HEI

COMMUNICATION 9

Evaluation of Human Health Risk from Cerium Added to Diesel Fuel

HEALTH EFFECTS INSTITUTE

August 2001

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Evaluation of Human Health Risk from Cerium Added to Diesel Fuel

ABSTRACT

The fuel efficiency and durability of diesel technology are particularly desirable in the transportation and construction industries. Concerns about the health effects of diesel particulate emissions have led to progressively stricter emission standards, which can be met only through new technologic advances and fuel modifications. The cerium-based fuel additive Eolys*, used in conjunction with a particulate filter, is one of the approaches being considered. However, this additive will result in emissions of cerium compounds and an increase in cerium in the ambient air and soil. HEI developed this report to provide a qualitative assessment of the possible health risk of cerium used as a fuel additive.

A limited number of short-term diesel engine tests have confirmed that cerium (20 to 100 ppm in the fuel) used with the particulate filter substantially decreases both particle mass (> 90%) and number (99%) concentrations in the exhaust. Despite the filter's high efficiency in trapping particulate matter (PM), however, a small amount of cerium is emitted in the particulate phase of the exhaust. Cerium measured in emissions was found primarily in the oxide form and in particles less than 0.5 µm in diameter. Cerium mass relative to the total particle mass was between 3% and 18% based on two tests using two different types of filters.

Because cerium is present in soil and is being used in some vehicle manufacturing and other industrial processes, a baseline level exists in both ambient air and soil. The most recent measurements in the Los Angeles area report cerium levels of about 0.5 ng/m^3 in fine PM. The average cerium level in the earth's crust worldwide has been estimated to be 20 to 60 ppm although higher levels have been measured in areas with anthropogenic sources of cerium. The one effort to estimate increases in environmental cerium concentrations from its use as a fuel additive suggested that the expected increase could be several orders of magnitude (in areas with a high volume of diesel traffic) and that cerium concentrations in soil may double over several decades. Specifically, an ambient cerium concentration of 0.6 µg/m^3 was estimated along a highway and of 1.25 µg/m^3 in a street canyon; concentrations due to deposition of cerium-containing PM in soil were predicted to be 5 to 30 ppm around roads with high traffic by the year 2050. Cerium in the soil may be absorbed into vegetation or may contaminate water, but the extent of such contamination cannot be estimated.

The main routes of exposure of the public to cerium-containing particles are inhalation and ingestion. Inhaled cerium is cleared from the respiratory tract by different pathways and at different rates depending on its solubility in body fluids. The clearance pathways include: mucociliary clearance to the mouth followed by swallowing and excretion via the feces; translocation to the pulmonary and tracheobronchial lymph nodes, and dissolution and absorption into the systemic circulation and distribution to various organs. Based on a 1978 classification by the National Council on Radiation Protection and Measurements (NCRP), relatively insoluble cerium compounds (such as hydroxides and oxides) are cleared from the lung over a period of years. The more soluble forms (such as chlorides, phosphates, and nitrates used in many of the experimental studies) are cleared over a period of weeks. Insoluble forms are also less likely than soluble forms to reach the circulation and be deposited in other organs, while a proportionally greater amount would be found in the lymph nodes. Modeling of particle (1 µm in diameter) clearance estimated that about 80% of inhaled cerium deposited in the lung would clear through the gastrointestinal tract, about 5% to 15% would translocate to the systemic circulation, and the remainder would translocate to the lymph nodes. Circulating cerium deposits primarily in the liver and bones and then is slowly removed. Other organs that may accumulate some cerium are spleen, heart, and brain.

Cerium taken up by ingestion is excreted in the feces after transiting in the digestive tract. Studies in rodents fed cerium salts (in relatively soluble forms) showed that less than 0.1% of the ingested dose is absorbed by the gastrointestinal tract and distributed to other organs.

* A list of abbreviations and other terms appears at the end of the Communication.

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Literature on the health effects of cerium is limited. Inhalation of cerium is of more concern than ingestion because cerium is poorly absorbed by the intestine. Primary targets after inhalation of cerium are the lung and the associated lymph nodes; other organs could be affected via clearance through the blood. Case reports of workers occupationally exposed to rare earth metals (including cerium) describe a condition termed *rare earth pneumoconiosis* with pathologic features including interstitial fibrosis, granulomatosis, and bilateral nodular chest x-ray infiltrates. Although the disease sometimes is associated with accumulation of cerium in particles, the role of cerium in this complex disease is unclear relative to other metals or gases to which workers may also have been exposed.

The only animal inhalation study involved exposure of rats to cerium oxide particles substantially larger than those in diesel emission. The exposure concentrations ranged between 5 and 500 mg/m^3 for 13 weeks. Effects observed included lung discoloration, enlargement of lymph nodes and increased lung and spleen weight at all concentrations. In comparison, ambient levels of cerium are estimated to increase above baseline by 1.2 µg/m^3 in high traffic areas.

Studies of cerium injected systemically have shown that, once in the circulation, cerium can cause liver toxicity with a NOAEL of 1 mg/kg after a single intravenous injection and a LOAEL of 2 mg/kg for effects on liver detoxifying enzymes. Effects on other organs where cerium can accumulate (such as spleen, bones, and kidney) have not been studied.

In the worst case for human inhalation of cerium oxide, the estimated dose to the lung would be about 6 µg (or 0.09 µg/kg); if 5% of this dose is cleared to the blood (based on the NCRP model), the resulting blood dose would be 0.004 µg/kg. Although these dose estimates are based on assumptions, they are about six orders of magnitude lower than those shown to cause systemic effects in rats.

Behavioral effects (such as reduced activity and reduced forelimb grip) were observed after subcutaneous administration (cerium citrate, LOAEL 136 mg/kg) and inhalation exposure (cerium oxide, NOAEL 50 mg/m^3), respectively. These doses are higher than those shown to cause toxicity to the major target organs (liver and lungs).

One single-dose study on the effects of in utero intravenous administration reported reduced weight in newborn mouse pups, with a LOAEL of 80 mg/kg. The potential carcinogenicity of cerium-containing particles has not been studied in conventional rodent bioassays; mutagenicity studies have been negative.

Based on the limited data available, toxicity of cerium oxide appears to be small, and cerium oxide might not be of concern when inhaled or ingested at the low levels that would be encountered in the environment from the use of Eolys (estimated to be in the low µg/m^3 range in the air). The absence of more complete information precludes fully assessing the possible health effects of using cerium as a fuel additive. Ultimately, decisions about the use of the cerium additive, or other metal additives, need to be made in the context of a variety of factors besides information on exposure, rate of clearance from the body, and health effects. Other considerations are the additive's ability to reduce harmful emissions, its persistence in the environment, and the feasibility and cost effectiveness of this technology in comparison with other technologies that can achieve these reductions.

INTRODUCTION

Cerium is a fuel-borne catalyst proposed for reducing PM emissions from diesel engines. These engines, an important part of the world's transportation and industrial infrastructure, contribute to PM mass and number in urban areas. Because of concerns about health effects of ambient PM in general and of diesel PM as a probable human carcinogen, the US Environmental Protection Agency (EPA), the European Commission, and other government agencies worldwide have set progressively tighter PM emission standards in the last three decades. As shown in Appendix A, however, recent and planned regulatory standards mandate reduction of such emissions beyond the present levels, and may necessitate new technologic advances. Concomitant reduction in emission of oxides of nitrogen (NO_x; gaseous compounds in diesel exhaust) needs to be achieved because they contribute to formation of ozone.

To meet the new PM emission standards, various approaches have been taken or are being considered. Some of these, such as lowering the sulfur content of the fuel or improving engine design, are currently being implemented, but may not be sufficient to meet requirements for further reduction in emissions. Moreover, reducing PM through changes in fuel or engine design is often achieved without also reducing NO_x. One approach to lowering PM emissions is to use a particulate filter alone or in conjunction with a fuel-borne catalyst. In addition to installing such filters in new diesel vehicles, consideration is being given to retrofitting older vehicles. Particulate filters are made of temperature-resistant porous material such as ceramic or fibers with a high surface area.

Although a filter is effective in lowering PM emissions, technical problems are associated with its use. Over time, the filter tends to become clogged with trapped particles,

increasing exhaust back pressure and reducing engine efficiency, which in turn leads to greater fuel consumption. This soot can be eliminated through filter regeneration (burning); however, generally, with a filter alone, soot cannot be burned off effectively at temperatures that are likely to occur during normal driving, and problems associated with soot accumulation tend to remain. One approach to improving the filter system and addressing the regeneration demands is to use the filter in conjunction with a fuel-borne catalyst. The role of the catalyst is to enhance the combustion of the soot collected on the filter by reducing the ignition temperature so that the soot can burn off during normal driving conditions. One such catalyst is a cerium-based organic compound developed by Rhodia Rare Earths (previously a subsidiary of Rhône-Poulenc Basic Chemical Company) under the trade name of Eolys.

The use of a cerium-based fuel additive can be expected to increase the levels of cerium in the environment, both in the ambient atmosphere and as deposits on soil, vegetation, and water close to roadways where significant numbers of diesel-powered vehicles are traveling. To address questions from sponsors about potential adverse health effects from a cerium-based additive with a particulate filter, HEI has developed this report, which evaluates and integrates information on:

- existing cerium occurrence and use,
- diesel engine emissions,
- resulting ambient concentrations of cerium,
- dose of cerium to target tissues after uptake into the body, and
- health effects associated with exposure to cerium compounds.

The report was developed by HEI scientific staff and members of the HEI Research and Review Committees and was submitted to peer review byscientific experts from industry, government, and academic institutions. The intent of the report is to provide a qualitative assessment of potential health risk from the cerium additive and not to evaluate the additive-plus-filter technology nor to compare this technology with competing technologies.

CERIUM OCCURRENCE AND USE

Cerium is a member of the lanthanide series of rare earth metals. This series consists of 15 elements, including (in order of increasing atomic number) lanthanum, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, and lutetium. While most rare earths exist in a trivalent state, cerium, promethium, and terbium also occur in a +4 state (Haley 1991). After europium, cerium is the most reactive of the rare earth metals, easily oxidizing at room temperature and forming a variety of salts, including (in decreasing order of solubility in body fluids): sulfates, nitrates, chlorides, phosphates, hydroxides, and oxides.

Although cerium is a rare earth element, it is relatively abundant in the earth's crust. Among the lanthanides, it is the most abundant, and among the 78 common elements in the earth's crust, it ranks 25th in occurrence at an average distribution of 20 to 60 ppm (Windholz 1983; Hedrick 1998). This makes it as abundant as cobalt, tin, zinc and vanadium. Cerium is found primarily in monazite and bastnazite ores in the form of orthophosphate and fluorocarbonate, respectively. The most important deposits of monazite sands, the primary source of cerium, are found in the United States, Australia, Brazil, India, South Africa, and China (Hedrick 1998). Large deposits of bastnazite are found in Southern California and in China (Hedrick 1998). These ores can be found in granite and sandstone (Sugimae 1980).

Rare earth elements are used in a number of industrial applications, and the annual worldwide demand for rare earth metals is expected to continue increasing. Current applications for cerium include lighters, carbon arc lamps, glass additives, ceramics, abrasives, and permanent magnets (Hedrick 1998). The element is widely used in the three-way catalysts for emissions control systems of modern gasoline engines to enhance oxidation efficiency of the catalyst. For this application, cerium is incorporated in the catalyst washcoat (a very thin porous layer coated on a metal or ceramic honeycomb), serving as an oxygen storage site.

Cerium is also likely to find future application as a steam-reforming catalyst in the process of conversion of hydrocarbon (HC) fuels to hydrogen for fuel cells. Future industrial growth for rare earths is forecast in magnetic refrigeration, rechargeable nickel hydride batteries, fiber optics, and medical equipment.

PROPOSED USE

Use of the Eolys fuel-borne additive has been considered a means to improve regeneration of the particulate filter. This product has been recently introduced by Peugeot Citroën on light-duty (LD) diesel engines. (See sidebar, PSA Peugeot Citroën System, on the following page.) In the Peugeot Citroën design, the cerium is carried in a canister on board and is mixed automatically with the fuel via a dosing system (rather than added to the fuel before sale), thereby assuring that diesel fuel containing cerium is used only on vehicles with filters. Fuel-borne

PSA Peugeot Citroën System

PSA Peugeot Citroën has developed and is beginning to market a direct-injection diesel engine that utilizes a sophisticated computer control system, an oxidative catalyst, a particulate filter (downstream of the catalyst), and the Eolys cerium additive.

Under the PSA Peugeot Citroën design, regeneration consists of periodically burning particles accumulated in the filter and occurs spontaneously when the exhaust temperature reaches 550°C. The Eolys additive lowers the spontaneous combustion temperature of the particles to 450°C (a temperature that can be reached in highway driving). This temperature is still higher than normal exhaust temperature during urban driving (150 to 200°C), however, and a two-stage system to increase the exhaust temperature has been developed. According to the manufacturer, complete regeneration takes 2 to 3 minutes and occurs every 400 to 500 km of urban driving. The cerium is stored in a reservoir with a 1-L capacity and is automatically added to the fuel tank after refilling (to a final concentration of about 30 ppm). The 1-L capacity gives a range of 100,000 km before refilling. At that time, the filter needs to be cleaned.

See also: www.rhodia-rare-earths.com.

catalysts based on sodium, iron, platinum, or strontium have also been developed and may be used in the future. Others, such as manganese-based and copper-based additives, were considered in the past.

The Eolys additive is registered with the EPA for use in diesel fuel with a particulate filter under the identification DPX. The Swiss and German governments have approved use of the Eolys cerium additive in conjunction with a particulate filter and mandate such a system in all heavy-duty (HD) vehicles to be used underground. To insure that filters meet certain performance standards, the Swiss government has implemented a testing protocol for filter certification.

In a related application, Clean Diesel Technologies has registered with the EPA a diesel fuel additive containing cerium and platinum (as organic compounds) under the identification Platinum Plus DPX. This additive can be used in bulk fuel or in individual vehicles without filters to promote soot oxidation or with filters to assist regeneration of the filter (the total metal concentration in the fuel would range between 4 and 8 ppm). That the additive appears to provide a fuel economy improvement of 5% to 7% may enhance its use by the trucking industry. This product is approved for use in combination with a particulate filter for Swiss and German markets.

This review considers only the use of the Eolys cerium additive, a fuel-borne catalyst used in association with a particulate filter, but the Clean Diesel application is likely to increase the ambient levels of cerium as well.

CHARACTERIZATION OF EMISSIONS WITH CERIUM ADDITIVE

The main purpose of using a fuel-borne catalyst is to reduce the ignition temperature of the carbonaceous exhaust particles, thereby reducing the PM mass emitted in the exhaust. The fuel-borne catalyst is most effective in conjunction with a particulate filter. Use of the filter alone has been reported to be associated with a higher exhaust back pressure, which increases fuel consumption, and elevated exhaust temperatures, which could damage the filter. Engine tests have shown that adding the cerium catalyst to diesel fuel, generally at concentrations ranging from 20 to 100 ppm, lowers the ignition temperature of the soot* to less than 500°C, thereby facilitating regeneration of the filter. Regeneration in the presence of cerium is generally smooth, engine back pressure remains more or less constant, and high local peak temperatures inside the trap do not occur (Lepperhoff et al 1995). However, problems with exhaust temperatures too low to ignite the soot (especially at low engine speeds) and with exhaust back pressure may remain (Lemaire et al 1994; Lepperhoff et al 1995; Pattas et al 2000). To solve these problems, substantial research has been conducted to improve the combustion process and facilitate soot burnoff. The PSA Peugeot Citroën includes a two-stage system to increase the exhaust temperature, which is needed during urban driving at speeds lower than 35 miles/hour.

A number of emission tests have been conducted to evaluate the effect of the cerium catalyst, alone and in conjunction with a particulate filter, on PM and gaseous emissions. Test results are summarized in the following text and in Tables 1 through 5. Details on the conditions of the tests are provided in Appendix B. These tests have been conducted with a range of engines, test cycles, fuel compositions, cerium concentrations, and exhaust dilution systems. Moreover, each report presents the emission rates in different units. For all these reasons, emissions cannot be compared directly across studies. However, by comparing the emissions in the absence and presence of cerium, or in the absence and presence of cerium and a particulate filter for each study, some information about the effect of the particulate filter-plus-cerium additive technology can be gleaned.

PM EMISSIONS WITH ADDITIVE BUT NO FILTER

Using the Eolys cerium additive without a filter is not currently under consideration by either Rhodia or regulatory

* Soot: porous carbonaceous material coated with HC components.

agencies. However, understanding the effect of using it alone is helpful as baseline information. Most of the studies using cerium alone (see Table 1) found a reduction in the PM mass emissions ranging from 15% to 50% (Japan Automobile Research Institute 1995; Lepperhoff et al 1995; Ladegaard et al 1997; Heeb 1998a; Skillas et al 2000), while two studies found no change (Samaras 1994; Southwest Research Institute 1997). A cerium concentration of 20 ppm was sufficient to obtain the mass reduction of 15% to 50% observed at different test cycles by Skillas and coworkers (2000) and higher concentrations did not provide additional benefits. The mass reduction affected mostly particles larger than 50 nm.

Some studies measured changes in the proportions of elemental carbon (EC) and organic carbon (OC) of the particles as a result of the use of cerium (see Table 2). Skillas and colleagues (2000) found that the overall mass reduction was associated with a decrease in OC content of the PM, while EC content remained more or less unchanged. The Japan Automobile Research Institute (1995) and Lepperhoff and colleagues (1995) studies reported a decrease in the amount of EC, but found no change in the organic fraction. These results are hard to interpret because particle composition depends on the interplay of such factors as fuel composition and test cycle in addition to use of the additive.

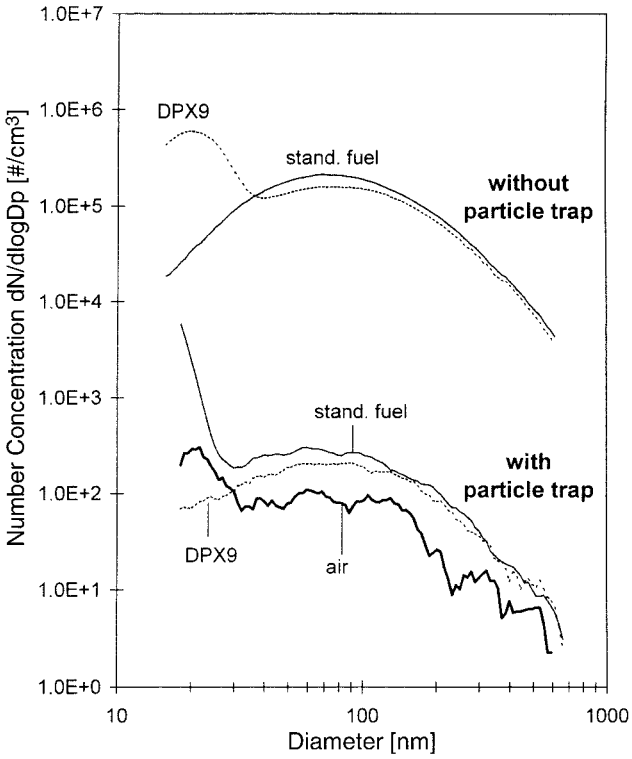

Figure 1. Number-weighted particle size distribution obtained from a Liebherr D914 T engine operated at rated rpm (2,000 rpm) and full load with a thermodenuder. Test conditions were with and without a Corning particulate filter, and with and without the Eolys cerium additive (DPX9). The ambient air particles were taken from the engine test room. (Obtained from Czerwinski et al 2000 courtesy of Jan Czerwinski, Biel School of Engineering and Architecture, Biel-Beinne, Switzerland, and Rhodia, LaRochelle Cedex, France.)

Czerwinski and coworkers (1999) measured the number of particles between 20 and 500 nm emitted after addition of 50 ppm cerium to the fuel (after passing the exhaust through a thermodenuder to remove the volatile particles). They noted an increase in total number of solid particles (up to 5-fold depending on operating mode and type of filter) and the emergence of a peak of very small particles (< 30 nm in diameter). An example of the size distribution without and with the additive is shown in Figure 1 (from Czerwinski et al 2000). Skillas and coworkers (2000) also reported formation of very small particles (≤ 20 nm) in the presence of cerium alone. These solid particles were composed of cerium oxide. Some cerium was also incorporated into the larger soot particles. Skillas speculated that the formation of ultrafine cerium particles (due to homogeneous nucleation) depended on the concentration of cerium in the fuel and occurred when the amount of cerium became too large to be incorporated into the soot. Lepperhoff and colleagues (1995) also found an increase in the number of fine and ultrafine particles in the presence of 50 ppm cerium alone (relative to the filter plus cerium). Although they attributed the increase in these particles to condensation of hydrocarbons, they did not conduct any chemical analysis to support this conclusion. Cerium content represented 15% to 20% of the particulate mass (Heeb 1998a; Skillas et al 2000) (data not shown in tables).

