F.S., Yamasaki, S., and Kimura, K. 2001a. Rare earth element content in various waste ashes and the potential risk to Japanese soils. Environ Int, 27(5):393-398.

Zhang, J., Wu, Z., Liu, T., Hu, L.T., Wu, Z., and Ju, X. 2001b. XANES study on the valence transitions in cerium oxide nanoparticles. J Sunchrotron Radiat, 8(Part 2):531-532.

Zhang, S., and Shan, X.Q. 2001. Speciation of rare earth elements in soil and accumulation by wheat with rare earth fertilizer application. Environ Pollut, 112(3):395-405.

Zhang, W.-J. [assignee: Philip Morris USA, Inc.]. 2003 pat. appl. Method for dispersing powder materials in a cigarette rod. U.S. Patent Application No. 20050039765 A1. Filed on August 22, 2003. Available from the US Patent & Trademark Office, Patent Application Full Text and Image Database at Internet address: http://appft1.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PG01&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.html&r=1&f=G&l=50&s1=%2220050039765%22.PGNR.&OS=DN/20050039765&RS=DN/20050039765. Last accessed on January 30, 2006.

Zhu, W., Xu, S., Shao, P., Zhang, W., Wu, D., Yang, W., and Feng, J. 1997. Bioelectrical activity of the central nervous system among populations in a rare earth element area. Biol Trace Elem Res, 57(1):71-77.

Zou, T., Shen, H., Zou, S., Duan, M., Song, L., and Dong, Z. 1992. Cytotoxicity of five rare earth dusts (Chin.). Gongye Weisheng Yu Zhiyebing, 18(2):82-85.

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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, 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

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 calcif*	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, ESBIOBASE, 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 SYNTHE?
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
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