Substance code
Cerium oxide and cerium compounds; CASRN 1306-38-3; 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR Cerium oxide and cerium compounds

File First On-Line 00/00/0000

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	discussion	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	on-line	00/00/0000
Carcinogenicity Assessment (II.)	discussion	00/00/0000

_I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Cerium oxide and cerium compounds
CASRN – 1306-38-3
Section I.A. Last Revised -- 00/00/0000

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed

threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgr-d.htm for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

This is the first IRIS assessment for cerium oxide and cerium compounds, no oral RfD for cerium oxide and cerium compounds was previously available on IRIS.

___I.A.1. CHRONIC ORAL RfD SUMMARY

The available human and animal studies demonstrate that cerium may have an effect on cardiac tissue and hemoglobin oxygen affinity. An association between exposure to cerium in food and the development of endomyocardial fibrosis has been suggested (Eapen et al., 1998; Kutty et al., 1996; Valiathan et al., 1989). In addition, Gómez-Aracena et al. (2006) suggest a relationship between chronic cerium exposures, characterized by cerium toenail concentrations, and increased risk of acute myocardial infarction.

The data set for long-term animal studies consists of a 13-month drinking water study in rats (Kumar et al., 1996), a 6-month drinking water study in rabbits (Kartha et al., 1998), a 12-week dietary study in mice (Kawagoe et al., 2005), and a 105-day gavage study in rats (Cheng et al., 2000). Kumar et al. (1996) demonstrated increased, highly variable cerium levels in cardiac tissue. Cerium chloride-treated rats, relative to untreated controls, had an increased level of collagen in the cardiac tissue, with an enhanced effect in rats fed a magnesium-deficient diet. This study suggested that cerium might increase the levels of collagen in the heart. This study was conducted on a small number of rats at one dose level (control and dosed rats) and evaluated few endpoints, and the observed effects were highly variable and not statistically significant.

Kartha et al. (1998) suggested that cerium chloride may intensify the cardiac effects of magnesium deficiency. Cardiac lesions were evident in 6/10 rabbits fed a magnesium-deficient diet with no cerium exposure and 9/10 rabbits fed a magnesium-deficient diet with cerium exposure. Rabbits fed magnesium-restricted diets, treated with or without cerium, showed endocardial, subendocardial, interstitial, and perivascular fibrosis and the lesions were more severe in those with cerium added to the drinking water. Cardiac lesions were absent from the groups fed the normal magnesium diet regardless of whether they consumed water with or without cerium. However, this study used only one dose group. The authors reported that cerium may intensify the cardiotoxicity associated with a magnesium-deficient or restricted diet but did not elicit a cardiac effect when tested under conditions of a normal magnesium diet.

Cheng et al. (2000) reported that cerium chloride exposure in rats produced a slight increase of hemoglobin content in erythrocytes after 40 days of treatment with an even greater increase in hemoglobin content after 80 days of exposure. The effect on the oxygen affinity of hemoglobin was demonstrated by altered oxygen saturation curves for the dosed rats compared to control rats. Hemoglobin in cerium-treated rats exhibited altered oxygen affinity up to 80 days of exposure, demonstrated by increased affinity up to 10 mm Hg and a double sigmoidal curve for 40-day rats and increased affinity above 20 mm Hg for 80-day rats.

Kawagoe et al. (2005) demonstrated that cerium chloride statistically significantly decreased liver lipoperoxide levels, increased liver GSH levels and liver MT activity, and decreased plasma SOD activity in mice. Cerium concentrations in the kidney, liver, lung, and spleen were statistically significantly elevated relative to controls, with the lung and spleen containing the highest levels. The study authors suggest that the endpoints showing changes as a result of cerium exposure in this study are indicators of reactive oxygen species generation in the liver. The authors did not report any other effects in the liver.

An RfD for cerium was not derived because the available studies were not suitable for quantitation of effects for various reasons, including unknown exposure concentrations in the available human studies, lack of a dose-response, uncertain toxicological significance (e.g., changes in measures of oxidative stress), and study design (e.g., effects noted only under conditions of a restricted diet).