PM EMISSIONS WITH ADDITIVE AND FILTER

As presented in Table 1, use of the cerium catalyst in conjunction with the filter reduced particulate mass emissions by 70% to 98% in comparison to emissions without the additive and filter (Samaras 1994; Lepperhoff et al 1995; Pattas et al 1996; Heeb 1998a; Czerwinski et al 1999, 2000; Khair et al 2000). The mass reduction was accompanied by an overall reduction of 99.9% in the exhaust solid particle number over the size distribution spectrum of 20 to 500 nm (Czerwinski et al 1999, 2000). This number reduction is illustrated in Figure 1, which compares the number-weighted size distribution in the presence of the filter alone and of the filter in conjunction with the additive, relative to that in the untreated exhaust. A study to evaluate the effect of the filter-plus-cerium additive technology in combination with engine gas recirculation (EGR) technology to reduce NO_x also showed a benefit of the filter-plus-fuel additive in reducing PM. While EGR increased PM mass emissions (during a transient cycle)

Table 1. Effects of Diesel Cerium Additive and Particle Filter on Particle Emissions (Mass or Number)

Study (Ce in Fuel)[a]	Filter Type/Test Cycle	Baseline	+ Ce[b]	+ Ce + Filter[b]	Filter Alone[b]
Czerwinski et al 1999 (50 ppm)	IBIDEN/average of data from 2 filters with different pore sizes; steady state mode at full load; mean rpm for 15 minutes for mass and full load rated rpm for number	0.098 g/kWh		0.0073 g/kWh (–93%)	0.009 g/kWh (new filter) (–91%) 0.007 g/kWh (soot-loaded) (–93%)
		9.5×10^6/cm^3	20.2×10^6/cm^3 (+125%)	1.76×10^3/cm^3 (–99.9%)	1.38×10^3/cm^3 (new filter) (–99.9%) 1.54×10^3/cm^3 (soot-loaded) (–99.9%)
Czerwinski et al 2000 (50 ppm)	Corning/steady state mode at full load; mean rpm for 15 minutes for mass and full load rated rpm for number	0.076 g/kWh	–0.053 g/kWh (–30%)	0.0075 g/kWh (–90%)	0.008 g/kWh (new filter) (–90%) 0.008 g/kWh (soot-loaded) (–90%)
		9.16×10^6/cm^3	12.4×10^6/cm^3 (+35%)	9.7×10^3/cm^3 (–99.9%)	9.9×10^3/cm^3 (new) (–99.9%) 15.9×10^3/cm^3 (soot-loaded) (–99.8%)
Heeb 1998a (64 ppm)	SHW (metal filter)/8-mode steady state test for 400 minutes	0.130 g/kWh	0.092 g/kWh (–29%)	0.005 g/kWh (–96%)	0.007 g/kWh (–95%)
	BUCK (knitted glass filter)/8-mode steady state test for 400 minutes	0.130 g/kWh	0.092 g/kWh (–29%)	0.013 g/kWh (–90%)	0.016 g/kWh (–88%)
JARI 1995 (100 ppm)	Japan 13-mode test	0.41 g/kWh	0.33 g/kWh (–20%)		
Khair et al 2000 (Ce concentration not specified [with selective catalytic reduction and 46% urea])	Corning/US HD transient cycle with or without cold start	0.079 g/bhp-h (Cold) 0.066 g/bhp-h (Hot)		0.005 g/bhp-h (Cold) (–94%) 0.002 g/bhp-h (Hot) (–97%)	
Ladegaard et al 1997 (100 ppm)	3 steady state tests at different loads	90 mg/Nm^3 (11 kW)[c] 110 mg/Nm^3 (20 kW) 160 mg/Nm^3 (28 kW)	60 mg/Nm^3 (–37%)[c] 70 mg/Nm^3 (–34%) 125 mg/Nm^3 (–22%)		
Lemaire and Khair 1994 (100 ppm)	EPA transient FTP with one cold followed by two hot starts; each run for 24 hours	0.23 g/bhp-h (Cold) 0.15 g/bhp-h (Hot)	0.21 g/bhp-h (Cold) (–9%) 0.14 g/bhp-h (Hot) (–7%) 0.28 g/bhp-h (Cold) (1000 hours) 0.14 g/bhp-h (Hot) (1000 hours)		

(Table continues next page)

[a] Details about the tests can be found in Appendix B.

[b] Change from baseline value in parentheses.

[c] Units as reported by authors.

Table 1 *(continued)*. Effects of Diesel Particle Filter and Cerium Additive on PM Emissions (Mass or Number)

Study (Ce in Fuel)[a]	Filter Type/Test Cycle	Baseline	+ Ce[b]	+ Ce + Filter[b]	Filter Alone[b]
Leperhoff et al 1995 (50 ppm)	Corning/test cycle not specified	6.2 µg/hr	5 µg/hr (−19%)	0.65 µg/hr (−90%)	
Pattas et al 1992 (100 ppm)	NGK/US transient test (FTP)	0.18 g/km	0.14 g/km (−22%)	0.03 g/km (−83%)	0.03 g/km (−83%)
Psaras et al 1997 (125 ppm Ce [with engine gas recirculation])	Corning/US HD transient cycle	0.17 g/bhp-h (EGR baseline 0.47 g/bhp-h)		0.02 g/bhp-h (with EGR) (−88%)	
Samaras 1994 (100 ppm)	Donaldson/US transient cycle with hot start	0.211 g/bhp-h	0.224 g/bhp-h (+6%)	0.034 g/bhp-h (−84%)	0.046 g/bhp-h (−78%)
	Pattas system (Corning EX-80) European 13-mode test procedure	1.19 g/kWh		0.26 g/kWh (−78%)	0.26 g/kWh (−78%)
Skillas et al 2000 (20 ppm)	four operating modes of EC 13-mode steady state cycle; each run for 15 minutes	20 mg/m^3 (mode A) 23 mg/m^3 (mode B) 20 mg/m^3 (mode C) 12 mg/m^3 (mode D)	17 mg/m^3 (−15%) 17 mg/m^3 (−26%) 12 mg/m^3 (−40%) 6 mg/m^3 (−50%)		

[a] Details about the tests can be found in Appendix B.

[b] Change from baseline value in parentheses.

[c] Units as reported by authors.

Table 2. Content of EC (Soot) and OC in Particle Emissions Under Various Test Conditions

Study[a]	Component	Baseline	+ Ce	+ Ce + Filter
JARI 1995[b]	Dry soot SOF	0.24 g/kWh 0.15 g/kWh	0.15 g/kWh 0.15 g/kWh	
Lepperhoff et al 1995[c] (derived from graph)	Soot SOF	2.7 g/hr 3.7 g/hr	1.5 g/hr 3.7 g/hr	0.13 g/hr 0.53 g/hr
Skillas et al 2000[d] (derived from a figure)	EC OC	12,17,10,4.5[e] mg/m^3 13,6,12,6.5[e] mg/m^3	11,13,8,2.5[e] mg/m^3 4,3,4,2.5[e] mg/m^3	

[a] Details about the tests can be found in Appendix B.

[b] Dry soot: mass remaining after drying the particles on the filter. SOF: soluble organic fraction of particles obtained by extraction with dichloromethane.

[c] Soot determined by ThermoGravimetric Analysis; SOF determined by extraction of the particles on the filter.

[d] EC and OC emission factors calculated from coulometric analysis of material collected on filters and the mass of fuel burned.

[e] Values for 4 operating conditions.

from 0.17 g/bhp-h to 0.47 g/bhp-h, the combination of EGR and the filter-plus-fuel additive lowered PM emission to 0.02 g/bhp-h, a reduction of 88% of the mass relative to baseline (without EGR) and 95% relative to EGR alone (Psaras et al 1997). Another technology to reduce NO_x emissions that was tested in combination with the filter-plus-cerium additive was selective catalytic reduction with urea in the fuel (Khair et al 2000). Particulate mass emissions were reduced by 94% by the filter-plus-cerium additive system during a transient test with a cold start and by 97% during a transient test with a hot start.

Analysis of the carbon content of the emitted particles conducted by Lepperhoff and colleagues showed a proportionally greater reduction in the soot content (used to indicate the EC content) (from 42% of the total carbon content to 20%; see Table 2). Heeb (1998a) also showed that the effect of cerium in combination with the filter was to provide a greater reduction in the insoluble soot (ie, EC) content (from 76% to about 40% to 66% of the PM mass, depending on the filter used) relative to the soluble organic content. Data are not shown in the table because no absolute values were reported.

In general, use of the filter alone was as effective as the combination of filter-plus-cerium additive in trapping particles and reducing the particle mass and number in emissions (see Table 1 and example in Figure 1; Samaras 1994; Pattas et al 1996; Heeb 1998a; Czerwinski et al 1999, 2000). A slightly higher number of ultrafine particles was observed for some operating conditions using the filter alone as well as the filter with the additive (Czerwinski et al 2000). This rise was attributed to the spontaneous condensation of volatile sulfates or hydrocarbons which were not retained by the thermodenuder due to saturation. Spontaneous condensation of volatile compounds has been described as being likely to have a greater potential to occur downstream of the filter, because solid carbonaceous agglomerates that may absorb volatile compounds are removed by the filter (Abdul-Khalek et al 1998).

In the presence of the cerium additive and the particulate filter, the particles emitted contained some cerium in the form of cerium oxide (see Table 3). One study reported the concentration of cerium oxide to be 0.4 ng/m^3 in the diluted exhaust during a one-hour period in the absence of regeneration, and 4.7 ng/m^3 during a 15-minute regeneration period (Khair et al 2000). In comparison, the amount of cerium oxide emitted in the absence of a filter over 1-hour period was 174 ng/m^3. The investigators concluded that the filter had a filtration efficiency for cerium of 99.8% during normal conditions and of 97.3% during regeneration.

Table 3. Cerium Mass Emissions With and Without the Particulate Filter

Study (Conditions)[a]	Ce Alone	Ce + Filter[b]	Ce + Filter During Regeneration[b]
Heeb 1998a (64 ppm Ce [400-minute test])	18.1 mg/kWh	0.1 mg/kWh (metal sintered filter) (–99.4%)	
		2.3 mg/kWh (fiber filter) (–87%)	
Khair et al 2000 (50 ppm Ce [1-hour test])	0.174 µg/m^3	0.0004 µg/m^3 (–99.8%)	0.0047 µg/m^3 (–97.3%) (15 min)
Skillas et al 2000 (50 or 100 ppm Ce [15-minute test])	249–296 µg/mass fuel burned (100 ppm Ce)		
	138 µg/mass fuel burned (50 ppm Ce)		
Southwest Research Institute 1997 (100 ppm Ce [24-hour test])	46.48 mg/bhp-h (Cold) 45.49 mg/bhp-h (Hot) 8.8 mg/bhp-h (no Ce)		

[a] Details about the tests can be found in Appendix B.

[b] Change from value with cerium alone in parentheses.

Table 4. Effects of the Filter and the Cerium Additive on Regulated Gaseous Emissions

Study[a] [Units]	NO_x		HC		CO	
	Baseline	+ Ce + Filter[b]	Baseline	+ Ce + Filter[b]	Baseline	+ Ce + Filter[b]
Czerwinski et al 2000 [**g/kWh**]	17.32	15.90 (–8%)	0.19	0.18 (0%)	0.42	0.63 (+50%)
Czerwinski et al 1999 [**g/kWh**]	16.38	15.54 (–5%)[c]	0.18	0.10 (–45%)[c]	0.41	0.63 (+54%)[c]
Heeb 1998a [**g/kWh**]	7.55	7.38 (–2%)[d]	0.34	0.19 (–44%)[d]	0.48	0.57 (+19%)[d]
Khair et al 2000 [**g/bhp-h**] (for all conditions a catalyst and urea were used)	1.94 (Cold) 1.09 (Hot)	1.56 (Cold) (–20%) 1.1 (Hot) (0%)	0.01 (Cold) 0.005 (Hot)	0.056 (Cold) (+500%) 0.009 (Hot) (+80%)	1.86 (Cold) 1.15 (Hot)	2.01 (Cold) (+8%) 1.1 (Hot) (0%)
Psaras et al 1997 [**g/bhp-h**] (EGR used in some of the tests as specified)	3.56 2.64 (with EGR)	2.1 (with EGR)				
Samaras 1994 DDC [**g/bhp-h**][e]	4.763	4.056 (–15%)	0.368	0.495 (+34%)	1.78	3.62 (+100%)
RABA/MAN [**g/kWh**][f]	16.2	15.0 (–8%)	1.15	1.15 (0%)	11.2	14.7 (+31%)

[a] Details about the tests can be found in Appendix B.
[b] Change from baseline value in parentheses.
[c] Average of emissions from two filters of different pore sizes.
[d] Average of emissions from two different filters.
[e] EPA transient cycle with hot start.
[f] 13-mode test.

Heeb (1998a) reported an emission rate of 0.1 mg/kWh cerium oxide with a sintered metal particulate filter, 2.3 mg/kWh with a fiber filter, and 18.1 mg/kWh without a filter. The mass filtration efficiency for cerium oxide in this study was greater than 99% with the first filter and 87% with the second filter. Heeb calculated that the particle-bound cerium represented 19% of the PM mass in the absence of the filter (see section above) and 2.7% or 18.2% in the presence, respectively, of the sintered metal filter or the fiber filter (data not shown in tables).

Pattas and colleagues (1992) analyzed the particulate deposit at the filter inlet area. They found that soot particles were rather homogeneous in size (50 nm), but that cerium oxide particles were nonhomogeneous, with sizes ranging from 10 to 150 nm. Many of the cerium oxide particles had a highly aggregate composition.

GASEOUS EMISSIONS WITH ADDITIVE AND FILTER

The results of a few studies measuring the effects of cerium in combination with the particle filter on regulated emissions (other than PM) and unregulated emissions are summarized in Tables 4 and 5, respectively. The studies (Heeb 1998b; Samaras 1998; Czerwinski et al 1999, 2000) showed that the use of cerium in conjunction with the filter either did not affect NO_x emissions, or reduced them; and increased emissions of carbon monoxide (CO) by about 8% to 100% (with the exception of one test, where they were unchanged). The maximum NO_x reduction (20%) was observed when the filter-plus-additive system was combined with a technology specifically designed to control NO_x, such as addition of urea to the fuel (Khair et al 2000), or EGR technology (Psaras et al 1997). Effects on hydrocarbons (HC) did not consistently show a trend toward a reduction or an increase. Only one report presents the effect of the cerium-plus-filter system on unregulated emissions (Heeb 1998b). Levels of benzene, 1,3-butadiene, and acetaldehyde were increased by about 50%, those of formadehyde were unchanged, and those of polynuclear aromatic hydrocarbons (PAHs) were reduced by about 80%.

DISCUSSION

The studies reported above have limitations. First, they used different amounts of cerium, different engines, test conditions, and sampling protocols, and fuels with different sulfur contents. All these factors can affect the baseline particulate emissions as well as the emissions after the control system. Second, the majority of the reported studies lacked information about regeneration, although it is likely that regeneration was occurring continuously in many of the tests at high load. Lack of such data is an

Table 5. Effects of Filter and Cerium Additive on Unregulated Emissions[a] (Heeb 1998b)

Component	Baseline	+ Ce + Filter[b]
Benzene (mg/kWh)	0.98	1.55 (+58%)
1,3-Butadiene (mg/kWh)	0.55	0.87 (+58%)
Acetaldehyde (mg/kWh)	1.76	2.47 (+40%)
Formaldehyde (mg/kWh)	13.6	13.7 (0%)
PAH (µg/kWh)	1.65	0.29 (–82%)
TCCD (pg/L)	3	2.5 (–17%)

[a] Details about the tests can be found in Appendix B.

[b] Change from baseline value in parentheses.

important limitation since the highest emissions are likely to occur during regeneration. Lastly, emissions were measured during short test periods, generally with new engines and new filters. Thus, results cannot be expected to provide information on the effect of filter and engine aging on the composition of emissions.

Despite these limitations, the studies demonstrate that, under controlled engine tests, the cerium additive in conjunction with the filter can reduce the PM mass emissions by 70% to 98%. As shown by Heeb (1998a) and Czerwinski and coworkers (1999, 2000) filter types vary in filtration efficiencies. Generally, tests showed that the filter plus the cerium additive was 1% to 2% more efficient in reducing the particle mass than the filter alone. The highest filtration efficiency, over 90% (both with filter alone and filter plus additive), was observed in the most recent studies. These measurements used relatively modern diesel engines and diesel fuel with lower sulfur content and a thermodenuder to remove volatile PM. Therefore, the potential of emissions to form volatile particles downstream of the filter could not be evaluated.

The only study that compared PM mass emissions during a test with and without a cold start showed that higher PM emissions, either in untreated exhaust or in the presence of the filter with cerium additive, occur during the cold start (Khair et al 2000); however, a similar reduction in the PM mass was achieved with or without the cold start when the filter-plus-additive system was used. The effect of cerium with the filter seems to be primarily a reduction of the PM insoluble soot content. The filtration efficiency for cerium (on mass basis) was calculated to be generally greater than 90%.

Czerwinski and coworkers (1999, 2000) also showed a greater efficiency (up to 99.9%) of both the filter alone and the filter plus cerium additive in reducing the number of solid particles that were between 20 and 200 nm in diameter than in reducing the total particle mass. One possible explanation for this observation is that the filter efficiency in trapping the particles is lowest for 0.1–0.2 µm particles where most of the mass is found (D Kittleson, personal communication, 2001).

The two studies that measured the level of cerium in emissions found that small amounts of cerium oxide particles are emitted (Heeb 1998a; Khair et al 2000). However, retention of cerium mass (measured in two studies) was reported to be generally greater than 99% (but could be lower depending on the type of filter used). An increase in cerium emission was observed during a test of filter regeneration relative to normal operating conditions (from 0.0004 µg/m^3 to 0.0047 µg/m^3). The form of cerium produced has been shown to be primarily cerium oxide; however, phosphate and sulfate forms are expected to be present. The phosphate form would result from the burning of the phosphate additive in the engine oil lubricating the cylinders (E Pellizzari, personal communication, 2001). At this time, it is difficult to speculate about how cerium-containing particles are formed and the particle size in which cerium is present. Given that nuclei of soot particles are substantially reduced in the presence of the filter and the additive, one would expect that a portion of the cerium oxide emitted will be present, at least initially, in nuclei-mode (ultrafine) particles. Findings with cerium alone and the limited analyses of the cerium-containing material deposited on the filter would support this hypothesis. However, the influence of the metal on the ratio of metal to soot and the concentration of metal in nuclei-mode particles has not been investigated.

The limited tests conducted to determine the effect of the filter with cerium additive on other emissions showed that this system may increase CO and air toxics such as benzene and butadiene, but reduce emissions of gaseous PAHs. NO_x emissions seem to be unaffected or slightly reduced. Effects on total HC were extremely variable.

CHARACTERIZATION OF EXPOSURE TO CERIUM FROM ADDITIVE

Identifying potential health risks from the use of cerium as a fuel-borne catalyst requires information on the nature and extent of exposure of the population. Although exposure to cerium can occur during manufacturing, use, and disposal of the compound, this review presents only data on ambient concentrations of cerium (in air and soil) that would derive from HD and LD diesel engines with particulate filters. People can be exposed to cerium in exhaust from diesel

vehicles by inhalation of cerium-containing particles or by ingestion of cerium-containing food or water (after deposition of the particles along roadways). Dermal contact may also occur. Because cerium is a naturally occurring element in the earth's crust and is used in many industrial applications, any exposure derived from its use as a fuel additive must be considered in the context of existing ambient levels.

CERIUM EMISSION FACTORS

Because the Eolys additive has been used only in limited applications in some European countries, measurements of exposure from its use are not available. Therefore, we have to rely on modeling calculations to estimate ambient levels of cerium. In a study conducted for Rhône-Poulenc, Samaras (1994) used a number of assumptions and models to estimate cerium emission rates for various types of diesel vehicles and to derive the cerium concentrations in two scenarios with high traffic.