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

___I.A.3. UNCERTAINTY FACTORS

Not applicable.

___I.A.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

___I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Not applicable.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document -- U.S. EPA (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Cerium Oxide and Cerium Compounds* (U.S. EPA, 2009).

Agency Completion Date -- __/__/__

___I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

__I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Cerium oxide and cerium compounds
CASRN -- 1306-38-3
Section I.B. Last Revised -- 00/00/0000

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

This is the first IRIS assessment for cerium oxide and cerium compounds, no inhalation RfC for cerium oxide and cerium compounds was previously available on IRIS .

___I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Increased incidence of lymphoid hyperplasia in the bronchial lymph nodes Subchronic inhalation study BRL, 1994 (unpublished study)	LOAEL: 5 mg/m^3 $LOAEL_{HEC}$: 0.48 mg/m^3	3000	2×10^{-4} mg/m^3 **

*Conversion Factors and Assumptions -- The human equivalent concentration (HEC) was estimated from the female LOAEL of 5 mg/m^3, 6 hours/day, 5 days/week (concentration adjusted to continuous exposure = 0.89 mg/m^3) and multiplication by a dosimetric adjustment factor (DAF), which, in this case, was the regional deposited dose ratio (RDDR) for the pulmonary region of the lung. The RDDR was calculated using the RDDR v.2.3 program.

** Note that the RfC was quantified for cerium oxide particles with an MMAD of approximately 2.0 μm and a GSD from 1.8 to 1.9, and may not characterize the potential toxicity from exposures to cerium oxide particles with smaller mass median diameters and geometric standard deviations, including nano-sized cerium particles. The use of the RfC for cerium compounds other than cerium oxide is not recommended as the similarity between this form of cerium and other cerium compounds is unknown.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES

A subchronic inhalation study using cerium oxide (CeO_2; ceric oxide) was conducted in 7-week-old Sprague-Dawley rats (BRL, 1994). This study is an unpublished study; accordingly, it was externally peer reviewed by EPA in August 2006 to evaluate the accuracy of experimental procedures, results, and interpretation and discussion of the findings presented (external peer review report available at www.epa.gov/iris).

Groups of 15 male and 15 female Sprague-Dawley CD rats were given nose-only exposure to a dry powder aerosol (mass median aerodynamic diameter [MMAD] = 1.8–2.2 μm, geometric standard deviation [GSD] = 1.8–1.9) of cerium oxide at concentrations of 0, 0.005, 0.0505, or 0.5075 mg/L (0, 5, 50.5, or 507.5 mg/m^3) 6 hours/day, 5 days/week for 13 weeks. The cerium oxide test material was 99% rare earth oxide with a maximum of 75 ppm Fe_2O_3. Of the 99% rare earth oxide, 99.95% was cerium oxide with a maximum of 25 ppm of both Pr_6O_{11} and Nd_2O_3. Praseodymium and neodymium are also rare earth metals. A functional observational battery was performed on all rats, as well as activity level testing, hematology, clinical biochemistry, urinalysis, ophthalmological examination, and a gross pathological examination of selected tissues weighed and retained for histopathologic examination. No deaths or clinical signs related to cerium oxide were noted. The results revealed statistically significant increases in absolute and differential neutrophil counts in the blood, treatment-related increases in the absolute and relative weight of the lungs in both males and females dosed at 50.5 and 507.5 mg/m^3 and in the relative spleen weight of male rats at 507.5 mg/m^3, discoloration or pale areas and uncollapsed parenchyma in the lungs of male and female rats at ≥50 mg/m^3 and pale foci in female rats at 5 mg/m^3, and dose-related alveolar epithelial and lymphoid hyperplasia and pigment accumulation in the lungs, lymph nodes, and larynx of males and females at ≥5 mg/m^3. This study identified a LOAEL of 5 mg/m^3 in rats, based on the increased incidence of lymphoid hyperplasia in the bronchial lymph nodes of male and female rats.