Emission rates were calculated from the concentration of cerium in the fuel (100 ppm), the retention efficiency of the filter (assumed to be 92% for cerium mass and 70% for particulate mass), fleet composition, and fuel consumption for various types of diesel vehicles over a range of driving conditions (Table 6). Specifically, emission rates were modeled for passenger cars, LD vehicles, HD trucks, urban buses, and coaches for urban, rural, and highway driving in the 12 European Union (EU) countries for the year 2010 assuming 75% of the vehicles would be equipped with the PM filter. A worst-case emission rate was determined by assuming that all diesel fuel contains cerium and that all cerium is emitted (0% retention). The model assumed that the filter-plus-additive technology would be introduced in the year 2002 and that existing urban buses would be retrofitted by the end of 2003.

From the emission factors, total emission rates were calculated for two driving scenarios: a highway and a street canyon. For the **highway**, the traffic density was assumed to be 14,000 diesel vehicles/hr (80% passenger cars and LD vehicles and 20% HD vehicles), all of them equipped with a filter. The resulting average cerium emission rate was 0.74 mg/km for one vehicle (derived from the data shown in Table 6) or 10.4 g/km/hr for all vehicles.

For the **street canyon**, the traffic density was assumed to be 8000 diesel passenger cars per hour (no HD vehicles). The average cerium emission rate was estimated to 0.64 mg/km for one vehicle or 5.12 g/km/hr for all vehicles.

ESTIMATED CERIUM LEVELS IN THE ENVIRONMENT

The ambient levels for both the highway and the street canyon were derived using the appropriate cerium emission factors and a dispersion model to account for the atmospheric and physical characteristics. The data obtained and the specific assumptions are presented below. Cerium deposition in soil was also estimated.

Air

The EPA's HIWAY2 model was used to project the ambient air concentrations for a 4-lane highway with both HD and LD traffic. The estimated concentrations (assuming that the emissions would be dispersed for 150 meters around the highway and up to 10 meters in height) ranged between 0.6 and 0.1 $\mu g/m^3$ for a distance of 10 and 150 meters from the highway, respectively. The worst case would result in exposure concentrations from 7.2 to 1.2 $\mu g/m^3$.

The street canyon was assumed to have only LD vehicles. The air concentrations were derived using the model described by Johnson and coworkers (1973) and ranged from 1.25 $\mu g/m^3$ (at a height of about 1 meter) to 0.25 $\mu g/m^3$ (at a height above 14 meters).

Samaras also estimated that use of the cerium additive, if introduced in 2002 at 100 ppm in all 12 EU member states (in trucks, buses, and a large number of passenger cars) would result, by the year 2010, in cerium emissions of 600 tonnes/year (10,000 tonnes/year in the worst case), and a reduction of 60,000 tonnes/year of PM emissions (relative to the emission levels in 1990). The PM reduction was calculated as the difference between the estimated PM

Table 6. Cerium Emission Factors (mg/km)[a]

Fleet	Urban	Rural	Highway	All Roads
Passenger cars	0.7 (8.2)	0.3 (4.2)	0.6 (6.9)	0.5 (6.2)
LD vehicles	1.0 (12.2)	0.5 (6.8)	0.5 (6.4)	0.7 (9.1)
HD vehicles	2.3 (28.3)	2.0 (25.3)	1.7 (21.4)	2.0 (24.7)
Urban buses	2.6 (33.0)			3.3 (33.0)
Coaches		2.6 (32.8)	2.4 (29.4)	2.5 (31.2)

[a] Emission factors are calculated assuming a concentration of the Eolys additive in fuel of 100 ppm and 92% retention efficiency of cerium by the filter. Data in parentheses represent the worst case: 0% filter efficiency. The data were taken from Samaras (1994).

emissions for the business-as-usual scenario (assuming emission reductions based on more stringent standards plus fuel improvements mandated in EU Directives) and the estimated PM emissions for the filter-with-cerium technology, accounting for the increased number of vehicles.

Soil

In addition, Samaras estimated (using an emission rate of 10.4 g/km/hr) that over 40 years (2010 to 2050), soil contamination along EU highways would increase by 5 to 30 µg/g up to a distance of 10 meters, assuming that cerium penetrates to depths of no more than 10 cm.

Considerations About Estimated Levels

In general, the assumptions in the Samaras study are conservative because they are based on a higher cerium fuel content than is being proposed currently (100 ppm versus about 30 ppm in the Peugeot Citroën system) and on a lower cerium filter efficiency (92%) than was measured in recent laboratory tests (generally greater than 93%). However, the assumption that no HD trucks and buses would be present in the street canyon may skew the ambient estimates toward lower concentrations than if they were included in the model. Moreover, filter efficiency, both under normal driving conditions and conditions of filter and engine aging, is not known and may be lower than that measured in laboratory tests. Despite the uncertainties, these estimates provide researchers with a reference for applying correction factors (for example using different traffic density) and for placing questions about human risk in the perspective of expected ambient exposure.

Comparing the ambient cerium concentrations estimated by Samaras to measurements in two other studies may help to put them in context. Khair and colleagues (2000) measured the concentration of cerium in exhaust from a HD diesel engine tested during a steady-state condition. The concentration of cerium was 0.4 ng/m^3 during a 1-hour test and 4.7 ng/m^3 during filter regeneration (see Table 3). Because the exhaust dilutions in this test are likely lower than those that would occur in real-world situations, the derived ambient concentration would be lower. From the Samaras calculations, the ambient contribution from one vehicle in the street canyon scenario is 1.2 ng/m^3 (or 1,200 ng/m^3 for all vehicles).

The other study measured levels of manganese in Toronto, where the gasoline additive methylcyclo-pentadienyl manganese tricarbonyl (MMT) has been used in gasoline (at a concentration of about 15 ppm) to enhance automotive performance for about 20 years (Pellizzari et al 1999). The Toronto exposure study reported ambient concentrations of manganese in PM_{10} (particles with an aerodynamic diameter of 10 µm or less) at a fixed monitoring site ranging from 18 ng/m^3 (10th percentile) to 43 ng/m^3 (90th percentile). These values represent an average over 24 hours and could be much higher during 1 hour of heavy traffic. In comparison, Samaras estimated that emissions of 8-ppm cerium (based on the assumed filter retention efficiency of 92%) would yield 1.2 µg/m^3 in a high-traffic area. The limitations of these comparisons not withstanding, the Samaras model is not likely to greatly underestimate the ambient levels of cerium.

BASELINE CERIUM LEVELS IN THE ENVIRONMENT

The limited information available on the concentration of cerium in ambient air or in soil is summarized in this section and in Table 7.

Air

Measurements of cerium oxide in ambient PM (probably total suspended particles, TSP) made by John and colleagues (1973) in the San Francisco Bay area ranged between 1.3 and 5.5 ng/m^3. The levels of iron (the most abundant metal in these samples) were between 610 and 3,900 ng/m^3. Based on correlation analysis with the known soil abundance of each element, the authors hypothesized that both elements, as well as several others, were derived from soil. In the Osaka region of Japan, ambient levels of cerium in PM (0.1 to 100 µm in size) varied between 4 ng/m^3 (rural area) and 11 ng/m^3 (urban area), suggesting that anthropogenic sources contributed to cerium in the urban area (Sugimae 1980). A more recent study in Pasadena, California, by Hughes et al (1998) reported cerium to be present in both fine (< 1.8 µm) and ultrafine (< 0.097 µm) ambient particles. The concentration was 0.43 ng/m^3 in fine particles and 0.19 ng/m^3 in ultrafine particles. By comparison, the concentration of iron was 286 ng/m^3 in fine particles and 67 ng/m^3 in ultrafine particles. Because PM levels (and levels of associated constituents) have decreased substantially in the last 20 years, only the more recent measures are used here as baseline for ambient cerium.

Soil

The average distribution of cerium in the earth's crust has been reported to be 20 to 60 ppm (Windholz 1983; Hedrick 1998). In the Osaka region, concentrations of cerium in sandstone and granite were found to range between 51 and 160 ppm (Sugimae 1980). A study in Great Britain reported a rural level of cerium in soil of 38 ppm and levels ranging from 47 to 136 ppm near a motorway with heavy traffic (Ward 1990). Levels in road

Table 7. Reported and Estimated Ambient Levels of Cerium

	Air	Soil	Vegetation
Average worldwide (Windholz 1983; Hedrick 1998)		20–60 ppm	
Rural, England (Ward 1990)		38 ppm (soil 0–2 cm) 142 ppm (dust)	0.7 ppm
Semi-rural, Osaka, Japan (Sugimae 1980)	4.3 ng/m^3	51–160 ppm	
Rural, India (Eapen 1998)			0.03–0.08 ppm
Urban, Osaka, Japan (Sugimae 1980)	11 ng/m^3 (0.1–100 µm)		
Near motorway, England (Ward 1990)		47–136 ppm (soil 0–2 cm) 114–149 ppm (dust)	3–9 ppm
Urban, San Francisco Bay Area (John et al 1973)	1.3–5.5 ng/m^3 (TSP)		
Urban, Los Angeles (Pasadena) (Hughes et al 1998)	0.43 ng/m^3 (fine) 0.19 ng/m^3 (ultrafine)		
Estimated increases from use of Ce in high traffic scenarios (Samaras 1994)	0.1–0.6 µg/m^3 (highway) 0.25–1.25 µg/m^3 (street canyon)	5–30 ppm	

dust were higher and did not differ between locations. Levels in vegetation surrounding the motorways were higher than background levels (3 to 9 ppm versus 0.7 ppm). The author attributed the presence of cerium to welded metal plating on the vehicles. Many other elements, except iron, were increased in association with traffic density. In the Indian region of Kerala, cerium in vegetables, especially tubers, was reported in two areas that have deposits of manazite: one area had cerium concentrations in tubers between 0.2 to 0.5 ppm and another had concentrations around 0.03 to 0.08 ppm (Eapen 1998).

The NCRP (1978) has reported that deposition of airborne radiocerium on the ground or on plants can lead to contamination of food crops by retention or absorption on plant surfaces or absorption through plant roots. After a radiation fallout, the amount of cerium oxide estimated to be taken up by vegetation through the roots ranged between 0.005 and 1% of the soil levels. Leafy vegetables had higher plant-to-soil concentrations, probably due to greater surface contamination than soil contamination. The NCRP also commented that radiocerium can gain entry into crops through irrigation or flooding of fields but that only a small amount of radiocerium would enter food crops by this route (because of low water solubility of cerium dioxide).

DISCUSSION

Ambient levels of cerium, both in the air and in the soil, will increase as a result of the widespread use of the filter plus the Eolys cerium additive in diesel vehicles. In the absence of actual measures of cerium concentrations, estimates of ambient concentrations for different traffic conditions, such as those obtained by Samaras (1994), contribute data that might be used to evaluate the potential health impact of the additive. Moreover, averaged and specific measurements of cerium concentrations in the earth's crust are useful to provide a baseline for comparison to the additional burden from deposition of cerium-containing PM in ambient air. The cerium concentrations measured in the air and soil and those estimated to derive from use of the Eolys additive are presented in Table 7.

To estimate the additional environmental burden of cerium, Samaras simulated concentrations of cerium for two representative cases. His team calculated cerium emission factors in a street canyon (with only LD diesel traffic) and along a four-lane highway (with both HD and LD diesel traffic). The model estimated that the ambient levels of cerium would increase above baseline by about 1.2 µg/m^3 in a street canyon and by about 0.6 µg/m^3 near a highway.

The estimated increases in ambient cerium levels would represent an increase, by several orders of magnitude, above the current ambient levels of about 0.5 ng/m^3 (measured in one recent study in an urban center in the Los Angeles area). Cerium would be present near the sources in PM of a size range between 0.02 and 0.5 µm, which is the size range measured in engine tests. The form of cerium produced would most likely be oxide; however, phosphate and sulfate forms may also be present and potentially have different degrees of toxicity. As a result of the use of the particulate control system, the model further estimated that PM emissions would decrease by about 60%.

Cerium would also deposit in soil around areas or roads with diesel traffic. Relatively high levels of cerium (47 to 136 ppm) were reported in Great Britain in soil near a motorway versus 38 ppm in noncontaminated areas (Wood 1990). Although the author attributed these levels to welded metal plating, it is possible that some cerium was derived from crustal material, as suggested by an analysis of ambient particles in the San Francisco Bay area in the early 1970s (John 1973). The potential amount of cerium added to the baseline soil levels for the scenarios presented above was estimated to be around 5 to 30 ppm over 40 years; this estimate over several decades is approximately double the average levels (with average earth crust concentrations estimated between 20 and 60 ppm). However, the resulting soil levels would be in the range of those measured in the past in the soil or dust of some urban areas with higher baseline levels.

Cerium can be taken in by crops, however, the amounts will depend on such factors as the concentration of the material, its solubility, the type of crop, and the atmospheric conditions. Considering these uncertainties and based on the estimated increases in soil levels of cerium, it is hard to determine whether significant increases in cerium levels in some crops may occur over time in locations with high traffic.

DEPOSITION AND FATE OF CERIUM IN THE BODY

Cerium (either as an oxide, phosphate, or sulfate) in diesel emissions is likely to be found primarily in particles of less than 0.5 µm in size, either alone or associated with soot. Intake by humans is expected to be primarily through inhalation. Because cerium oxides are expected to persist in the environment and to deposit on roadside soil, however, oral and dermal exposures may also occur.

This section summarizes studies on the deposition and fate of cerium in the body following exposure by inhalation, oral intake, and other routes of exposure (ie, by intravenous, intraperitoneal, or intramuscular injection) that, although not physiologic, provide information on the fate of cerium once in the systemic circulation (see Table C.1 for details of the studies). Much of the information is derived from a review by the NCRP (1978) and relies on animal studies. Because skin absorption of cerium was found to be negligible (NCRP 1978; Hirano and Suzuki 1996), dermal uptake studies will not be presented here.

Most laboratory studies investigating the kinetics of particle deposition and clearance have used particles of several cerium chemical forms (ie, chlorides, nitrates, hydroxides and oxides) containing the radioactive isotope ^{144}Ce, which is a major component of nuclear fission reactors. In several of these studies only the radiation dose was reported and the actual tracer dose delivered was not provided.

INHALATION EXPOSURE

Inhaled cerium particles deposit in various regions of the respiratory tract as illustrated in the sidebar on the following page, which provides an overview of the basic concepts of particle deposition and clearance. The mechanisms of clearance of inhaled particles are also illustrated in Figure 2. The NCRP panel that evaluated the physical, chemical, and biological properties of radiocerium for the purpose of setting guidelines for radiation protection (NRCP 1978) classified cerium compounds into three categories according to their estimated rate of clearance from the respiratory tract in humans (derived from modeling animal data). Oxides and hydroxides of cerium, which are poorly soluble in body fluids, are in the

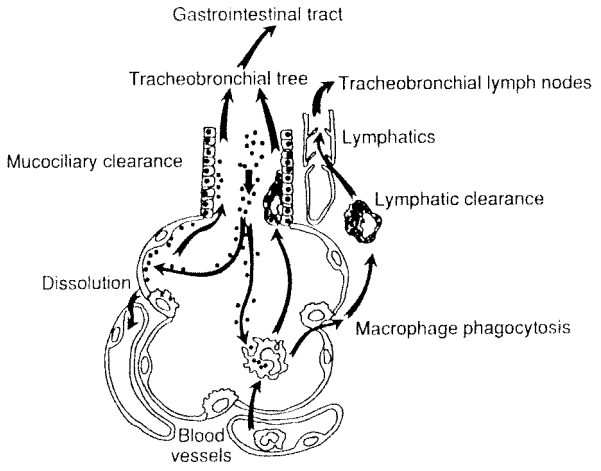

Figure 2. Mechanisms of clearance of inhaled particles (black dots) deposited in the tracheobronchal and alveolar region. (Figure obtained from McClellan 2000, courtesy of Patrick Haley, Dupont Pharmeceutical Co, Newark DE).

Overview of Inhaled Particle Deposition and Clearance

Ambient particles tend to fall into a trimodal distribution with three distinct sizes: ultrafine, or nucleation mode, particles (0.01 to 0.1 µm in diameter); fine, or accumulation mode, particles (0.1 to 1 µm in diameter), and coarse particles (greater than 1.0 µm in diameter). For consideration of particle deposition in the respiratory tract, size is generally defined as the aerodynamic diameter: the diameter of a unit density sphere that has the same settling velocity as the particle in question. For ultrafine particles, the diameter is described by the equivalent diffusion diameter. The most common indicator of particles is mass. The rate at which particles are emitted by mobile sources is expressed as gram per unit of work or gram per mile traveled; the concentration of particles in ambient air is expressed as gram per volume of air. Although ultrafine particles contribute only marginally (1% to 3%) to particle mass in the ambient air, they represent the major component in terms of particle number.

Deposition of Particles in the Respiratory Tract

An important factor in the characterization of the toxicity of inhaled pollutants is the extent to which the pollutant reaches various parts of the respiratory tract. The respiratory tract is generally divided into three main regions: the nasopharyngeal, the tracheobronchial, and the alveolar (NCRP 1978). Particle deposition in the various regions depends on particle size and density and on the subject's breathing patterns and airway geometry (Ménache et al 1996). Ultrafine particles are deposited by diffusion, primarily in the alveolar regions (Heyder et al 1986). Fine particles are deposited by both diffusion and sedimentation. In this group, total deposition is smallest when the sedimentation and diffusion processes are equal (with lowest deposition for particles 0.3 µm in diameter). For larger particles (> 1 µm) inertia plays a major role in deposition; as particle size increases (up to about 10 µm), total deposition increases but lower respiratory tract deposition decreases. Very few particles above 10 µm are inhaled.

Nose breathing, relative to mouth breathing, generally increases total deposition, but decreases the fraction of particles (especially coarse particles) that reach the lower respiratory tract due to the ability of the nose to filter particles.

Species differ in the patterns of particle deposition. In rats, for example, particles larger than 3 µm in diameter have a low probability of being deposited in the alveolar regions, whereas in humans, particles between 3.0 and 5 µm in diameter still have a relatively high probability of reaching the alveolar region (McClellan 2000). Although deposition data for fine particles are limited, Miller and colleagues (1995) concluded that deposition in the bronchoalveolar regions does not vary significantly between rats and humans. Deposition of ultrafine particles has not been modeled in rats. A significant fraction is estimated to be deposited in the lower respiratory tract. The fraction deposited in the alveolar region is also expected to be similar between rats and humans because the nose is a relatively inefficient filter for ultrafine particles. While the mass of ultrafine particles would be much lower than for larger sizes, a large number of ultrafine particles would be present.

Clearance of Inhaled Particles

Removal, or clearance, of inhaled particles depends on their site of deposition and on their physical, chemical, and biological properties (see reviews in Churg 2000; Kreyling and Scheuch 2000; McClellan 2000; Shultz et al 2000). Particles are removed from the nasopharyngeal region by the nasal mucous or by ingestion. The predominant mechanism for removing insoluble particles from the tracheobronchial and alveolar regions is transport via the mucociliary escalator to the pharynx (from where they are ingested) or transport to the tracheobronchial and pulmonary lymph nodes (via penetration through the airway epithelium). These processes are usually mediated by the alveolar macrophages, but free particle transport, especially of ultrafine particles, cannot be excluded.

The process of phagocytosis by macrophages is in competition with uptake of particles by alveolar epithelial cells (which can result in increased access of particles to the interstitium, where they can cause damage). Some studies have shown that small particles are more readily taken up by the epithelial cells than by macrophages and show greater rates of transfer across the epithelium. The role of alveolar macrophages in the migration of particles to the interstitium is still equivocal. (For a review of the role of macrophages in particle clearance, see Lehnert 1992). Studies have shown that dogs, monkeys, and human alveolar macrophages are predominantly directed toward interstitial sites, but rodent macrophages are predominantly directed toward the ciliated airways.

Dissolution of particles, followed by absorption in the blood, is another pathway by which particles can be removed from the airways. Through this process particles translocate to, and can accumulate in, various organs. Dissolution can occur either within the alveolar macrophages or in the fluids lining the extracellular spaces. The dissolution rate is proportional to the particle surface: smaller particles are more likely to be dissolved than larger particles. Many metallic particles (including cerium compounds) have been shown to dissolve and precipitate inside macrophages as phosphate compounds, thus preventing in part their transport through the circulation. The mechanisms of clearance of inhaled particles are presented in Figure 2.

slow-clearance category (years); nitrates, phosphates, and chlorides, with intermediate solubility, are in the intermediate-clearance category (weeks); sulfates and sulfides, which are readily soluble, are in the rapid-clearance category (days).

The forms of cerium used in most animal studies reviewed in this document (as well as forms that may be found in the ambient air) are included in the slow- and intermediate-clearance categories. The following discussion will be limited to those categories. Note that none of the animal studies have examined the fate of cerium oxide particles in the size ranges of those that would be emitted from diesel engines.

Animal studies have shown that clearance from the nasopharyngeal and tracheobronchial regions is fairly rapid for both groups of compounds and that about 80% to 90% of the initial body burden (IBB) is cleared within 7 days after inhalation (Sturbaum et al 1970; Thomas et al 1972; Lundgren et al 1974, 1992b). A higher fraction of the more soluble forms relative to less soluble forms of cerium is

more likely to be absorbed into the blood than removed by mucociliary clearance from these regions (NCRP 1978). For example, in humans, 5% to 10% of the deposited particles with intermediate clearance would be absorbed into the blood from the nasopharyngeal region and 50% from the tracheobronchial region; in contrast, only 1% of the deposited particles with slow clearance would be absorbed into the blood from these regions.

Clearance of material from the lung is slower than from the other regions of the respiratory tract and generally can be described by a two-phase curve with an initial, relatively rapid phase and slow longer-term phase. Cerium deposited in the alveolar region can be cleared to the gastrointestinal tract (via mucociliary movement) or to the lymph nodes, or absorbed into the systemic circulation. A portion may remain in the lung.

Although soluble forms of cerium can rapidly dissolve and be absorbed in the circulation, clearance to the tracheobronchial lymph nodes is thought to be an important pathway by which insoluble cerium forms leave the pulmonary region. The NCRP predicted that in the intermediate-clearance group 80% of the material deposited in the lung would clear to the gastrointestinal tract (40% with a halflife of 1 day and 40% with a halflife of 50 days), 15% would translocate to the blood, and 5% would translocate to the pulmonary lymph nodes (with a halflife of 50 days). For cerium with slow clearance, 80% would also be cleared to the gastrointestinal tract (40% with a halflife of 1 day and 40% with a halflife of 500 days), 5% would enter the blood, and 15% would reach the lymph nodes (with a halflife of 1,000 days). For example, cerium in the lymph nodes increased for up to 250 days after a single inhalation of cerium oxide but not after inhalation of cerium chloride (NCRP 1978).

Figure 3 provides a schematic of the distribution of slow-clearance cerium compounds in the body. Cerium reaching the lymph nodes is assumed to be absorbed into the blood stream at rates similar to the rates of absorption from the lung. Repeated exposures to cerium oxide significantly increased retention of each additional body burden (Lundgren et al 1992b). No information exists on the effect

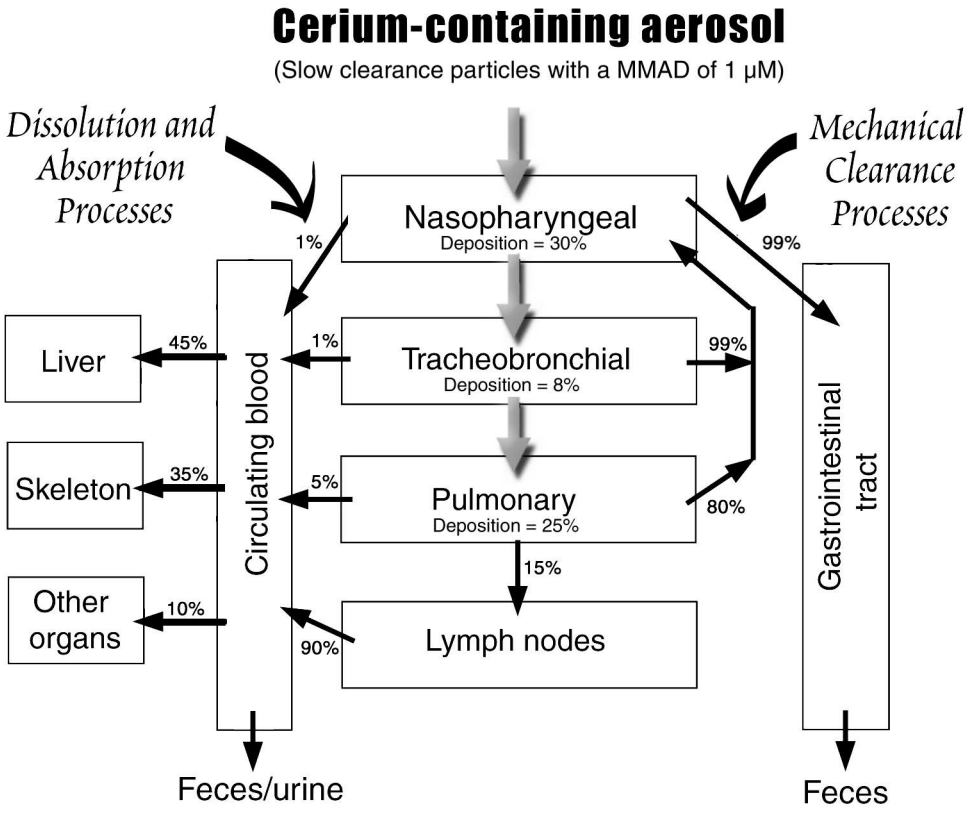

Figure 3. Clearance of inhaled cerium particles (of low solubility, such as cerium oxide) in humans. The deposition percentages represent the portion of inhaled particles that are deposited (International Commission on Radiological Protection 1979). The distribution percentages represent the portion of deposited dose cleared over time by mechanical processes or dissolution and absorption processes. The rate of clearance can vary from less than a day for clearance from the nasopharynx to more that 1,000 days for clearance from the lymph nodes.

of dose delivered on translocation of rare earth compounds, and generally clearance of PM (including cerium) has been modeled assuming that it is not dependent on the dose. However, all insoluble PM has a threshold concentration above which clearance is impaired due to overload (Oberdörster 1996). This occurs when the rate of particle deposition exceeds the rate of particle clearance.

A 1997 study conducted by Berry and coworkers examined the intracellular behavior of soluble and insoluble cerium aerosols in rats. Findings indicate that cerium, inhaled either as an oxide or as a chloride aerosol, becomes concentrated and precipitates as insoluble phosphates in lysosomes of alveolar macrophages. The authors attributed this finding to the high levels of phosphates in the lysosomes due to the action of phophatases that release phosphate from substrates. The time course over which the cerium phosphate deposits were formed differed according to the chemical form of cerium and the method of administration. Cerium chloride salts (dose not specified) were nebulized and administered by inhalation. Deposits in alveolar macrophages (measured after 5 days of inhalation) were in the form of clusters of fine granules or fine needles (30 nm long) and contained phosphorus.

Cerium oxide crystals (< 1 µm in diameter) were delivered by the intratracheal route (5 µg/day on days 0, 2, 3, 30, and 60). After the first two exposures, many crystalline particles were present in the alveolar macrophage lysosomes, but did not contain phosphorus. A month later, the particles were associated with phosphorus and were in the form of very fine needles or granules, suggesting that the cerium was first released from the particle and then precipitated as phosphate. Because the oxide particles were delivered in a bolus dose, it is not clear whether these results can be generalized to inhaled particles. The authors suggested that the process by which elements are concentrated in the lysosomes (which was shown also to occur in renal cells) may inhibit the toxicity and diffusion of the element.

The primary sites of deposition of cerium absorbed in the blood are liver, skeleton, and, to a lesser extent, spleen and kidney. Deposition at other sites (such as brain and heart) has not been studied after inhalation exposure. Although the pulmonary retention is greater for less soluble forms of cerium (ie, oxides) than for more soluble forms (chlorides), the NCRP model estimated that the internal organ transfer rates were the same for cerium chloride and cerium oxide, suggesting that cerium is metabolized in a similar manner independently of its chemical form. The NCRP model estimated that, in humans, the loss of cerium from the liver and the bones would occur with a halflife of several years. In the bones, cerium compounds appear to be deposited on the bone surface, rather being distributed throughout the bone volume (NCRP 1978).

This review has focused on forms of cerium with intermediate and slow clearance; one form of cerium that may be present in diesel emissions but would be in a rapid-clearance group is cerium sulfate. Clearance of this form from the respiratory tract would be quite fast and a higher proportion of the dose deposited would partition into the blood and reach target tissues than would the less-soluble forms such as chloride and phosphate.

Species differences in pulmonary clearance of cerium have been observed. Rats, Syrian and Chinese hamsters, and mice generally lost cerium from the pulmonary region at similar rates, but at a more rapid rate than dogs (NCRP 1978). Possible factors in this difference may be differences in deposition sites or in the size of the particles delivered. Human data are limited. Kreyling and coworkers (1998) compared the retention of inhaled 1.0 µm ^{160}Tb-labeled terbium oxide particles in humans, monkeys, dogs, and rats (terbium is another rare earth element). Rats lost radiolabeled terbium from the lung faster than dogs, and humans, monkeys, and dogs had similar lung-retention kinetics. Moreover, during the first few months after exposure, organ uptake was faster in humans, monkeys, and dogs than in rats (with the skeleton being the predominant site of uptake). This study suggests either that particle dissolution may be slower in rats than in the other species tested or that particle clearance in rats occurs preferentially via the mucociliary escalator (see Overview of Inhaled Particle Deposition and Clearance sidebar).

Analyses of lung samples from people occupationally exposed to rare earth metals (including cerium) confirm that cerium-containing particles can remain in the lung long after the exposure stops and can translocate to other organs (Waring and Watling 1990; Pairon et al 1994, 1995; McDonald et al 1995). McDonald and colleagues (1995) reported particulate lung deposits containing cerium, many inside cells, ranging in size from less than 1 µm to 5–10 µm in a patient with a history of optical lens grinding. Pairon and coworkers observed cerium-containing particles within alveoli and in interstitial tissue in a worker occupationally exposed to cerium oxide powders approximately 20 years prior to the observations. In a case report of an autopsy of a film projectionist occupationally exposed to rare earth elements from oxidation of a carbon arc lamp (Waring and Watling 1990), granules of rare earth elements were found in macrophages from the tracheobronchial lymph nodes and hepatic Kupffer cells.

INGESTION EXPOSURE

Orally administered cerium is generally poorly absorbed by the digestive tract. The NCRP (1978) reported that, in adult rodents, between 0.01% and 0.1% of administered radioactivity (in soluble forms of cerium) was absorbed by the gastrointestinal tract. A case study of an individual accidentally contaminated with ^{144}Ce (form not specified) in the area of the nose and mouth indicated that less than 1% was absorbed (Sill et al 1969). Ji and Cui (1988) showed that after oral administration of a single dose (1,000 mg/kg) of a 43% cerium mixture of rare earth nitrates in rats, less than 1% of the dose was distributed to tissues. The highest levels were found in the liver and skeleton, followed by the heart and kidney.

Results were similar in rats fed 1,800 mg/kg of rare earth nitrate mix for 8 months and in monkeys fed 500 mg/kg for 90 days with the exception that after repeated exposures, the spleen also accumulated small amounts of the metals (Ji and Cui 1988). The total amount of rare earths in the organs and tissues at the end of the repeated exposures was 0.26 mg/kg (0.01% of a single dose) in rats and 3.8 mg/kg (0.8% of a single dose) in monkeys. In monkeys fed a single dose of the same rare earth compounds, 94% of the dose was excreted, primarily in the feces, in the first three days.

Stineman and colleagues (1978) reported that intragastric administration of cerium chloride (in the presence of citrate) at doses of 1,000 mg/kg (equivalent to the lowest dose that causes death in 5% of animals [LD_5]) and 1,163 mg/kg (equivalent to the lowest dose that causes death in 25% of animals [LD_{25}]) in mice resulted in accumulation of cerium in the stomach and duodenum and minimal accumulation in other organs. The highest levels in all organs were observed 4 hours after exposure and decreased over the 7-day observation period. Decreased levels in the stomach and duodenum did not appear to be associated with a corresponding increase in other organs, suggesting that cerium was excreted rather than distributed to the body. Relative to intragastric administration, spleen levels per gram of tissue reported in the same paper were 31-fold higher than stomach levels at 4 hours after intraperitoneal dosing and 420-fold higher after 7 days.

Studies of ingestion of relatively insoluble forms of cerium (such as oxides or hydroxides) have not been conducted, but absorption of these compounds is expected to be less than for chlorides and nitrates (NCRP 1978).

Eapen and colleagues (1996) reported that rats on a magnesium-deficient diet which were fed cerium sulfate (35 mg/kg) for three months had higher cerium levels in liver, kidney, heart, and bones than rats on a normal diet, suggesting that diet may affect the absorption of orally ingested cerium. However, no effect on the accumulation of cerium (present at a concentration of 1 g/L of a mixture of rare earth chloride in drinking water for about 7 months) in the body was observed in rabbits periodically fed a magnesium-restricted diet (Kartha et al 1998).

Some evidence suggests that the gastrointestinal tract of newborn rodents has higher and more prolonged retention of, and may be more permeable to, ingested cerium than that of older animals. Inaba and Lengemann (1972) compared the percent of a single dose of ^{141}Ce nitrate (dose not specified) retained by suckling rat pups at 0, 7 and 14 days after birth to that retained by weaned 26-day-old pups until day 28. Generally, weaning started around 16 days of age and was completed by 26 days.

Although weaned pups excreted cerium rapidly via feces, suckling pups lost radioactivity at a slower rate with newborn pups having the lowest rate of loss. For pups at age 0 days, 0.34% of the administered dose was calculated to be in body tissues (excluding the gastrointestinal tract) after 1 day, 2.1% after 16 days, and 2.5% after 24 days. Conversely, in weaned pups, only 0.04% of the administered dose remained in the body 3 days after dosing. The increased tissue retention was associated with increased uptake of cerium by intestinal epithelial cells, which eventually are sloughed off into the intestinal lumen. Retention was also affected by the type of diet. Pups whose diet was changed to commercial food at 17 days of age lost radioactivity faster than pups of a similar age still suckling, and 43-day-old rats fed dried whole milk had a much slower loss than rats of the same age on a commercial grain diet.

Similar results were obtained by Shiraishi and Ichikawa (1972), who showed a slow loss of cerium in suckling rats (delivered as ^{144}Ce chloride by intragastric tube on days 0, 7, and 14 after birth) and more rapid loss of radioactivity after weaning began. Although the cerium distribution pattern was almost identical in suckling and adult rats (100 days old), the tissue concentration in bone, liver, spleen, and kidney was 2 to 3 orders of magnitude higher in suckling rats. Most of the retained radioactivity was found in the skeleton.

Eisele and coworkers (1980) studied the uptake of ^{144}Ce chloride and citrate (carrier free) after a single intragastric administration in newborn (0 to 24 hours old) mice, rats, and pigs and found that mice absorbed and retained the most cerium. Retention after dosing increased over time reaching a maximum at day 7 in pigs, day 15 in rats, and day 15 to 18 in mice. At the end of observation (age 21 days), 24% of the dose retained was found outside the gastrointestinal regions of the body in mice, 10% in rats, and 4% in pigs.

A study in neonatal mice exposed in utero and suckling from mothers injected once with ^{144}Ce citrate (carrier free)

2 days before delivery showed an increase in the neonate's cerium body burden during suckling until postnatal day (PND) 11, assumed to be due to absorption through the gastrointestinal tract; cerium levels then decreased (Naharin et al 1969). At PND 10 radioactivity was distributed in the digestive tract (60% of the litter body burden), the liver (3.9%), and the carcass (including skeleton, 35%). An increase, albeit modest, in whole body cerium level was also observed in suckling pups whose mothers were exposed before mating, suggesting that cerium deposited in the mammary glands or was released from organs in which it was originally deposited (such as bones or liver). Uptake of cerium continued during suckling. Pups born from mothers dosed before mating had negligible levels of radioactivity at birth but had increased levels during suckling suggesting removal from maternal deposition sites.

INTRAVENOUS, INTRAPERITONEAL, AND SUBCUTANEOUS ADMINISTRATION

Although intravenous, intraperitoneal, and subcutaneous injections would not be modes of exposure, information from studies which use these dose routes is helpful in understanding the distribution of cerium once it is in the body. Various studies of the fate of intravenously injected cerium have shown that cerium disappears quickly from blood after injection. Nakamura and colleagues (1997) found that about 70% of the initial dose of cerium chloride administered to rats (10 or 20 mg/kg) was found in serum 2 hours after administration and had almost entirely disappeared from the blood within 24 hours. At this time point, only 3% of the initial dose remained in the blood, while the majority of the dose was found in liver (70%), bone (12%), spleen (3%), and lungs (1%) where it was retained for a long time. No substantial difference was observed in the distribution pattern at the two dose levels. A study in mice also showed that one day after injection of 5.5 mg/kg, less than 1% of the initial dose was present in serum, but a concomitant accumulation of cerium was noted in the liver (Bjondahl 1976). Excretion through the feces was fairly slow and was still noticeable 14 days after injection. Arvela et al (1991) showed that the major organs accumulating intravenously injected cerium chloride (0.5 to 2 mg/kg) were the liver and spleen.

The distribution of ^{144}Ce chloride or citrate (dose not specified) administered intraperitoneally appears to be similar to that of cerium administered by inhalation, based on a study in Chinese hamsters (Sturbaum et al 1970). Compared with inhalation, however, the whole body retention (percent of administered cerium retained) was much greater after intraperitoneal administration. For example, 7 days after inhalation, 20% of the IBB was still retained, but 20 days after intraperitoneal injection, 60% to 80% of the initial dose was retained. At 256 days after inhalation, 0.27% of the IBB was found in the lung, 3.5% in the liver, and 1.3% in the skeleton. In contrast, after intraperitoneal administration, 22% of the IBB was in the liver and 9.5% in the skeleton. In both cases, however, the fraction of activity retained in the liver (70%) and skeleton (30%) was the same, suggesting that once distributed in the body, the fate of cerium in organs is independent of the route of administration.

A study of neonatal mice born from mothers subcutaneously (intramuscularly) injected once with ^{144}Ce citrate 2 days before delivery showed some placental transfer of cerium to the fetus (Naharin et al 1969). The percentage of uptake by the fetus during that period was estimated to be 0.23% of the maternal body burden, with the largest accumulation in the liver (55% of total fetal burden) and the carcass, including the skeleton (32% of fetal body burden). The extent of cerium retention did not differ between pregnant and nonpregnant mice.

In the blood, cerium either forms complexes with serum protein or is found as colloids of large size, composed of phosphate, hydroxide and carbonate. Cerium may be transported to various organs, in part, contained in these complexes (Nakamura et al 1997; Hirano and Suzuki 1996). Generally, when the blood concentration of cerium does not exceed the capacity of the protein transport system, cerium partitions primarily between liver and bones. If the amount of cerium exceeds the protein binding capacity, however, cerium will hydrolyze and form colloidal aggregates at the site of delivery, and it will distribute preferentially in the liver and spleen (National Council on Radiation and Protection 1978). These different mechanisms may account for some of the differences observed among studies in the proportion of cerium in the various organs.

The major route of clearance of intravenously delivered cerium is thought to be via the feces, with a smaller amount excreted in the urine, but the mechanisms of excretion remain to be elucidated.

DISCUSSION

The internal dose and distribution of cerium that is taken up by the body depend on the route of administration, the chemical form, and for inhaled cerium, the size of the particles. Inhalation is the mostly likely route of uptake of particles containing cerium derived from diesel exhaust. Inhaled cerium particles can reach various regions of the respiratory tract depending on the particle size. Deposits in the upper respiratory and tracheobronchial regions are cleared primarily by mucociliary transport, ingestion, and finally excretion in the feces; depending on the solubility of the

deposited particles, a substantial fraction (especially of material deposited in the tracheobronchial region) also will be dissolved and absorbed into the systemic circulation (Figure 3).

Clearance from the pulmonary region is slower than from other regions and results from the competition between mechanical processes and absorptive processes. A portion of cerium deposited in the alveolar region is cleared via the mucociliary escalator or to the tracheobronchial lymph nodes; particles that are retained can undergo dissolution and absorption into the blood and eventually partition into various organs. This process is more rapid for more soluble forms of cerium which are, therefore, cleared more rapidly from the lung into the circulation, and are less likely to reach the lymph nodes, than less soluble forms (such as cerium oxide). These less-soluble forms may be retained in the lung and the lymph nodes for several years. Although very little information is available on the effect of repeated exposure on clearance of cerium particles, it appears that, at least in rodents, repeated exposure increases the retention half-time of each additional body burden. Both soluble and insoluble forms of cerium deposited in the lower respiratory tract can be precipitated, as phosphates, in the alveolar macrophages (Berry et al 1997). Because of the very low amount of cerium absorbed by the gastrointestinal tract, particles of soluble or insoluble cerium ingested as a result of mucociliary clearance are unlikely to be reabsorbed to a significant extent.