Exposure (mg/m^3)	Control	5	50.5	507.5
Males				
Larynx				
metaplasia	0/15	3/15	9/15[a]	13/15[a]
pigment accumulation	0/15	6/15[a]	9/15[a]	12/15[a]

Exposure (mg/m^3)	Control	5	50.5	507.5
Lung				
lymphoid hyperplasia	0/15	0/15	0/15	12/15[a]
alveolar epithelial hyperplasia	0/15	1/15	11/15[a]	14/15[a]
pigment accumulation	0/15	15/15[a]	15/15[a]	15/15[a]
Bronchial lymph node				
lymphoid hyperplasia	0/15	11/13[a]	15/15[a]	15/15[a]
pigment accumulation	0/15	13/13[a]	15/15[a]	15/15[a]
Females				
Larynx				
metaplasia	0/15	3/15	6/15[a]	9/15[a]
pigment accumulation	0/15	0/15	7/15[a]	9/15[a]
Lung				
lymphoid hyperplasia	0/15	0/15	1/15	7/15[a]
alveolar epithelial hyperplasia	0/15	0/15	5/15[a]	15/15[a]
pigment accumulation	0/15	15/15[a]	15/15[a]	15/15[a]
Bronchial lymph node				
lymphoid hyperplasia	0/15	13/15[a]	15/15[a]	15/15[a]
pigment accumulation	0/15	14/15[a]	15/15[a]	15/15[a]

[a]Significantly different from vehicle control group ($p < 0.05$ by Fisher's exact test)
Source: BRL, 1994.

The only available study reporting low-dose effects of subchronic inhalation exposure to cerium oxide in animals, BRL (1994), was chosen as the principal study. This study was well designed with three dose groups of 30 animals per group per sex. Numerous tissues and endpoints were assessed, and methods and observed effects were thoroughly reported. This study identified statistically significant dose-dependent effects on the lungs and lymphoreticular system in both male and female rats. The observed effects included increased lung weight; discoloration or pale areas, pale foci, and uncollapsed parenchyma in the lungs; enlargement or pale discoloration of the bronchial, mediastinal, and pancreatic lymph nodes; and dose-related alveolar epithelial and lymphoid hyperplasia and pigment accumulation in the lungs and lymph nodes. The lung and lymphoreticular system effects observed by BRL (1994) are consistent with effects observed in humans, that were characterized by the accumulation of cerium particles in the lungs and lymphoreticular system and histologic effects throughout the lung. EPA has selected lymphoid hyperplasia in the bronchial lymph nodes as the critical effect because it was determined that this effect represents the most sensitive endpoint occurring at the lowest dose that was indicative of lung and lymphoreticular system toxicity.

___I.B.3. UNCERTAINTY FACTORS

UF = 3000

A factor of 3 was selected to account for uncertainties in extrapolating from rats to humans (UF_A). This value is adopted by convention where an adjustment from an animal-specific $LOAEL_{ADJ}$ to a $LOAEL_{HEC}$ has been incorporated. Application of a full UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component is mostly addressed by the determination of a HEC as described in the RfC methodology (U.S. EPA, 1994). The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method.

A factor of 10 was used to account for variation in susceptibility among members of the human population (UF_H). Insufficient information is available to predict potential variability in susceptibility among the population to inhaled cerium oxide and cerium compounds.

A factor of 10 was used to account for uncertainty in extrapolating from a subchronic to chronic (UF_S) exposure duration, since the BRL (1994) study, which was selected as the principal study, is a subchronic study. The critical effect, increased incidence of lymphoid hyperplasia in the bronchial lymph nodes, may be more pronounced at longer exposure durations.

A factor of 3 was used to account for uncertainty in extrapolating from a LOAEL to a NOAEL (UF_L) because the point of departure was a LOAEL. The critical effect selected to determine the point of departure for this analysis, lymphoid hyperplasia in the bronchial lymph nodes, represents a minimally biologically significant effect; therefore, an uncertainty factor of 3 was applied.