Cerium taken into the bloodstream enters, in order of preference, into the liver, skeleton, spleen, and kidney, where it can stay for over a thousand days). According to the NCRP, 45% of cerium in the blood partitions to the liver, 35% to the skeleton, 10% to other organs, and 10% to feces and urine.

Inhalation studies of the disposition and clearance of cerium have not measured cerium uptake in the brain. Some evidence suggests that some soluble metals can be taken up by neurons contained in the nasal olfactory epithelium and pass intraneurally to other parts of the brain (Tjälve and Henriksson 1999; Tjälve et al 1996). Among the metals studied, manganese has the greatest ability to be taken up by neurons and be transported to the brain, while cadmium and mercury do not seem to pass the synapsis to the secondary neurons. Whether cerium particles, especially in the insoluble forms, can be transported into the brain via neurons remains to be investigated. As mentioned in the next section, measurable levels of cerium in the brain were found by Stineman and colleagues (1978) after subcutaneous exposure, but the mechanisms of transport were not studied.

No data are available on how particle size affects the deposition and fate of cerium in the lower respiratory tract. However, information from studies of other particles suggest that cerium particles in the accumulation or nucleation mode (< 0.5 μm in diameter) are more likely to reach the alveolar region and to be dissolved due to their large surface area than are the larger particles used in the animal studies. (See sidebar on Overview of Inhaled Particle Deposition and Clearance.)

Cerium appears to have species-specific differences in its rate of clearance. It is generally lost at a more rapid rate from the pulmonary region of rats, Syrian hamsters, Chinese hamsters, and mice than dogs. The limited data suggest that humans would be similar to dogs in their handling of inhaled cerium.

Ingested cerium is cleared primarily via excretion of the unmodified compound in the feces, with a smaller portion excreted in the urine. Less than 0.1% of the dose delivered translocates to tissues in all these adult animals, but findings suggests that newborn pups may absorb a higher percentage of ingested cerium than adults.

Available data suggest that cerium disappears from the circulation very quickly after intravenous administration and that a significant amount is distributed to the liver, skeletal tissues, spleen, lymph nodes, kidney, and heart from which it slowly clears. At least in its soluble form, cerium appears to be able to cross the placenta and deposit in the fetus (primarily liver and skeleton). Because pups have been shown to take up cerium during suckling (from mothers exposed only while pregnant), cerium may deposit in the mammary glands or enter the mother's milk from other sites.

HEALTH EFFECTS OF CERIUM

Once inhaled or ingested, cerium may have a number of health consequences on the respiratory tract, lymph nodes, liver, skeleton, and other organs. This section reviews existing data on the potential effects of cerium after exposure via various routes. Because data on the effects of cerium oxides are limited and to provide as comprehensive an overview as possible, studies on all salts of cerium are summarized. However, results of studies in which radiation effects predominated due to dosing with highly radioactive cerium are not discussed.

ACUTE TOXICITY

Generally, cerium salts displayed low acute mortality effects (see Table C.2). The LD_{50} (lowest doses causing death in 50% of the animals) of cerium salts were administered intravenously. The LD_{50} values reported in rats ranged from 4mg/kg to 50 mg/kg for cerium nitrate with female rats being more sensitive than males (Bruce et al 1963). After peritoneal injection, the LD_{50} of cerium nitrate was 470 mg/kg in female mice and 290 mg/kg in female rats; the LD_{50} of cerium chloride was 353 mg/kg in mice and 103 mg/kg in guinea pigs (Graca et al 1957; Bruce et al 1963). The toxicity of cerium nitrate after ingestion was much lower (LD_{50} of 4,200 mg/kg in female rats and 1,178 mg/kg in female mice) than after intravenous or intraperitoneal administration (Bruce et al 1963; Ji and Cui 1988). The LD_{50} of ingested cerium oxide could not be determined in rats when delivered at a dose of 1,000 mg/kg (Bruce et al 1963) or 5,000 mg/kg (Rhône-Poulenc 1983a). Ji and Cui (1988) reported an LD_{50} of 622 mg/kg cerium oxide ingested by mice. The LC_{50} (lowest concentration that causes death in 50% of animals) after inhalation of cerium oxide in rats was greater than 50 mg/m^3 (Rhône-Poulenc 1983b).

TARGET ORGAN EFFECTS

As noted in the previous section, the target organ where cerium will deposit depends on the route of administration. Once absorbed in the blood, however, the fate of cerium seems to be independent of the route of exposure and the chemical form. The organs of concern are:

- the respiratory tract and associated lymph nodes after inhalation exposure; and
- the liver, skeleton, spleen, and kidney, where cerium can be distributed after absorption into the circulation.

The digestive system and other organs seem to be of less concern.

Inhalation Exposure

Exposure to cerium oxide and other rare earth oxides has been reported for several occupations, primarily those involving carbon arc lamps and optical lens grinding, and has been associated with a pulmonary disease termed *rare earth pneumoconiosis*. Case reports of pneumoconiosis (a respiratory disease associated with altered pulmonary function and histopathology) associated with exposure to rare earth-containing materials in the workplace have been published by Sabbioni et al (1982), Vocaturo et al (1983), Sulotto et al (1986), Vogt et al (1986), Waring and Watling (1990), McDonald et al (1995), and Pairon et al (1994). However, none of these studies reported on cerium exposure among the subjects. The pathologic features of rare earth pneumoconiosis varied from granulomatosis to bilateral nodular infiltrates on chest radiographs to interstitial fibrosis. Pulmonary function in these subjects varied. The individuals described in the reports often had concomitant exposure to carbon black or silicates; however, pathology of materials taken from biopsy samples or lavage fluid was not characteristic of these other materials. Cerium in several of the biological samples examined was generally the bulk of the rare earth metals found.

One study measured cerium and similar metals in the lung and lymph nodes of one worker diagnosed with interstitial pneumoconiosis (who worked for 46 years in the engraving industry), relative to a control group (Sabbioni et al 1982). The control samples were obtained from autopsies of subjects living in the same area who had no evidence of lung disease. The lung levels of cerium were about 2000-fold higher in the worker than in the controls, while the lymph node levels were about 50-fold higher. Although the presence of cerium in the lung sometimes was associated with pathological evidence of disease (Vocaturo et al 1983; McDonald et al 1995), the role of cerium has not been ascertained (Sabbioni et al 1982; Waring and Watling 1990; Pairon et al 1994).

The most comprehensive animal inhalation study of cerium was commissioned by Rhodia, and involved 13 weeks of nose-only exposure to cerium oxide particles ranging from 1.8 to 2.2 µm in diameter, administered to rats in concentrations of 5, 50, and 500 mg/m^3 for 6 hours/day, 5 days/week (Viau 1994). The endpoints measured were body and organ weight, hematology, gross pathology, and histopathology. All treatment groups had elevated lung weights, areas of discoloration and uncollapsed parenchyma in the lung, and hyperplasia and discoloration of bronchial and mediastinal lymph nodes. Similar findings were reported for other parts of the respiratory system. (The significance of the uncollapsed parenchyma is not clear because the authors did not discuss whether it could be due to experimental artifacts.) Dose-dependent increases in spleen weight were also noted, but no effects on body weight were reported. Lymphoid hyperplasia was characterized by an increase in the number of lymphocytes and expansion of the paracortices and cortices of the lymph nodes. These findings were attributed to an antigenic response to the particles, but could also represent a nonspecific response to the toxicity of the particles.

Histopathologically, accumulation of pigmented material was observed for all treatment groups in the lungs and other

parts of the respiratory system, lymph nodes (bronchial, mandibular, and mediastinal), spleen, and liver, indicating translocation of particles from the sites of initial deposition. In the lungs of animals exposed to the lowest cerium concentration, the pigment was present almost exclusively in the alveolar macrophages. In animals exposed to the higher concentrations, however, pigment was also found in the extracellular matrix, suggesting that the normal mechanisms of phagocytosis were overwhelmed at these high concentrations. Analysis of blood and urine revealed only a dose-dependent increase in segmental neutrophil counts in blood, which could indicate a systemic inflammatory response.

Ingestion Exposure

Because cerium compounds are poorly absorbed through the digestive system, toxicity of cerium delivered orally is not likely to be a major concern. In one subchronic study (Ji and Cui 1988) a 43% cerium mixture of five rare earth nitrates was repeatedly fed to rats in doses of 2, 60, and 1,800 mg/kg/day. Food consumption and weight decreased after 20 to 24 weeks of exposure to 1,800 mg/kg, but hematologic parameters and histopathology did not change (organs examined not specified). Although many details about the study design are lacking, the authors report that the total residue of rare earth after 8 months of continuous feeding was 0.26 mg/kg.

In a study by Stineman et al (1978), mice developed gastritis and enteritis 7 days after one intragastric dose of 1,000 or 1,163 mg/kg ^{141}Ce (another radioactive isotope) chloride complexed with citrate (corresponding to the 7-day LD_5 and LD_{25}, respectively). These effects could have been due to the high levels of the element (possibly as colloids) in the gastrointestinal tract or to radiation effects. Another observation was the presence of hypertrophy, reticular hyperplasia, and hyperactive lymphoid follicles in the spleen. This observation is hard to explain because an effect of the same magnitude was noted in animals exposed subcutaneously to 136–173 mg/kg, which had much higher levels of radioactivity in the spleen than the animals exposed intragastrically. The authors hypothesize that the spleen may sequester cerium and thus protect more sensitive target organs such as the brain.

A possible exception to the view of lack of toxicity from oral intake has been reported by researchers in southern India regarding a possible relationship between dietary cerium intake, dietary magnesium deficiency, and endomyocardial fibrosis (Valiathan and Kartha 1990; Kutty et al 1996). The disease is generally found among poor and malnourished people, especially children and young adults, living in tropical regions. A number of hypotheses about the disease etiology of the have been advanced. The finding of high levels of cerium and thorium (especially cerium) and a magnesium deficiency in the cardiac tissues of some patients with endomyocardial fibrosis has led to the hypothesis that cerium may be related to the condition (Valiathan and Kartha 1990). The exposure was attributed to cerium in monazite, a mineral found in the Indian region of Kerala where the patients lived (Kutty et al 1996). In these monazite areas, cerium was reported to be elevated in various tubers (Eapen 1998).

A study comparing blood from 4 patients with endomyocardial fibrosis to 4 individuals without cardiac symptoms reported that the blood sera of controls had significantly lower cerium levels than blood sera from patients (7.6 ± 8.1 ng/mL versus 21.4 ± 5.1 ng/mL in patients) (Eapen et al 1998). However, cerium intake was not determined.

The hypothesis that low magnesium and elevated cerium levels may play a role in development of endomyocardial fibrosis has been investigated in several animal and in vitro studies reported by this group in India. Two animal studies observed conflicting results on heart cerium levels in relation to diet. One study of rats fed 35 mg/kg cerium chloride showed that higher levels of cerium were present in the hearts of rats fed a magnesium-deficient diet relative to rats on a normal diet (Kumar et al 1996). The other study did not report any difference in the heart cerium levels between rabbits kept on a magnesium-restricted diet (with a 56% cerium mixture of rare earths) and rabbits on the same diet without cerium (Kartha et al 1998). Elevated rates of fibroblast proliferation and collagen deposition (due to a reduction in collagen degradation) were observed in the hearts of rats administered a single intravenous dose of 1.3 mg/kg cerium chloride (Kumar and Shivakumar 1998). Overall, epidemiologic evidence and the finding of accumulated cerium in the heart and its effects in vitro on cardiac cells (described below) suggest a possible relation between intake of cerium in the development of endomyocardial fibrosis in malnourished individuals; as noted, animal studies (in different species) provided conflicting results.

Intravenous and Subcutaneous Administration

After intravenous and subcutaneous exposure, generally to cerium chloride or cerium nitrate, the highest level of cerium was found in the liver. Evidence of acute hepatotoxicity has been reported in mice and rats exposed to doses of cerium ranging from 2 to 20 mg/kg. Liver necrosis, disorganization and destruction of liver morphology, and accumulation of fat droplets were observed in DBA/2 mice 72 hours after intravenous administration of 2 mg/kg

cerium chloride, but not at lower doses of 0.5 and 1 mg/kg (Arvela et al 1991). Another strain of mice, C57BL/6N, appeared to be much less sensitive than the DBA2, but this reduced sensitivity was not due to differences in cerium content of the liver (which was similar in the two strains). The pathologic changes were associated with changes in the activity of various detoxifying enzymes and cytochrome P450 levels, which increased with slight-to-moderate liver damage, but decreased with more aggravated injury (also noted by Salonpää et al 1992). Liver necrosis and regenerative changes were noted in mice subcutaneously dosed with136 or 173 mg/kg ^{141}Ce chloride (Stineman et al 1978). Nakamura and coworkers (1997) reported findings of hepatotoxic symptoms, including fatty liver, jaundice, elevated activity of serum enzymes GOT (glutamic-oxaloacetic transaminase) and GPT (glutamic-pyruvic transaminase), increased serum bilirubin and hepatic lipids in rats after intravenous administration of 10 or 20 mg/kg cerium chloride. These changes were accompanied by an increase in the levels of calcium in liver and spleen and were attributed to the cerium toxicity to the organs.

Other acute toxic effects that have been reported include a decrease in ethoxyresorufin *O*-deethylase (EROD) activity in the livers and kidneys of mice injected intravenously with 2 mg/kg cerium chloride (Salonpää et al 1992). These changes were strain dependent (greater in DBA mice than in C57BL mice). Marciniak and coworkers (1988) reported an increase in liver and spleen permeability (measured as increased uptake of aminobutyric acid and thymidine) in pregnant mice after intravenous injection of cerium chloride at a concentration of 3.56 mg/kg on gestational day (GD) 7 and GD 19. These results were attributed to an effect of cerium on either the vascular endothelium or cellular membranes. These same investigators reported no effect on the function of the placental barrier.

IMMUNE SENSITIZATION

The ability of cerium oxide to induce immune sensitization was measured in two studies: the popliteal lymph node proliferation assay (using ^{3}H-thymidine incorporation) and the immunoglobulin E (IgE) test (Spanhaak 1996). In the popliteal assay, rats were injected with a single subcutaneous dose of cerium oxide (suspended in dimethyl sulfoxide [DMSO]) in the foot pad at levels of 0.35, 3.5, and 35 mg/kg). A positive-control group of animals were treated with trimellitic anhydride (TMA), a known contact and respiratory sensitizer. No statistically significant increase in thymidine incorporation (measured 7 days after the treatment) was observed after cerium exposure. However, the investigators noted a large variation within each group, which made it difficult to determine statistical significance given the small sample size. The positive controls also did not show any increase in thymidine incorporation.

For the IgE test, rats were first treated with 300 mg/kg of cerium oxide intradermally (in the abdominal skin) and a week later with 150 mg/kg subcutaneously (in the foot pad). Serum IgE levels (measured weekly up to 5 weeks after the initial treatment) were similar in the cerium-exposed and control rats, but they increased in the positive control group. The weight of the lymph nodes (measured up to 35 days after treatment in the IgE study) was not modified by administration of cerium. However, the lymph nodes showed discoloration and accumulation of granulated substances. These test results seem to indicate that an acute treatment does not cause immune sensitization but do not rule out other types of immune responses after prolonged exposures.

BEHAVIORAL AND DEVELOPMENTAL EFFECTS

The nervous system and developing fetus are particularly susceptible to the effects of many metals, but little research has evaluated the possible effects of cerium compounds on neurotoxic and developmental effects. Behavioral changes (which provide a measure of toxicity to the nervous system) have been observed in mice 4 and 24 hours after subcutaneous injection with relatively high concentrations of cerium chloride mixed with citrate (136 and 173 mg/kg, Stineman et al 1978). The effects included reduced general activity (at both concentrations) and reduced exploratory behavior (only at the high concentration). The authors interpreted these findings as resulting from cerium competing for calcium sites within the brain. No effects were observed after intragastric administration of 1,000 mg/kg cerium chloride mixed with citrate, probably because of the much lower systemic dose of cerium via this route The behavioral effects were associated with the concentration of cerium in the brain regions. No clear behavioral effects (measured as changes in motor activity count or in functional observations), except for a reduced forelimb grip strength in females exposed up to 500 mg/m^3, were observed in a 13-week inhalation study of rats (Viau 1994). The total dose delivered during this period corresponded to about 1,460 mg/kg body weight; the dose delivered after a single exposure would correspond to 22.5 mg/kg.*

* The total dose resulting from an exposure to 500 mg/m^3 can be estimated using the following equation and assuming a 20% deposition of 2 µm particles in the rat lung (Miller et al 1995): 500 mg/m^3 × hours (6 hours × 5 days × 13 weeks) × rat ventilation rate (0.015 m^3/hr)/body weight (400 g) × 0.2 = 1,460 mg/kg (or 585 mg/rat). The dose after a single exposure would be approximately 9 mg/rat or 22.5 mg/kg.

The only study investigating the effects of cerium on fetal or neonatal development is that of D'Agostino and coworkers (1982). They reported that offspring of mice intravenously injected on GD 12 with a single dose of 80 mg/kg body weight cerium citrate had significantly reduced body weights. The only significant behavioral effect in these pups was an increased rearing frequency measured from PND 60 to 65. Because other measures of activity, coordination, and simple learning were not affected, the authors did not know how to interpret this finding. One interesting observation was the decreased retrieval latency of foster mothers for pups exposed in utero relative to unexposed pups. No effects on body weight or behavior were observed in offspring exposed on PND 7 or during lactation (PND 2).

CARCINOGENICITY AND GENOTOXICITY

Limited data are available on the carcinogenic potential of cerium salts, and no chronic rodent inhalation bioassays have been conducted. In the Ji and Cui study (1988) involving a 2-year oral administration of a 43% cerium mixture of five rare earth nitrates in concentrations of 2 to 1,800 mg/kg/day, the incidence of tumor was lower in test rats than in controls. Because of the low absorption of ingested cerium, however, the actual internal dose (estimated to be less than 0.1% or less than 2 mg/kg of the highest dose of rare earth mixture) was substantially lower than the dose delivered. Thus the study probably did not have sufficient power to detect an effect.

In an inhalation study conducted by Lundgren and colleagues (1992a) to test the carcinogenic effects of radiation, a group of rats were exposed nose-only to stable cerium for about 25 minutes, either once or at bimonthly intervals for a year (total of 7 exposures). The concentration of cerium oxide in the exposure air ranged between 11 and 22 mg/m^3 (F Hahn, personal communication, 2001). The rats were monitored for their life spans. No statistically significant increase in the incidence of primary tumors was found in the exposed rats relative to the unexposed rats. The authors estimated that approximately 10 µg of stable cerium was deposited in the lung during each exposure or a total of 67 µg during the 7 exposures. By comparison, the total dose delivered to the lung in the 13-week rat inhalation study by Viau was about 580 mg.

Genotoxicity tests conducted by Ji and Chu (1988) were negative. These experiments used a mixture of lanthanide nitrate and cerium nitrate and did not test cerium alone. Few details of the tests are available, although Ji and Cui report that the cerium-containing mixture was negative in the Ames test of mutagenicity (at 0.05, 0.5, 5, and 50 mg/mL) and in studies of chromosomal aberrations in mouse bone marrow cells (animals exposed to 18 to 375 mg/kg) and in spermatocytes (animals exposed to 200 to 600 mg/kg). As reported by Technology Sciences Group (1997) Ames mutagenicity tests using several strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and *Escherichia coli* (WP2uvrA) with and without metabolic activation were negative (not shown in Table C.3). Many details of these tests are not available.

A micronucleus test (which detects chromosomal aberrations in bone marrow erythrocytes) was conducted by Pichard (1993) in mice administered cerium oxide suspended in carboxymethylcellulose by the oral route, at a dose of 2,000 mg/kg. The animals were killed after 24 or 48 hours. No significant differences in the number of micronucleated polychromatic erythrocytes was observed between control and treated animals. However, it is not clear how much of the cerium oxide actually was taken up by the gastrointestinal system and reached the target tissue over the observation period.

IN VITRO CELLULAR EFFECTS

Some in vitro studies have reported effects of cerium on cells, such as macrophages and myocytes, and cell components (see Table C.3).

Macrophages

Palmer and coworkers (1987) examined toxicity to rat pulmonary macrophages of chlorides and oxides of several rare earth metals (cerium, lanthanum, and neodymium) in vitro. For comparison, the toxicity of cadmium chloride and cadmium oxide was determined. Although the specific size of the cerium oxide particles was not given, the oxide (suspended by sonication before use) was able to pass through a filter with a 0.8-µm pore diameter without loss of potency. The endpoints measured were cell viability, extracellular enzyme release, and cell morphology.

Of the oxides, only neodymium oxide was considered comparable to cadmium oxide with respect to cell viability (LC_{50} of 15 µM). Among the chlorides, cerium chloride was the most potent (LC_{50} of 29 µM) and its potency was comparable to that of cadmium chloride (LC_{50} of 28 µM). Cerium oxide was about 100-fold less potent than cerium chloride. At these concentrations, a moderate increase in the levels of enzymes released by the cells was observed, but the increase was not comparable in magnitude with effects on cell viability. Changes in cell morphology, on the other hand, appeared to be more sensitive indicators of cytotoxicity than cell viability, at least for cadmium (chloride or oxide). Relative to cadmium salts, cerium oxide was about 200-fold less potent in inducing morphologic

changes. A 1992 study (Lizon and Fritsch 1999) showed that cerium chloride (at concentrations between 5 µM and 100 µM) induced cell death (by apoptosis) in rat alveolar macrophages in culture.

Myocytes

In vitro findings indicate that cerium at concentrations between 5 and 20 µM inhibited protein synthesis in neonatal rat cardiac myocytes grown in culture and that this effect was enhanced in cells grown in a low-magnesium medium (Shivakumar and Nair 1991). The authors hypothesized that cerium alters intracellular magnesium availability by acting on the plasma membranes. Another possible explanation is that cerium competes for Mg-binding sites. Low levels of cerium stimulated collagen synthesis in neonatal rat heart explant cultures, while relatively high concentrations (10 and 100 µM) inhibited synthesis (Shivakumar et al 1992).

Biological Molecules

Rare earth metals have also been shown to compete for calcium (Ca) at the metal-binding sites of a variety of proteins. Findings by Funakoshi and coworkers (1992) revealed that chlorides of rare earth metals inhibit the activity, in human plasma, of two Ca^{2+} binding factors (factor Xa and thrombin) which are involved in the formation of fibrin, thus having anticoagulant action. A recent study in Wistar rats looking at cerium binding to hemoglobin reported conformational changes that affect the oxygen binding capacity of hemoglobin (Cheng et al 2000) (see Table C.1).

DISCUSSION

The data presented above suggest that cerium is less toxic when inhaled or ingested than after intravenous, intraperitoneal, or subcutaneous injections, which yield higher body burdens than those achieved with comparable doses administered via the other routes. The effects appear to closely correlate with the amount of cerium that reaches the target organs, with the lung and the tracheobronchial lymph nodes being the major organs affected after inhalation exposure, the gastrointestinal tract after oral exposure, and the liver after administration by injection into the blood. Other organs that can accumulate cerium and may be affected include the skeleton, spleen, kidney, heart, and brain.

The major effect in humans occupationally exposed to cerium and other rare earth elements is rare earth pneumoconiosis, but the role of cerium in this disease is not clear because cerium was never the only metal component of the aerosols, and the presence of cerium deposits in the lung was not always associated with the presence of the disease. With the exception of a 13-week inhalation study of cerium oxide in rats (Viau 1994), none of the other studies reviewed in this section involved exposure by inhalation, and none of the studies using other routes of exposure involved cerium oxide, the major form of cerium expected to be present in diesel emissions. Because the oxides are less soluble than other forms of cerium, their acute toxicity may be less, although they may be transformed into more soluble forms once taken into the body. The no observable adverse effect level (NOAEL) and the lowest observable adverse effect level (LOAEL) values derived from the animal studies discussed in this section (for all forms of cerium) for various types of effects are summarized in Table 8 according to the route of exposure.

Rats exposed by inhalation to high concentrations (≥ 5 mg/m^3) for 13 weeks of fine to coarse cerium oxide particles (1.8 to 2.2 µm in diameter) displayed an increase in lung and spleen weight, lung discoloration, and enlargement of bronchial and mediastinal lymph nodes (Viau 1994). An increase in blood neutrophils was also reported. Because these effects were observed also at the lowest concentration tested of 5 mg/m^3, no NOAEL could be derived. Although a PM lung overload condition was achieved at the two highest concentrations (based on the observation of a large number of particles found in the extracellular matrix) it is not clear whether overload occurred after exposure to the lowest concentration of 5 mg/m^3. The particle overload phenomenon has been observed in rat inhalation studies after protracted exposures to high concentrations (in the mg/m^3 range) of several types of insoluble particles such as diesel exhaust particles, carbon black, and titanium dioxide. Neoplastic responses induced by overload doses are not thought to be predictive of effects at lower doses (Mauderly 1996). The NOAEL of 5 mg/m^3 would correspond to a dose of about 1 mg/kg/day (material deposited in the entire respiratory tract) or about 0.22 mg/kg/day (material deposited in the lung).

The Viau study used larger particles (~2.0 µm) than those found in the emission studies (0.01 to 0.5 µm). Smaller particles are more likely to deposit deep in the lung than larger particles and to move through the interstitium and thus be translocated to tissues such as the lymph nodes, bones, and liver (Ferin et al 1991; Oberdörster et al 1994). Chronic or semichronic studies at low doses and with fine and ultrafine cerium particles are lacking.

Oral exposure studies have revealed only reduced food consumption and localized effects to the gastrointestinal tract in rats; these effects are probably related to the high doses used (NOAEL of 60 mg/kg of rare earth nitrate mix daily for 24 weeks or LOAEL of 1,000 mg/kg daily for

7 days) (Stineman et al 1978 and Ji and Cui 1988, respectively). The limited evidence in humans appears to show little difference between rodents and humans in the extent of gastrointestinal absorption of ingested cerium compounds (NCRP 1978). As noted in the southern India studies, however, some studies of humans suggest that ingestion of food grown in certain tropical areas rich in deposits of cerium (or other rare earth metals) by malnourished individuals whose diet is poor in magnesium may be associated with endomyocardial fibrosis.

Cerium has been shown to cause hepatotoxicity when delivered intravenously or intragastrically. The effects observed included necrosis, cell destruction, accumulation of fat droplets, and changes in activity of liver detoxifying enzymes (NOAEL of 1 mg/kg cerium chloride after a single intravenous injection) (Arvela et al 1991). In a

Table 8. Summary of LOAEL and NOAEL in Animal Studies for Different Routes of Exposure

Effects	Inhalation	Ingestion	IV or SC
Organ toxicity (acute exposure)			
			NOAEL 1 mg/kg (Ce chloride) IV Mice; liver necrosis and injury (Arvela et al 1991) **LOAEL 2 mg/kg (Ce chloride)** IV Mice; decreased EROD in liver and kidney (Salonpää et al 1992) **LOAEL 2 mg/kg (Ce chloride)** IV Mice; liver necrosis and injury (Arvela et al 1991)
General toxicity (repeated exposure)			
	LOAEL 5 mg/m^3 (Ce oxide) Rat; increased lung weight and lung damage (Viau 1994, 13 weeks)	**NOAEL 60 mg/kg (rare earth nitrate mix)** oral Rat; decreased food consumption and weight gain (Ji and Cui 1988, 24 weeks) **LOAEL 1000 mg/kg (Ce chloride)** IG Mice; gastritis and enteritis, spleen hypertrophy and hyperplasia (Stineman et al 1978, 7 days)	
Carcinogenicity			
		NOAEL 1800 mg/kg (rare earth nitrate mix) oral Rats; tumor incidence (Ji and Cui 1988, lifespan)	
Behavioral effects (adult)			
	NOAEL 50 mg/m^3 (Ce oxide) Rat; reduced forelimb grip (Viau 1994, 13 weeks)	**NOAEL 1000 mg/kg (Ce chloride)** IG Mice; reduced activity (Stineman et al 1978)	**LOAEL 136 mg/kg (Ce chloride)** SC Mice; reduced activity (Stineman et al 1978)
Developmental effects (in utero exposure)			
			LOAEL 80 mg/kg (Ce citrate) IV Mice; reduced newborn body weight after in utero exposure on GD 12 (D'Agostino et al 1982)

13-week inhalation study, Viau saw no indication that clinical biochemical parameters (general indicators of liver metabolism) in blood were affected by the exposure, but parameters of liver detoxification function were not specifically measured. Accumulation of pigmented material in the liver was observed at the highest exposure concentration, but was not associated with an increase in liver weight or changes in morphology. The estimated dose delivered in the lung after the single exposure of 50 mg/m^3 was approximately 22 mg/kg; using the factor estimated by the NCRP of 0.05 for the fraction of the material deposited in the lung that is dissolved and distributed to blood in humans, one can estimate that the blood burden of cerium would have been equivalent to 1.1 mg/kg body weight per day.

Assuming that the proportion of material cleared from the lung by the different pathways is not affected by repeated exposure, the total systemic dose after the 13-week exposure would correspond to an intravenous dose of cerium oxide of about 70 mg/kg body weight. This dose is higher than the LOAEL for effects of cerium chloride on liver enzymes for a single dose. The difference in the extent of liver toxicity after intravenous versus inhalation exposure could be due to the different forms of cerium delivered and different modes of administration (bolus dose versus repeated exposure) and to the fact that particle clearance from the lung was overwhelmed at the high inhalation concentrations.

In vitro studies showed that rare earth metals can alter macrophage function and structure, increase collagen in rat myocytes, and bind to protein (for example, fibrin or hemoglobin) and other macromolecules, thereby affecting their activity.

Few studies exist on the potential immunologic effects of cerium administration. A single dose of cerium oxide delivered subcutaneously in rats was not antigenic (Spanhaak 1996). The 13-week inhalation study, also of cerium oxide in rats (Viau 1994), showed bronchial and mediastinal lymphoid hyperplasia in many exposed animals, but it is not clear if this was due to a nonspecific response to the high particle concentrations in these organs or to an antigenic response.

Cerium may cause behavioral effects, measured as activity or grip strength in rats, if sufficiently high doses reach critical areas of the brain. A NOAEL of 50 mg/m^3 (cerium oxide) was derived for inhalation (reduced grip strength) in rats by Viau (1994), and a NOAEL of 1,000 mg/kg (cerium chloride) was reported for intragastric administration (reduced activity) by Stineman et al (1978). A LOAEL of 136 mg/kg (cerium chloride) in mice was derived for subcutaneous administration (reduced activity) by Stineman et al (1978). One single-dose study on the effect of in utero exposure reported reduced weight in newborn mice with a LOAEL of 80 mg/kg after intravenous administration (D'Agostino et al 1982). The dose required to induce these effects is higher than those shown to cause toxicity to lung and liver.

Conclusions about the carcinogenic potential of cerium cannot be drawn at this time due to insufficient data. An inhalation study of cerium oxide found no increase in lung tumors in rats delivered a lung dose of approximately 70 µg over 7 brief exposure periods (Lundgren et al 1992a). A study of ingestion in rats did not show any tumors after doses up to 1,800 mg/kg of a 42%-cerium mixture of rare earths, but the actual available dose was reportedly much lower due the low absorption of ingested cerium through the gastrointestinal tract (Ji and Cui 1988). For example, the total rare earth residue in rats fed 1,800 mg/kg for 8 months was only 0.26 mg/kg. The genotoxicity tests conducted have been negative, but carcinogenic effects after inhalation are not ruled out by any of these studies.

OVERALL ASSESSMENT

The cerium-based fuel additive Eolys in conjunction with a particulate filter is being proposed to reduce PM emissions from diesel engines. The additive's role is that of reducing soot combustion temperature, thereby facilitating filter regeneration. Regeneration requires burning of the particulate carbon trapped on the filter and usually can occur continuously in the presence of the fuel catalyst during high-load engine operation or high-speed driving. When exhaust temperatures are low (as during low-speed driving), however, regeneration needs to be induced, usually by heating the exhaust (as in the Renault-PSA system).

This report provides a summary of information available on cerium emissions, exposure, dosimetry, and health effects and identifies numerous gaps in our knowledge. In particular, actual data on human exposure are not available and studies on the health effects of cerium are few. For example, Viau (1994) conducted the only study on the effects of protracted inhalation exposure of rodents to cerium oxide, and no inhalation studies have adequately evaluated the carcinogenicity of nonradiaoctive cerium particles. Likewise, only the studies by Ji and Cui (1988) and Kartha (1998) evaluated the effects of ingestion of cerium (combined with other rare earths), and neither of them used cerium oxide, the main form of cerium in diesel emissions.

The next four sections draw together and integrate the salient information from the preceding review of the literature and reiterate the major findings. The last section presents

considerations about the possible public health risk of cerium in the context of introducing new technologies.

EMISSION OF CERIUM

A few recent, short-term, diesel engine tests have confirmed that cerium (20 to 100 ppm) with a particulate filter results in a greater than 90% decrease in particle mass and a greater than 99% decrease in particle number in the exhaust. Similar effects have been observed with the filter alone, but none of these tests had sufficient duration to determine the filter's efficiency over prolonged operation (either alone or in the presence of the additive). The cerium additive with a particulate filter increased emissions of CO, benzene, and butadiene, did not affect (or reduced) NO_x emissions, and reduced PAH emissions.

Despite the high efficiency in trapping PM with a filter, engine tests have shown that a small amount of cerium is emitted in the exhaust in the particulate phase. Cerium measured in emissions was primarily in the form of oxide but may be present also in other chemical forms (such as phosphate or sulfate). The mass of cerium relative to the total particle mass was between 3% and 18% in two tests with continuous regeneration and two different types of filters. Depending on how filter regeneration is induced, cerium emissions may be higher during regeneration. Little is known about emissions from regeneration conditions during real world situations.

CERIUM IN AIR AND SOIL

The tests measuring cerium emissions have a number of limitations, and there is, accordingly, uncertainty about the amount of cerium that will be released in the environment as a result of its use as a fuel additive. Because cerium is already present in soil and is used in some vehicle manufacturing and other industrial processes, a baseline level exists in both ambient air and soil. Thus the expected increase from the use of the cerium-based additive needs to be put in the context of these existing levels. The most recent measurements in the Los Angeles area report levels of cerium in the urban PM of about 0.5 ng/m^3. The average cerium level in the earth's crust worldwide has been estimated to be 20 to 60 ppm, although higher levels have been measured in areas with anthropogenic sources of cerium.

The one effort to date to estimate the increases in cerium in the environment suggested that the increase above current urban ambient air levels could be as high as several orders of magnitude, and that cerium concentrations in soil may double in the next several decades. For this modeling effort, cerium emission factors were projected for the year 2010 for 12 EU member countries for a range of diesel vehicle types and driving scenarios (highway, urban, rural), assuming that 8% of the cerium added to the fuel at a concentration of 100 ppm would be released in the filtered exhaust. The resulting emission factors were then used to calculate air concentrations of cerium in two scenarios expected to have the highest traffic density, in the vicinity of a highway and in a street canyon.

For the highway scenario, the average emission factor was 0.74 mg cerium/km (assuming 80% LD passenger cars and 20% HD vehicles), and the projected ambient concentration was 0.6 $\mu g/m^3$. For the street-canyon scenario, the average emission factor was 0.64 mg cerium/km (assuming 100% LD diesel passenger cars) and the projected ambient concentration was 1.25 $\mu g/m^3$. Thus, the use of the Eolys additive could increase the amount of cerium in ambient air in certain scenarios with high diesel traffic by several orders of magnitude. Cerium would be present in PM, either alone or associated with soot.

These ambient estimates are conservative, because the cerium filtration efficiency in more recent tests has been shown to be generally greater than the 92% assumed in the European estimates by Samaras (1994). Also, lower levels of cerium are proposed to be added to the fuel. However, emissions calculated with a computer model may not reflect emissions from engines operating in the real world. Fleet composition and traffic density may also be different from those used in the current modeling effort.

From the projected ambient air cerium concentrations, the accumulation of cerium from deposition of cerium-containing particles in soil for the EU countries was estimated to be 5 to 30 ppm around roads with high traffic by the year 2050, suggesting that average soil levels may double over 40 years. Where baseline levels of cerium are elevated due to the presence of other cerium sources, the percentage increases would be more modest. Cerium in the soil may be absorbed into vegetation or contaminate water. At this time it is difficult to estimate the potential exposure from ingestion of food or water containing cerium, given uncertainties about cerium uptake in crops and transport through water. However, some uptake of cerium in vegetation has been reported. Exposures to cerium by ingestion, if they occurred, would be intermittent.

FATE OF CERIUM IN THE BODY

The extent to which cerium taken up by humans reaches target organs depends on the route of exposure. Exposure by inhalation results in deposition of cerium in the respiratory tract from which the material is cleared at rates and via pathways determined primarily by its size and solubility

in body fluids. The pathways of clearance from the respiratory tract are:

- removal by mucociliary clearance to the mouth followed by swallowing and excretion via the feces;
- translocation to the pulmonary and tracheobronchial lymph nodes (for particles deposited in the pulmonary region); and
- dissolution and absorption into the systemic circulation and distribution to various organs.

Based on the NCRP classification, less soluble forms (such as hydroxides and oxides) are cleared more slowly from the lung (over a period of years) than the more soluble chloride, phosphate, and nitrate forms used in many of the experimental studies, and are also less likely to reach the circulation and be deposited in other organs. A proportionally greater amount of these less soluble forms would be found in the lymph nodes. A similar trend toward higher blood uptake versus lower mucociliary clearance was estimated for more soluble cerium particles deposited in the upper respiratory and tracheobronchial regions.

Once in the circulatory system, cerium distribution to organs seems to be independent of the original chemical form; principal organs of deposition are liver and bones, from which it is slowly removed. Other organs that accumulate some amount of cerium are spleen, heart, and brain. Cerium deposits in macrophages of various organs, at least in part, in the form of insoluble orthophosphate.

Several studies support the conclusion that after ingestion of cerium salts (in relatively soluble forms such as nitrate and chloride), only a small portion of the ingested dose (less than 0.1%) is absorbed by the gastrointestinal tract and distributed. Because the digestive tract of newborn rodents is more permeable to cerium chloride or nitrate, however, a larger fraction of ingested cerium is distributed systemically. Whether a similar phenomenon occurs in human infants is unknown. A portion of cerium delivered to pregnant rats (approximately 0.3%) has been shown to cross the placenta and accumulate in the fetus (primarily in the liver).

HEALTH EFFECTS OF CERIUM

Based on the results of the studies on distribution and clearance summarized above, inhalation of cerium derived from its use as a fuel-borne catalyst is the route of most concern, while ingestion of cerium would be of less concern because cerium is poorly absorbed by the intestinal tract. The primary targets after inhalation of cerium are the lung and the associated lymph nodes; other organs could also be affected via clearance through the blood.

Rare earth pneumoconiosis has been described in case reports of workers occupationally exposed to rare earth metals, with pathologic features such as interstitial fibrosis, granulomatosis, and bilateral nodular chest x-ray infiltrates. Although the disease in some cases was associated with accumulation of deposits containing cerium, the role of cerium in this complex disease relative to that of other metals or gases to which workers may also have been exposed remains to be clarified.

The only animal inhalation study, which involved exposure to cerium oxide (1.8 to 2.2 µm in size), showed lung discoloration and enlargement of lymph nodes and increased lung and spleen weight in rats after exposure to very high concentrations (5 to 500 mg/m^3) for 13 weeks. No effects on blood parameters were reported with the exception of an increase in segmented neutrophil counts. This study involved exposures to cerium oxide particles with an average diameter larger than that of the particles containing cerium emitted from diesel engines, which will have a different deposition pattern and different clearance pathways from those of smaller particles. Because effects were observed at the lowest concentration of 5 mg/m^3, no NOAEL for effects to the lung could be derived. In comparison ambient levels were estimated to increase by about 1.2 $\mu g/m^3$ in scenarios of high traffic. The estimated lung burden in rats exposed to 5 mg/m^3 for 6 hours (single exposure) is 225 µg/kg body weight while the estimated lung burden for a human subject exposed for 8 hours (working day) to 1.2 $\mu g/m^3$ of cerium is 0.09 µg/kg per day as illustrated in the sidebar, Dosimetric Considerations for Lung and Body Burdens in Humans. Thus, the risk of inhaling cerium at the estimated worst-case ambient levels for some period of time appears to be small. However, the risk of chronic exposure is more difficult to estimate due to the lack of adequate studies.