A factor of 3 was used to account for deficiencies in the cerium oxide database (UF_D). The database includes multiple case reports of inhalation exposure to workers and a single 13-week subchronic inhalation study in rats. The effects from the subchronic rat inhalation study that are used for the derivation for the RfC (i.e., lymphoid hyperplasia in the bronchial lymph nodes) may be early indicators of the more overt toxicity that is found in humans (i.e., interstitial lung disease) exposed to cerium oxide in the workplace. The database does not include an exposure and recovery study that could demonstrate the persistence or, conversely, the adaptive nature of the lymphoid hyperplasia in the bronchial lymph nodes.

Toxicity via the inhalation route is expected to be a portal-of-entry effect. Cerium oxide is a relatively insoluble metal oxide and absorption or translocation from the lung to the circulation is expected to be minimal at low doses. The pulmonary effects observed in the human case reports and in the BRL (1994) study are likely due to the physical deposition of cerium oxide particles in the lung and the immunological reaction to the particles, and are not due to a chemical reaction of cerium oxide with lung tissues. The observed immunological response is a portal-of-entry effect and systemic circulation and effects are not expected because of the insoluble nature of the cerium oxide particles.

In considering the impact of database deficiencies on the derivation of the RfC, substantial weight was given to the available data demonstrating similarities between the effects observed in humans following prolonged exposure to cerium oxide and the effects observed in rats in the subchronic principal study, along with the data on deposition and absorption of cerium oxide in the lung. Thus, these data support the assumption that the respiratory system may be the most sensitive target of toxicity following inhalation exposure to cerium and that inhalation exposure to cerium may primarily involve portal-of-entry effects.

The database for cerium oxide lacks both a two-generation reproductive toxicity bioassay and a developmental toxicity bioassay. Systemic effects following the inhalation of cerium oxide, with an MMAD of approximately 2.0 μm and a GSD from 1.8 to 1.9, are not likely to be observed. While it is recognized that the investigation of systemic effects following cerium oxide exposure has not been the focus of existing studies, there is no reason to expect that reproductive,

developmental, or other systemic effects would occur, and a UF of 3 is applied in the absence of data on these effects.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

Inhalation data in humans consist of reports describing numerous cases of workers who developed pneumoconiosis associated with accumulation of cerium in the lungs after prolonged occupational exposure to cerium fumes or dust (Yoon et al., 2005; Porru et al., 2001; McDonald et al., 1995; Pairon et al., 1995, 1994; Sulotto et al., 1986; Vogt et al., 1986; Pietra et al., 1985; Vocaturo et al., 1983; Sabbioni et al., 1982; Husain et al., 1980; Kappenberger and Bühlmann, 1975; Heuck and Hoschek, 1968). In these cases, the exposure was to cerium oxide, and cerium-induced pneumoconiosis was characterized by accumulation of cerium particles (and other rare earth particles) in the lungs and lymphoreticular system. Exposure was not quantified in any of these cases. Potentially sensitive subgroups were not identified in the available human studies.

The proposed mode of action for the pulmonary effects observed following cerium oxide exposure is the overloading of the pulmonary alveolar macrophages by cerium oxide particles at high doses, leading to immobility of the PAMs in the alveoli, resulting in the sustained release of inflammatory cytokines and fibrogenic growth factors and subsequent cell damage. The mode of action for pulmonary toxicity in humans following chronic inhalation of cerium oxide is not known. However, pathological data from human case reports demonstrate accumulation of cerium in the lungs following occupational exposure to cerium fumes or dust. Animal data provide evidence that supports a hypothesized mode of action for effects observed in the lungs. The occurence of alveolar epithelial and lymphoid hyperplasia in the lungs of test animals accompanied by pigmentation in the lungs due to the accumulation of cerium oxide suggests that the mode of action for cerium oxide inhalation toxicity may be mediated by cytokine and fibrogenic effects resulting from pulmonary macrophage activation and immobilization. Taken together, the accumulation of insoluble cerium oxide particles in the respiratory tract of humans and animals following chronic and subchronic inhalation exposures, respectively, suggests that at high exposure concentrations impaired clearance may influence pulmonary toxicity for both species. Pathology observed in the lung may be due to an immune response to inhaled cerium dust in which clearance by pulmonary macrophages becomes overloaded.