The review of two studies in which animals were exposed to cerium (in the form of relatively soluble forms such as nitrate and chloride) by ingestion suggests few toxic effects. Findings revealed only reduced food consumption and localized effects to the gastrointestinal tract (gastritis and enteritis), likely related to the high doses used (NOAEL of 60 mg/kg of rare earth nitrate mix for 24 months of exposure or LOAEL of 1,000 mg/kg of cerium chloride for 7 days of exposure in rats). Although none of the ingestion studies involved ingestion of cerium oxide, based on the NCRP evaluation, absorption of the poorly soluble forms of cerium (including cerium oxide) should be considerably less than for the more soluble forms tested. Overall, the risk from ingesting cerium-containing

Dosimetric Considerations for Lung and Body Burdens in Humans Exposed to Cerium Oxide Particles

In order to place the lung burdens achieved in Viau's rat inhalation study in perspective, we can estimate the body burdens that might result in a human exposed to cerium at the predicted ambient concentrations. Maximum exposure to cerium-containing particles from diesel exhaust is likely to occur in areas with high traffic (such as a street canyon) where the highest estimated cerium level was 1.25 μg/m^3 (Samaras 1994) with an MMAD of 0.2 μm (which is the MMAD of exhaust accumulation mode particles on a mass basis) (Graskow et al 1999). The worst-case inhalation dose to the lung (lung burden) would be for an individual working in this environment and can be calculated for a given situation as follows:

- an 8-hour exposure,
- a ventilation rate 1.5 m^3/hr (light activity),
- body weight 70 kg, and
- percentage of particles wth an MMAD of 0.2 μm reaching the alveolar region: about 40% of total inhaled particles (International Commission on Radiological Protection 1979)*.

Based on these assumptions, the calculated cerium lung burden would be approximately 6 μg (or 0.09 μg/kg). If 80% of these particles are cleared via mucociliary movement, about 1.2 μg (or 0.02 μg/kg) would remain available for transport to the lymph nodes or dissolution in blood. This lung burden would be similar for all forms of cerium, but the overall clearance rate and the fraction of cerium distributed to tissues would be higher for more soluble forms of cerium. The lung burden calculated from an exposure of rats to 5 mg/m^3 (LOAEL in Viau's study) was 90 μg (225 μg/kg) per day. The NOAEL for intravenous administration was 2 mg/kg.

In sum, for the worst-case single cerium exposure, the lung burden (and body burden) would be substantially lower than that shown to produce effects, and thus would not be expected to cause adverse effects. However, a NOAEL could not be derived. A thorough evaluation of potential effects of repeated exposure with relevant forms of cerium and particle sizes and lower exposure levels than in the studies reviewed here would be useful.

** Percentages of deposition vary depending on the model used and the assumptions made. NCRP (1997) reported a percentage deposition of about 20% in the pulmonary region. The highest percentage was chosen for these calculations to represent a worst-case scenario.*

food or water appears to be small, but estimates of possible intake of cerium are lacking. Some individuals (such as people on a diet poor in magnesium or newborns) may be at increased risk.

Studies of cerium injected systemically showed that, once in the circulation, cerium can cause hepatotoxicity (NOAEL of 1 mg/kg after a single intravenous injection and LOAEL of 2 mg/kg for effects on liver detoxifying enzymes). Effects in other organs where cerium may accumulate have not been investigated. In the worst-case scenario for human exposure to cerium oxide, the estimated daily dose to the lung would be about 6 μg (or 0.09 μg/kg) (see sidebar on Dosimetric Considerations for Lung and Body Burdens in Humans); if 5% of this dose is cleared to the blood (based on the NCRP model), the resulting blood dose would be equivalent to 0.004 μg/kg. This value is about 6 orders of magnitude lower than those shown to cause effects in rats. Despite uncertainties in extrapolating from animals to humans and differences in the chemical forms of cerium and the size of the particles used in animal studies, this comparison suggests that cerium derived from additives absorbed in the blood is unlikely to cause acute effects in humans. Conclusions about chronic effects cannot be reached at this time, however.

The potential carcinogenicity of cerium-containing particles has not been studied in conventional rodent bioassays; mutagenicity studies have been negative.

The brain and the developing organism are known to be particularly sensitive to exposure to a number of metals; however, the potential for cerium to cause neurotoxic or developmental effects has not been adequately investigated. Behavioral effects (such as reduced activity and reduced forelimb grip) were observed, respectively, after subcutaneous administration in mice (cerium citrate, LOAEL 136 mg/kg) and inhalation exposure in rats (cerium oxide, NOAEL 50 mg/m^3); these doses are higher than those shown to cause toxicity to the major target organs (liver and lungs respectively). One single-dose study on the effects of in utero exposure reported reduced weight in newborn mouse pups with a LOAEL of 80 mg/kg (intravenous administration). Additional inhalation studies should be conducted with relevant particles and animal models.

CONCLUSIONS

In summary, it appears that using cerium as a fuel-borne catalyst with a particulate filter would result in a measurable increase in the ambient levels of cerium oxide in particles less than 0.5 μm (perhaps up to several orders of magnitude greater than current levels) depending on the level of cerium actually used, the filter efficiency in trapping the particles, and the degree of penetration in the vehicle fleet. Cerium levels in the soil near roads would also increase as a result of ambient particle deposition. Based on the limited animal data available, cerium oxide appears to have low toxicity and might not present a concern when inhaled or ingested for some period of time at the low levels caused by Eolys additive (estimated to be in the low μg/m^3 range in the air). In the absence of sufficient information about exposure and health effects, however, fine and ultrafine cerium oxide particles cannot be fully assessed for potential health effects from using a cerium fuel additive. Additional research is needed to better understand:

- size of emitted particles containing cerium;
- effects of engine aging and regeneration on emission of cerium;
- adverse effects of cerium particles (emissions size) inhaled over time on target organs (not only the lung and associated lymph nodes, but also liver, bones, and heart); and
- neurotoxic and developmental effects of cerium particles.

Studies are also needed on the carcinogenicity of cerium-containing particles.

The use of cerium in combination with a filter is proposed primarily to reduce emission of particles and, ultimately, the level of particles in ambient air. Engine tests have shown that the system is effective in achieving substantial reductions in particle mass and number. Ultimately, decisions about the use of the cerium additive, or other metal additives, need to be made in the context of a variety of factors besides information on exposure, rate of clearance from the body, and health effects. Other considerations are the additive's ability to reduce harmful emissions, its persistence in the environment, and the feasibility and cost effectiveness of this technology in comparison with other technologies that can achieve these reductions.

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APPENDIX A. Diesel Emissions Standards for PM

USA STANDARDS

LD Vehicles Tier 1 emission standards apply to cars and LD vehicles under 8,500 pounds. The certification test is the FTP 75. A supplemental FTP will be phased in between 2002 and 2004; it adds test cycles to measure emissions during aggressive highway driving and while the air conditioning system is operating.

Tier 2 emission standards apply to passenger vehicles up to 10,000 pounds. Engines in commercial vehicles above 8,500 pounds certify as HD engines. The same emissions apply regardless of the fuel used. For testing, manufacturers can choose one of 8 certification levels (with varying stringency). Some of these will expire after 2008 model year. The Tier 2 regulations also require a low sulfur content in the fuel.

HD Vehicles Current regulations require certification of the engine and testing over an engine dynamometer. The test cycle is the transient FTP. In 1998 a supplemental steady-state test was introduced for the 2004 and later standards. This test is identical to the EU 13-mode test (ESC, also termed the *Euro III cycle*). The supplemental test has the same emission limits as the transient FTP.

Buses California has developed a plan to reduce emission of NO_x and PM from urban buses. Based on this plan, fleet operators must choose between a diesel path and an alternative fuel path. The alternative fuel path requires that 85% of buses purchased or leased each year through model year 2015 be fueled by alternative fuel. The diesel path contains a number of provisions, one of which is that all pre-2004 diesel buses be retrofitted with an 85% efficient diesel particulate filter certified by the California Air Resources Board. The retrofit begins in 2003.

Off-Road Vehicles Emissions are measured using an 8-mode steady-state test cycle (the same as the International Standards Organization test cycle, ISO 8178).

Table A.1. USA

	Time (Model Years) When Standards Become Effective			
	1994–1997	1996–2000	2004–2008	2006–2008
Cars and LD trucks	0.08 g/mi (Tier 1)		0.02 max[a] g/mi (Tier 2)	
HD trucks	0.1 g/bhp-h			0.01 g/bhp-h[d]
Buses	0.07–0.05 g/bhp-h	0.05 g/bhp-h		
Off-road engines[d]		0.75–0.40[b] g/bhp-h (Tier 1)	0.8–0.2 g/bhp-h[c] (Tier 2)	to be proposed during a review of new regulations in 2001

[a] Range depends on certification level and varies from 0.00 to 0.02 g/mi.

[b] Values depend on engine power and are smaller for engines with higher power.

[c] Model year varies between 2002 and 2006 depending on the engine power.

[d] Proposed.

EU STANDARDS

LD Vehicles The test for the Euro II regulations is the Economic Commission of Europe test (ECE) + European extra urban driving cycle. Effective year 2000, that test procedure is modified to eliminate the 40-second engine warm-up. Gasoline vehicles are exempted from PM standards.

HD Vehicles According to the Euro III standard, manufacturers have a choice between the new 13-mode cycle (ESC) and a transient cycle (ETC). With Euro IV (year 2005) limit values, the emissions have to be determined on both the ETC and the ESC. The emission limit values set for 2005 and 2008 (Euro V, same PM limit as Euro IV) are expected to require all new diesel-powered HD vehicles to be fitted with exhaust gas aftertreatment devices (such as filters and $DeNO_x$ catalysts).

Off-Road Vehicles Emissions are measured using a 8-mode steady-state test cycle (the same as the ISO 8178).

Table A.2. EU

	Time (Model Years) When Standards Become Effective			
	1992–1994	1996–1999	2000–2001	2005–2006
Cars	0.14 g/km (Euro I)	0.08 g/km (IDI) 0.1 g/km (DI) (Euro II)	0.05 g/km (Euro III)	0.025 g/km (Euro IV)
LD trucks	0.14–0.25 g/km[a]		0.05–0.1 g/km[a]	0.025–0.1 g/km[a]
HD truck and bus engines	0.612–0.36 g/kWh[b] (Euro I)	0.25–0.15 (1998) g/kWh[b] (Euro II)	0.13–0.10[b,c] 0.21–0.16[b,d] g/kWh (Euro III)	0.03 g/kWh[f] (Euro IV)

[a] Values depend on class (weight) of the engine.

[b] Values depend on engine power and are smaller for engines with higher power.

[c] This standard applies to engines tested on the European Steady-State Cycle.

[d] This standard applies to engines tested on the European Transient Cycle. Manufacturers have the choice between either of these two tests.

[e] Year of implementation depends on engine power.

[f] It is expected that the emission limit values set for 2005 and 2008 (same as 2005 for PM emissions) will require all new diesel-powered HD vehicles to be fitted with exhaust gas after-treatment devices, such as particulate filters and $DeNO_x$ catalysts.

JAPAN STANDARDS

LD Vehicles Slightly different emission standards apply to diesel cars and diesel LD commercial vehicles. The current test cycle is the 10 to 15 mode cycle for all these types of vehicles. Cars are divided into two categories based on weight (< 1265 kg and > 1265 kg). LD vehicles also are divided into two weight categories (< 1700 kg and 1700 to 2500 kg).

HD Vehicles The current test cycle is a 13-mode cycle.

Off-Road Vehicles Emissions are measured using an 8-mode steady-state test cycle (the same as the ISO 8178).

Source: DieselNet 2000.

Table A.3. Japan

	Time (Model Years) When Standards Become Effective			
	1993–1994	1996–1999	2002–2003	2004–2006
Cars	0.2 g/km	0.08 g/km	0.052–0.056 g/km[a]	
LD trucks and buses	0.2–0.25 g/km[a]	0.08–0.09 g/km[a]	0.052–0.06 g/km[a]	
HD trucks	0.70 g/kWh	0.25 g/kWh		0.18 g/kWh
Off-road engines (construction vehicles)		First stage[b]		0.8–0.3 g/kWh[a] (Second stage)

[a] Values depend on the vehicle weight.

[b] Standards for gaseous emissions only.

APPENDIX B. Details About Studies Reported in Tables 1 Through 5

CZERWINSKI ET AL 1999

Engine: 6.11-L, DI D914T HD Liebherr

Operating conditions: In total 4 operating modes of the ISO 8178 cycle for off-road engines were used: Each mode was run for 15 minutes in the following order: mode 2, full load (606 Nm), mean rpm (1,400); mode 6, 50% load (297 Nm), mean rpm; mode 5, 50% load, rated rpm (2,000); mode 1, full load, rated rpm; mode 2, full load, mean rpm (second measure). Volatile particles were separated with an activated charcoal trap (thermodenuder) after heating the exhaust. The emission data reported in the table were obtained in the presence of the charcoal trap. The mass emission data in the table are the average of data from two separate tests at each of the two runs at mode 2 (full load/mean rpm); the number emission data are from one test at mode 1 (at this point tendencies to higher counts were noted in the lowest size range after the trap due to saturation of the charcoal trap).

Fuel: Swiss standard diesel

Sulfur content: 0.05% (by weight)

Cerium content: 50 ppm

Filters: IBIDEN SiC. Two filters were tested: (A) 10-µm pore and (B) 6-µm pore. The mass data in the table are the averages of data from both filters (emissions from the two filters differed very little). The tests were conducted with new or soot-loaded filters in the absence of cerium as indicated. When cerium was also used, self regeneration occurred.

CZERWINSKI ET AL 2000

Engine: 6.11-L, DI D914T HD Liebherr

Operating conditions: In total four operating modes of the ISO 8178 cycle for off-road engines were used: Each mode was run for 15 minutes in the following order: mode 2, full load (606 Nm), mean rpm (1,400); mode 6, 50% load (297 Nm), mean rpm; mode 5, 50% load, rated rpm (2,000); mode 1, full load, rated rpm; mode 2, full load, mean rpm (1,400) (second measure). Volatile particles were separated using an activated charcoal trap (thermodenuder) after heating the exhaust. The emission data reported in the table were obtained in the presence of the charcoal trap. The mass emission data in the table are the average of data from two separate tests at each of the two runs at mode 2 (full load/mean rpm); the number emission data are from one test at mode 1 (at this point tendencies to higher counts were noted in the lowest size range after the trap due to saturation of the charcoal trap).

Fuel: Swiss standard diesel

Sulfur content: 0.05% (by weight)

Cerium content: 50 ppm

Filter: Corning EX-80

HEEB 1998a

Engine: 6.6-L, DI 924T1 HD Liebherr

Operating conditions: ISO 8178 C1 cycle for construction site engines consisting of four load modes at maximum rpm (2,000) followed by three load modes at an intermediate rpm (60% of rated) and an idling phase (total 100 minutes) repeated 4 times without interruptions (for a total test time of 400 minutes). Volatile particles were separated using a thermodenuder and were not measured.

Fuel: commercially available diesel

Sulfur content: 0.043% (by weight)

Cerium content: 64 ppm

Filter: SHW (sintered metal) and BUCK (fiber). The data in the tables are the average of the two filters unless otherwise specified.

HEEB 1998b

Engine: 6.6-L, DI 924T1 HD Liebherr

Operating conditions: ISO 8178 C1 cycle for construction site engines consisting of four load modes at maximum rpm (2,000) followed by three load modes at an intermediate rpm (60% of rated) and an idling phase (total 100 minutes) repeated 4 times without interruptions (for a total test time of 400 minutes). Volatile particles were separated using a thermodenuder and were not measured.

Fuel: commercially available diesel

Sulfur content: 0.043% (by weight)

Cerium content: 64 ppm

Filter: SHW (sintered metal).

JAPAN AUTOMOBILE RESEARCH INSTITUTE 1995

Engine: unspecified engine meeting the Japanese 1994 emission standards

Operating conditions: Japan 13-mode test for diesel vehicles

Fuel: not specified

Sulfur content: 0.04% (by weight)

Cerium content: 100 ppm

Filter: none

KHAIR ET AL 2000

Engine: 12.7-L, HD Detroit Diesel Corp

Operating conditions: US HD transient federal test procedure (FTP) with and without cold start (for the data in

Table 1); steady state operation for 30 minutes at mode 10 of the European 13-mode test (for the data in Table 3). Baseline condition included the use of a catalyst and urea. These conditions were maintained when the filter and the cerium additive were used. The baseline data in Table 1, 4, and 5 are the average emissions from two FTP tests.

Fuel: grade 2 diesel

Sulfur content: 368 ppm by weight

Cerium content: 50 ppm

Filter: Corning EX-80

LADEGAARD ET AL 1997

Engine: 2.5-L, DI Ford Transit

Operating conditions: 3 loads (11, 20, and 28 kW) at 2,250 rpm (56% of rated)

Fuel: commercially available diesel

Sulfur content: 0.3% (by weight)

Cerium content: 100 ppm

Filter: none

LEPPERHOFF ET AL 1995

Engine: 1.9-L, Volkswagen AG

Operating conditions: not specified

Fuel: not specified

Sulfur content: not specified

Cerium content: 50 ppm and 100 ppm

Filter: Corning EX-47

PATTAS ET AL 1992

Engine: Mercedez 240 passenger car

Operating conditions: US FTP

Fuel: not specified

Sulfur content: not specified

Cerium content: 100 ppm

Filter: NGK 221E

PSARAS ET AL 1997

Engine: 7.3-L, HD Navistar with EGR system

Operating conditions: 9-mode steady state test or the hot portion of the US HD transient cycle

Fuel: not specified

Sulfur content: not specified

Cerium content: 125 ppm

Filter: Corning EX-80

SAMARAS 1994

1. Engine: two-stroke Detroit Diesel Corp

Operating conditions: EPA transient cycle with hot start

Fuel: standard diesel

Sulfur content: not specified

Cerium content: 100 ppm

Filter: Donaldson

2. Engine: RABA/MAN bus

Operating conditions: European 13-mode test procedure

Fuel: standard diesel

Sulfur content: not specified

Cerium content: 100 ppm

Filter: Corning EX-80 (Pattas System)

SKILLAS ET AL 2000

Engine: 6.11-L, DI D914T HD Liebherr

Operating conditions: four operating modes from the ECE R49 13-mode steady state test (each mode was run for 15 minutes). The four modes used are: mode A-2,000 rpm/500 Nm (speed/torque); mode B-1,400 rpm/600 Nm; mode C-2,000 rpm/250 Nm; mode D-1,400 rpm/300 Nm. The data presented in Table 1 derive from a test at mode D only.

Fuel: standard diesel

Sulfur content: not specified

Cerium content: 20 to 100 ppm

Filter: none

SOUTHWEST RESEARCH INSTITUTE 1997

Engine: 8.3-L, HD Cummins

Operating conditions: EPA transient test (with one cold- followed by two hot-start runs; each was run for 24 hours). The data for the hot cycle in Tables 1 and 3 are the average of two hot tests. A durability test for 1,000 hours of operation was conducted at a steady state condition (10% overspeed and 10% load).