Section 4.6.3 of the Toxicological Review for Cerium Oxide and Cerium Compounds provides more detail on the mode of action for respiratory effects.

___I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study -- medium
Data Base -- low
RfC – low

The overall confidence in this RfC assessment is low. Confidence in the principal study (BRL, 1994) is medium. EPA conducted an external peer review to evaluate the accuracy of the experimental procedures, results, and interpretation and discussion of the results presented in this study. The peer reviewers considered the BRL (1994) study conclusions to be supported by the data. The peer reviewers were not specifically asked to comment on their confidence in the

study. In addition, the results observed in the BRL (1994) study were consistent with the observed effects in the human case reports (Yoon et al., 2005; Porru et al., 2001; McDonald et al., 1995; Pairon et al., 1995, 1994; Sulotto et al., 1986; Vogt et al., 1986; Pietra et al., 1985; Vocaturo et al., 1983; Sabbioni et al., 1982; Husain et al., 1980; Kappenberger and Bühlmann, 1975; Heuck and Hoschek, 1968). Confidence in the database is low. The database lacks chronic exposure information on cerium via any route of exposure and multigenerational developmental and reproductive toxicity studies. However, there is evidence of cerium pneumoconiosis in humans exposed to cerium compounds, and the anticipated critical effects observed are point-of-entry effects that would be expected in humans. Reflecting medium confidence in the principal study and low confidence in the database, confidence in the RfC is low.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document -- U.S. EPA (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Cerium Oxide and Cerium Compounds* (U.S. EPA, 2009).

Agency Completion Date -- __/__/__

___I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Cerium oxide and cerium compounds
CASRN -- 1306-38-3
Section II. Last Revised -- 00/00/0000

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a)and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA,

2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

This is the first IRIS assessment for cerium oxide and cerium compounds, no carcinogenicity assessment was previously available on IRIS.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

No information is available on the carcinogenicity of cerium oxide and cerium compounds in humans.

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Data were unavailable regarding the carcinogenicity of cerium compounds in humans or experimental animals. In addition, the available information is insufficient to ascertain the mutagenicity of cerium compounds. In accordance with U.S. EPA (2005a) *Guidelines for Carcinogen Risk Assessment*, there is "inadequate information to assess the carcinogenic potential" of cerium in humans.

___II.A.2. HUMAN CARCINOGENICITY DATA

No relevant human data are available.

___II.A.3. ANIMAL CARCINOGENICITY DATA

No relevant animal data are available.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

No relevant human or animal data are available. In addition, the available information is insufficient to ascertain the mutagenicity of cerium compounds. The NTP has recently begun an evaluation of the chronic inhalation toxicity of cerium oxide, including a cancer bioassay. The date of completion and public availability of the results is unknown but may be expected in 2009.

A study in various strains of *S. typhimurium* demonstrated negative evidence of mutagenicity under the conditions of the assay (Shimizu et al., 1985). Cerium chloride did not induce DNA damage in two strains of *B. subtilis* by using the rec-assay (Nishioka, 1975), but cerium nitrate was reported to induce chromosomal breaks and reduce the mitotic index in rat bone marrow in vivo, and cerium sulfate was reported to cause differential destaining of chromosomal segments in plants (Sharma and Talukder, 1987).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Not applicable.

___II.B.2. DOSE-RESPONSE DATA

Not applicable.

___II.B.3. ADDITIONAL COMMENTS

Not applicable.

___II.B.4. DISCUSSION OF CONFIDENCE

Not applicable.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

Not applicable.

___II.C.2. DOSE-RESPONSE DATA

Not applicable.

___II.C.3. ADDITIONAL COMMENTS

Not applicable.

___II.C.4. DISCUSSION OF CONFIDENCE

Not applicable.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Cerium Oxide and Cerium Compounds* (U.S. EPA, 2009).

___II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

___II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Cerium oxide and cerium compounds
CASRN -- 1306-38-3
Section VI. Last Revised -- 00/00/0000

__VI.A. ORAL RfD REFERENCES

Cheng, Y; Li, Y; Li, R; et al. (2000) Orally administered cerium chloride induces the conformational changes of rat hemoglobin, the hydrolysis of 2,3-DPG and the oxidation of heme-Fe(II), leading to changes of oxygen affinity. Chem Biol Interact 125(3):191–208.

Eapen, JT. (1998) Elevated levels of cerium in tubers from regions endemic for endomyocardial fibrosis (EMF). Bull Environ Contam Toxicol 60:168–170.

Gómez-Aracena, J; Riemersma, RA; Guitiérrez-Bedmar, M; et al. (2006) Toenail cerium levels and risk of a first acute myocardial infarction: The EURAMIC and heavy metals study. Chemosphere 64: 112–120.

Kartha, CC; Eapen, JT; Radhakumary, C; et al. (1998) Pattern of cardiac fibrosis in rabbits periodically fed a magnesium-restricted diet and administered rare earth chloride through drinking water. Biol Trace Elem Res 63(1):19–30.

Kawagoe, M; Hirasawa, F; Wang, S-C; et al. (2005) Orally administered rare earth element cerium induces metallothionein synthesis and increases glutathione in the mouse liver. Life Sci 77:922–937.

Kumar, BP; Shivakumar, K; Kartha, CC; et al. (1996) Magnesium deficiency and cerium promote fibrogenesis in rat heart. Bull Environ Contam Toxicol 57(4):517–524.

Kutty, VR; Abraham, S; Kartha, CC. (1996) Geographical distribution of endomyocardial fibrosis in South Kerala. Int J Epi 25(6):1202–1207.

U.S. EPA. (2009) Toxicological Review of Cerium Oxide and Cerium Compounds. Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. EPA/635/R-08/002. Available online at http://www.epa.gov/iris.

Valiathan, MS; Kartha, CC; Eapen, JT; et al. (1989) A geochemical basis for endomyocardial fibrosis. ICMR Centre for Research in Cardiomyopathy, Trivandrum, India. Cardiovasc Res 23(7):647–648.

__VI.B. INHALATION RfC REFERENCES

BRL (Bio-Research Laboratories). (1994) Final report for a 90-day inhalation neurotoxicity and toxicity study by exposure to a dry powder aerosol of ceric oxide in the albino rat with cover letter dated 013095. Produced by Bio-Research Laboratories, Montreal, Canada for Rhone-Poulenc Inc. Submitted under TSCA Section 8E; EPA Doc. No. 89-950000107; NTIS No. OTS0556254. [An external peer review was conducted by EPA in August 2006 to evaluate the accuracy of experimental procedures, results, and interpretation and discussion of the findings presented. A report of this peer review is available through the EPA's IRIS Hotline, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (e-mail address) and on the IRIS website (www.epa.gov/iris).]

Heuck, F; Hoschek, R. (1968) Cer-pneumoconiosis. Am J Roentgenol Radium Ther Nucl Med 104(4):777–783.

Husain, MH; Dick, JA; Kaplan, YS. (1980) Rare earth pneumoconiosis. J Soc Occup Med 30:15–19.

Kappenberger, L; Bühlmann, AA. (1975) [Lung lesions caused by "rare earths"]. Schweiz Med Wochenscher 105:1799–1801. (German with English summary).

McDonald, JW; Ghio, AJ; Sheehan, CE; et al. (1995) Rare earth (cerium oxide) pneumoconiosis—analytical scanning electron microscopy and literature review. Mod Pathol 8(8):859–865.

Pairon, JC; Roos, F; Iwatsubo, Y; et al. (1994) Lung retention of cerium in humans. Occup Environ Med 51(3):195–199.

Pairon, JC; Roos, F; Sebastien, P; et al. (1995) Biopersistence of cerium in the human respiratory tract and ultrastructural findings. Am J Indus Med 27(3):349–358.

Pietra, R; Pietra, R; Sabbioni, E; et al. (1985) Trace elements in tissues of a worker affected by rare-earth pneumoconiosis. A study carried out by neutron activation analysis. J Radioanal Nucl Chem 92(2):247–269.

Porru, S; Placidi, D; Quarta, C; et al. (2001) The potential role of rare earths in the pathogenesis of interstitial lung disease: a case report of movie projectionist as investigated by neutron activation analysis. J Trace Elem Med Biol 14(4):232–236.

Sabbioni, E; Pietra, R; Gaglione, P; et al. (1982) Long-term occupational risk of rare-earth pneumoconiosis: a case report as investigated by neutron activation analysis. Sci Total Environ 26:19–32.

Sulotto, F; Romano, C; Berra, A; et al. (1986) Rare-earth pneumoconiosis: a new case. Am J Ind Med 9(6):567–575.

Vocaturo, G; Colombo, F; Zanoni, M; et al. (1983) Human exposure to heavy metals: rare earth pneumoconiosis in occupational workers. Chest 83(5):780–783.

Vogt, P; Spycher, MA; Ruttner, JR. (1986) [Pneumoconiosis caused by "rare earths" (cer-pneumoconiosis)]. Schweiz Med Wochenscher 116:1303–1308. (German with English summary).

Yoon, HK; Moon, HS; Park, SH; et al. (2005) Dendriform pulmonary ossification in patient with rare earth pneumoconiosis. Thorax 60(8):701–703.

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, Washington, DC; EPA/600/8-90/066F. Available from: National Technical Information Service, Springfield, VA; PB2000-500023, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (Environmental Protection Agency). (1995) Use of the benchmark dose approach in health risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-94/007. Available from the National Technical Information Service, Springfield, VA, PB95-213765, and online at http://cfpub.epa.gov/ncea/raf/raf_pubtitles.cfm?detype=document&excCol=archive.

U.S. EPA (Environmental Protection Agency). (2000a) Science policy council handbook: risk characterization. Office of Science Policy, Office of Research and Development, Washington, DC. EPA/100-B-00-002. Available online at http://www.epa.gov/OSA/spc/pdfs/prhandbk.pdf.

U.S. EPA (Environmental Protection Agency). (2000b) Benchmark dose technical guidance document [external review draft]. Risk Assessment Forum, Washington, DC; EPA/630/R-00/001. Available online at http://cfpub.epa.gov/ncea/cfm/nceapublication.cfm?ActType=PublicationTopics&detype=DOCUMENT&subject=BENCHMARK+DOSE&subjtype=TITLE&excCol=Archive.

U.S. EPA (Environmental Protection Agency). (2002) A review of the reference dose concentration and reference concentration processess. Risk Assessment Forum, Washington, DC; EPA/630/P-02/002F. Available online at http://cfpub.epa.gov/ncea/raf/raf_pubtitles.cfm?detype=document&excCol=archive.

U.S. EPA (Environmental Protection Agency). (2006a) Science policy council handbook: peer review. 3rd edition. Office of Science Policy, Office of Research and Development, Washington, DC; EPA/100/B-06/002. Available online at http://www.epa.gov/OSA/spc/2peerrev.htm.

U.S. EPA. (2009) Toxicological Review of Cerium Oxide and Cerium Compounds. Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. EPA/635/R-08/002. Available online at http://www.epa.gov/iris.

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

U.S. EPA. (2005a) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from:<http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA. (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA. (2009) Toxicological Review of Cerium Oxide and Cerium Compounds. Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. EPA/635/R-08/002. Available online at http://www.epa.gov/iris.

_VII. REVISION HISTORY

Cerium oxide and cerium compounds
CASRN -- 1306-38-3
File First On-Line 00/00/0000

Date	Section	Description
00/00/0000	I., II.	RfD, RfC, and cancer assessment first on-line

---

_VIII. SYNONYMS

Cerium oxide
CASRN -- 1306-38-3
Section VIII. Last Revised -- 00/00/0000

ceric oxide
cerium dioxide
ceria