Fuel: grade 2 fuel

Sulfur content: 0.05% by weight

Cerium content: 100 ppm

Filter: none

APPENDIX C. Summary Tables of Animal and In Vitro Studies

Table C.1. Summary of Animal Studies

Chemical Form [Particle Size] **Species Information**	**Route of Administration and Experimental Conditions**	**Endpoints**	**Findings**	**Reference**
^{144}Ce chloride Mouse (male DBA/2 and C57BL/6)	**IV (caudal vein).** For body distribution 2 mg/kg ^{144}Ce chloride, killed at 72 hr; *n* = 5/strain. For liver morphology and enzyme activity, 0.5, 1.0, and 2.0 mg/kg ^{144}Ce chloride, killed at 24 or 72 hr; *n* = 4–6/group.	Ce level in liver and spleen (measured by gamma counter); Enzyme level or activity: cytochrome P450 level, activity of COH, ECOD, EROD; Liver morphology by light microscopy.	Ce level: slightly higher levels (~1.5 fold) of Ce in DBA than in C57BL in liver and significantly higher (3 fold) in spleen. Enzymes: increase in P450 levels in both strains at 1 and 2 mg; dose-dependent increase (significant at 1 and 2 mg/kg) in COH activity at 24 hr, then decrease at 72 hr in DBA, increase at 72 hr in C57BL (at all doses). Similar pattern for other enzymes. Liver morphology: disorganization and disintegration of liver structure (including necrotic hepatocytes and hepatocytes with cytoplasmic accumulation of fat droplets) in DBA mice, slight widening of sinusoids and congestion in liver of C57BL at 2 mg/kg.	Arvela et al 1991
^{144}Ce chloride Mouse (female NMRI)	**IV.** 5.5 mg/kg. Three groups (*n* = 43/group) treated with nafenopin, pregnolone-16-α-carbonitrile, or solvent (control) for 3 days. On day 4, IV injection with ^{144}Ce in all groups.	Ce level in blood, liver, urine, and feces (in control animals exposed to Ce only). Effect of compounds on the retention of Ce (not reported here).	Ce level: < 1% of dose in serum after 1 day; increased liver content through day 1 (4.5% of initial dose), then constant for several days, decreased by day 6. Amount in feces increased up to day 3 (3% of initial dose), then decreased.	Bjondhal 1976

(Table continues on next page)

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] Species Information	Route of Administration and Experimental Conditions	Endpoints	Findings	Reference
Ce chloride Rat (male Wistar)	**Oral.** 0.2, 2.0, and 20 mg/kg/day for up to 105 days. Killed at 0 days and at intervals up to 105 days (intervals not specified). Number of animals not reported.	Hemoglobin level and oxygen affinity (by oxygen equilibrium and Mössbauer and ESR spectra); Hemoglobin conformational changes and 2,3- DPG hydrolysis (2,3-DPG controls oxygen release from hemoglobin). In vitro production of OH radicals from reaction of Ce (4 mM) with H_2O_2 (Fenton reaction).	Hemoglobin level and oxygen affinity: increased hemoglobin content after feeding with 20 mg/kg for 80 days, but no changes observed at lower doses; change in oxygen saturation curve after feeding with 20 mg/kg for 40 days (with increased affinity at low oxygen pressure and decreased after that), but no effect on final degree of saturation. After 80 days, normal saturation curve, but higher oxygen saturation level suggesting increased oxygen affinity of hemoglobin with long-term feeding. Affinity did not return to normal 15 days after feeding was terminated. A lower dose (2 mg/kg) increased oxygen affinity after 90 days of feeding, but to a lesser extent. Mössbauer and ESR spectra confirm increased oxygen affinity. Hemoglobin conformational changes and 2,3-DPG hydrolysis: conformational changes (α-helical content decreased and turn structure increased) with increased feeding time after feeding with 20 mg/kg; increased hydrolysis of 2,3-DPG after 20 mg/kg for 60 days. Production of OH radicals: enhanced in vitro production of OH radicals, which can cause oxidation of heme-Fe (II) to heme-Fe (III).	Cheng et al 2000
Ce citrate Mouse (pregnant female Swiss ICR)	**SC.** 80 mg/kg injection in pregnant animals on GD 7 or 12 or PND 2. Offspring divided into 4 groups (n = 10–22/group): (A) Exposed in utero to Ce and reared by a postpartum-exposed mother; (B) Exposed in utero to Ce and reared by a nonexposed mother; (C) Not exposed in utero, reared by a postpartum-exposed mother; (D) Not exposed in utero, reared by a nonexposed mother.	Weight, gross motor activity of neonates on PND 8 or 13. Behavioral measures on PND 60–65 (activity in an open field [ambulations and rearings], balance and coordination on an accelerating, rotating rod [rotarod] performance, and simple learning [passive avoidance behavior]); maternal pup retrieval latency on PND 3.	Weight and gross motor activity: neonatal weight significantly reduced in offspring exposed in utero on GD 12 (group A), or nursing from mothers exposed on PND 2 (group C). Behavioral effects: only effect on rearing in the open field in offspring exposed in utero on GD 12 (group A); decreased retrieval latency by foster mother of pups exposed in utero (groups A and B).	D'Agostino et al 1982

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] Species Information	Route of Administration and Experimental Conditions	Endpoints	Findings	Reference
Ce sulfate Rat (male and female CFY/NIN)	**Oral.** 35 mg/kg in the diet ad libitum. Four exposure groups (*n* = 9/group) based on diet: (A) +Mg,–Ce; (B) +Mg,+Ce; (C) –Mg,–Ce; (D) –Mg,+Ce. Mg-deficient diets replaced with Mg-restricted diets after 1 month; killed after 3 months of exposure.	Ce and Mg distribution and level (measured by neutron activation analysis) in heart, kidney, skeletal muscle, liver, lung, and bone.	Distribution and levels of Ce: Ce present in all tissues of animals on Ce diet; Ce levels in bone, liver, kidney, and heart in Mg-restricted group (D) significantly higher than in Mg-sufficient group (B). Bone accumulated highest amount of Ce. Distribution and levels of Mg: decreased level in bones of all animals on Mg-deficient/restricted diet independent of Ce exposure; no difference in Mg levels in other tissues among four groups.	Eapen et al 1996
^{144}Ce chloride and ^{144}Ce citrate Male and female neonate mouse (C_3H), rat (Sprague-Dawley), or pig (Yorkshire) age 0–24 hr	**Oral (by plastic tubing).** ^{144}Ce carrier-free exposure at age 0–6 hr or 6–24 hr (pigs received only Ce chloride); killed between PND 1 and 21; *n* = 7–12 mice or rats/timepoint or 1–4 piglets/timepoint.	Absorption and retention (by radioactivity counting) in GI tract and its contents, femur, liver, lung, brain, and remaining carcass (data for Ce chloride and Ce citrate pooled).	Absorption and retention: *Mice*: increased body and liver retention over time, trend of more rapid retention in 0- to 6-hr-old group, but no difference after 21 days (about 3% of initial dose in liver and 24% in whole body, excluding GI tract); mice dosed at 0–6 hr retained more Ce in GI tract and its content during 21 days than mice dosed at 6–24 hr; Ce rapidly removed from GI tract with 1.5% of initial dose remaining in GI tract on day 15. *Rats*: retention trends similar to mice but smaller percentage deposited in liver (1% of initial dose) and in whole body excluding GI tract (8% and 11% of initial dose) after 21 days; longer retention of Ce in GI tract (about 8% remaining after 15 days). *Pigs*: minimal uptake from GI tract with 0.3% in liver on day 18. *Overall:* body uptake reaches plateau earlier in pigs (day 7 after dosing) than in rats (day 15) and mice (day 15–18). Total absorption (excluding GI tract) 21 days after dosing was higher in mice (24%) than in rats (8–11%) followed by pigs (about 4%); clearance of Ce from GI tract fastest in pigs, then mice, then rats. Retention of Ce in femur similar for mice and rats.	Eisele et al 1980

(Table continues on next page)

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] **Species Information**	**Route of Administration and Experimental Conditions**	**Endpoints**	**Findings**	**Reference**
^{141}Ce nitrate Rat (Sprague-Dawley) age 0–43 days	**IG.** Dose not reported; 0-, 7-, 14-, and 26-day-old; 17-day-olds separated into sucklings and weanlings (fed commercial diet) dosed at age 19 days; 43-day-old rats fed either commercial diet or powdered whole milk. *n* = 6–9/group. **IP**. 1-day-old pups only.	Absorption and retention (by whole body counting) or by counting GI tract and carcass radioactivity after killing (determined in pups dosed at age 1 day). Localization of Ce in GI tract (*n* = 1/day).	Absorption and retention (IG): *Rats dosed at age 0, 7, and 14 days*: high initial retention, then faster loss as pups approached weaning (around age 16 days, somewhat less rapid loss for rats dosed on day 0); levels plateaued during period on commercial diet (around age 26 days) (3%, 1.5%, and 0.9% of initial dose for 0-, 7-, and 14-day-olds, respectively). *Rats dosed at age 26 days*: very rapid decline without reaching a plateau (0.04% of initial dose present 3 days after dosing). *0-day-old rats*: whole body radioactivity decreased to 29% (of initial dose) by day 16 and 3% by day 26; the percentage of initial activity found in the GI tract decreased from 99% on day 1 to 7% on day 24 and increased in remainder of the body from 0.3–2.5%. *19-day-old weaned rats*: dosed on day 19 (two days after being on a commercial diet), very rapid decline of whole body radiaoctivity. *19-day-old suckling rats*: dosed on day 19, slow decline until weaning (age 26 days), then rapid decline. In both groups levels reached a plateau, but levels were 10-fold higher in suckling rats. *43-day-old rats*: less rapid loss in rats fed powdered milk versus those fed commercial diet; however, 43-day-old rats fed powdered milk lost Ce faster than 25-day-old (suckling) rats. *IP*: rate of decline of retained Ce not affected by change in diet. *Localization of Ce in GI tract*: at 1 day after dosing activity found in all epithelial cells lining the villi; 5 days later activity found primarily in cells in upper 2/3 of villi, reflecting migration of epithelial cells.	Inaba and Lengemann 1972

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] Species Information	Route of Administration and Experimental Conditions	Endpoints	Findings	Reference
Rare earth nitrate (Ce representing 42.8%); also Ce nitrate and Ce oxide in LD_{50} studies Mouse, rat (Wistar), guinea pig, monkey (male and female)	**Oral.** Acute toxicity (LD_{50}) for Ce nitrate and Ce oxide in female mice. Distribution: *Rats:* single dose of 1,000 mg/kg or repeated doses of 1,800 mg/kg for 8 months; *Monkeys*: 500 mg/kg single dose or repeated for 90 days. Subchronic toxicity *Rats:* 0, 2, 20, 200, 2,000 mg/kg in basic diet for 24 weeks; *Mice*: 40, 200 mg/kg for 24 weeks. Carcinogenicity: *Rats*: 2, 60, 1,800 mg/kg for 2 years. Teratogenesis: *Pregnant rats*: 55, 165, 331 mg/kg from GD 16–21. Mutagenicity: Ames test: 0.05, 0.5, 5, and 50 mg/mL. Micronucleus test: 40, 200, and 400 mg/kg. Aberration in mouse marrow cell chromosomes: 1/100, 1/50, 1/10, and 1/5 LD_{50}. Aberration in mouse testicle cell chromosomes: 200, 400, and 600 mg/kg. Malformation of mouse sperm: 55 and 331 mg/kg.	LD_{50} in mice, rats, and guinea pigs. Distribution of rare earths (by neutron activation analysis) in liver, spleen, skeleton, kidney, heart, lung in rats and monkeys 24 hr after single or repeated exposure. Subchronic toxicity: growth and development in rats, hematologic and biochemical determination in rats, immune function determination (function of antibody-forming cells) in mice, organ weight in rats, histopathology in rats. Carcinogenicity: tumor incidence. Teratogenesis: malformation of the fetus. Mutagencity: Ames test, micronucleus test, aberration in mouse marrow cell chromosomes, aberration in mouse testicle cell chromosomes, malformation of mouse sperm.	LD_{50} oral: *Female mice*: 1,178 mg/kg for Ce nitrate, 622 mg/kg for Ce oxide. Distribution: *Rats*: after single dose of 1000 mg/kg, highest levels found in liver and skeleton, next highest in heart and kidney (dose retained was less than 1 mg/kg). After 8 months of feeding, highest levels found in spleen and skeleton, next highest in liver and kidney (dose retained was 0.26 mg/kg). *Monkeys*: 94% of single gavage dose excreted in feces in first 3 days; highest levels found in liver, spleen, and skeleton after repeated exposure (dose retained was 3.8 mg/kg). Subchronic toxicity: decreased weight gain from week 14 and weekly food consumption in female rats exposed to 2,000 mg/kg. Normal hematologic and biochemical parameters but higher blood phosphorus in male rats exposed to 2,000 mg/kg for 6 months. No effects on immune function. Decreased liver weight (relative to body weight) in rats exposed to 2,000 mg/kg. No evidence of histopathologic alterations. Carcinogenicity: tumor incidence lower in exposed groups than in controls. Teratogenesis: no malformations. Mutagencity: all endpoints normal except for slight effect on spermatogonia aberrations.	Ji and Cui 1988
Rare earth chloride (REC) (Ce representing 56%) Rabbit (male and female New Zealand white) approximately 2 kg in weight	**Oral.** REC mix 1 g/L in water; feeding ad libitum for about 7 months. Four exposure groups, *n* = 10/group: (A) +Mg,–REC; (B) +Mg,+REC; (C) Mg restricted,–REC; (D) Mg restricted,+REC; (restricted diet alternated with normal diet).	Levels of Ce, Mg, and Ca in heart. Cardiac weight and histology. Collagen level (measured by level of hydroxyproline). Collagen type (phenotyping of types I and III) in heart ventricles.	Heart level of Ce, Mg, and Ca: Ce levels higher in rabbits dosed with Ce, but not different in rabbits on Mg-sufficient and Mg-restricted diet; Ca levels significantly higher and Mg levels lower in animals on Mg-restricted diet (± REC). Heart weight and histology: slight increase in heart weight in animals on Mg-restricted diet; cardiac lesions (in subendocardium) in animals on Mg-restricted diet, but slightly more severe in group also exposed to REC. Collagen level and type: not statistically significant increase in mean level of total collagen in both ventricles, but significant decrease in collagen type I/III ratio in groups on Mg-restricted diet (± REC).	Kartha et al 1998

(Table continues on next page)

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] Species Information	Route of Administration and Experimental Conditions	Endpoints	Findings	Reference
^{114}Ce nitrate (also chloride of ^{197}Hg, ^{115}Cd, and ^{65}Zn) Rat (male Wistar) 200–350 g in weight	**IV (femoral vein).** 0.5 mg/animal immediately before bile duct sampling. (Some animals pretreated with single or multiple doses of spironolactone.) Bile collection at 30-min intervals for first hr, then every hr for next 3 hr. *n* = 3 animals/group.	Biliary excretion of Ce and other metals (by counts in the bile). Effect of spironolactone on biliary metal excretion (this compound was reported to protect against damage induced by various metals).	Biliary excretion: Recovery of radioactivity in bile varied with metal with maximum level after 2 hr. After 4 hr, total amount of Ce recovered was 0.13% of the injected dose. Recovery of other metals was 16% Cd, 2% Zn, 1% Hg. No effect of spironolactone on biliary excretion of Ce.	Kitani et al 1977
^{160}Terbium oxide [MMAD 1.28 µm] ^{160}Terbium citrate Human (male), monkey (male), dog, rat (female)	**Inhalation (particle nebulized after suspension in ethanol).** Humans (*n* = 4) exposed by mouthpiece; monkeys (*n* = 9) exposed by nose mask; dogs (*n* = 3) exposed by endotracheal tube; rats (*n* = 32) exposed nose-only.	Clearance (by gamma counting) of the chest and fecal and urinary material.	Clearance: Particles disappeared from alveolar region at similar rate in humans, monkeys, and dogs, fastest in rats. Systemic uptake faster in humans, monkeys, and dogs than in rats during first 2 months, afterward similar (fraction taken up about 50–60% of initial lung burden [ILB]). Predominant site of deposition was skeleton followed by liver. Liver uptake peaked one week after inhalation (8% of ILB in monkeys, 18% in dogs, and 3% in rats; 10% estimated for humans) and persisted in monkeys and dogs for more than six months (period of observation). Some radioactivity found in urine in all four species.	Kreyling et al 1998
Ce chloride Rat (male and female Sprague-Dawley)	**Oral.** 35 mg/kg ad libitum. Four exposure groups: (A) +Mg,–Ce; (B) +Mg,+Ce; (C) –Mg,–Ce; (D) –Mg,+ Ce; killed 13 months after exposure; *n* = 5–9 animals/group.	Ce level in cardiac tissue by inductively coupled plasma mass spectrometry (ICP-MS). Cardiac histology.	Level: Cardiac Ce level higher in Mg-deficient animals. Cardiac histology: increase in collagen content in all groups except +Mg,–Ce.	Kumar et al 1996
Ce chloride Rat (female Sprague-Dawley)	**IV (caudal vein).** 1.3 mg/kg; killed at 24 and 48 hr after treatment; *n* = 3–4 animals/endpoint.	Liver lipid peroxidation (measured by thiobarbituric acid reaction) in serum or heart. DNA synthesis (measured as ^{3}H-thymidine incorporation) in heart. Rate of collagen synthesis and degradation (measured as incorporation of ^{3}H-hydroxyproline) in heart. All measured 24 hr after dosing.	Lipid peroxidation: 3-fold increase in serum and 30% increase in cardiac tissue. DNA and collagen synthesis: increased cardiac fibroblasts proliferation, but no change in collagen synthesis. Significant decrease in collagen degradation at 48 hr resulting in increased deposition of new collagen.	Kumar and Shivakumar 1998

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] Species Information	Route of Administration and Experimental Conditions	Endpoints	Findings	Reference
Ce oxide [MMAD 0.9–2.2 µm] (also ^{144}Ce oxide, but not reported here) Rat (male and female Fisher 344) 64 days old	**Inhalation.** Single (n = 35) or repeated exposure (every 60 days for a total of 7 exposures over 1 year) to establish lung burdens of 10 µg/exposure (n = 40). Unexposed n = 70. Animals kept for lifespan.	Lung, liver and skeletal neoplasia; survival.	Neoplasia: no increase in incidence of lung tumors in animals exposed once at age 64 days or repeatedly exposed beginning at age 64 days relative to control animals. No effect on survival.	Lundgren et al 1992a
Ce oxide [MMAD 0.9–2.2 µm] Rat (male and female Fisher 344) 64 or 500 days old	**Inhalation.** Young rats: single (5–50 min) or repeated (each for 25 min) exposure every 60 days for 1 year (total of 7 exposures) to establish different lung radiation doses; older rats exposed once (concentration not specified). Animals killed at 1 hr and at 2, 7, 14, 28, 56, 112, 224, 448, 560, and 672 days after single exposure or 7 days after each repeated exposure; n = 6/kill time.	Clearance (by whole body counts). Distribution (counts in lung, heart, liver, spleen, kidney with adrenals attached, skeleton).	Clearance: approximately 90% of IBB cleared within first 7 days after single exposure. Significant difference in lung retention between male and female (longer in female, independent of age of exposure) and between young and old (longer in old) at the two highest radiation doses (for particles deposited in lower respiratory tract). After single exposure, majority of ILB (56–90%) cleared with $T_{1/2}$ of 6–42 days, lesser amount (10–41% of ILB) cleared with $T_{1/2}$ of 36–180 days. Clearance decreased with increasing lung burden and with each repeated exposure. Distribution: translocation to liver and skeleton reaching maximum level during first few weeks (about 0.3% and 1.5% of ILB, respectively) after a single exposure. Similar distribution pattern after repeated exposure. No radioactivity found in kidney or spleen.	Lundgren et al 1992b
^{144}Ce oxide [MMAD 1.35–1.42 µm] Mouse (female C57BL/6J)	**Inhalation.** Nose-only for 20 min (concentration not specified); mice kept for lifespan observations; total n = 178.	Ce lung clearance after serial killings from day 61–160 and also on day 218–454 for mice that died in that period.	Clearance: rapid clearance between days 0 and 6 (assumed to be due to external contamination and material deposited in upper respiratory tract and large airways). After day 6 clearance of material deposited in lower respiratory tract, after a 3-component clearance curve with retention $T_{1/2}$ at 7, 28, and 145 days. Majority of body burden at various killing times between days 101 and 454 was in the lung (from 95%–84%). No substantial differences in animals that received two different radiation doses.	Lundgren et al 1974

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Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] Species Information	Route of Administration and Experimental Conditions	Endpoints	Findings	Reference
Ce chloride (also La chloride) Mouse (pregnant female Swiss)	**IV (tail vein).** 3.56 mg/kg (corresponding to LD_{50-30}) on GD 7 and 19; two days after end of exposure injection with ^{14}C-AIB (marker of damage to cell membranes), ^{3}H-thymidine (marker of cell permeability or increased cell proliferation), and ^{125}I-albumin (marker of increased cell permeability). Killed 2 hr after injection of markers; *n* = 6/exposure group.	Markers of cell permeability (radioactivity counts) in maternal liver and spleen, fetus, and placenta 2 days after exposure to Ce or La relative to control.	GD 9: increase in thymidine levels in liver, spleen, and placenta + fetus (highest in placenta + fetus, 2.7 times that of control), no change in albumin level, AIB not determined. GD 21: substantial increase in AIB in liver, spleen, and placenta (highest for liver, 5 fold that of control), slight increase in thymidine in spleen, but not in other tissues; no change in albumin uptake. Similar results with lanthanum. Considering results with both Ce and La, authors concluded that rise in levels of AIB and thymidine in maternal liver, spleen and placenta suggests some damage to the blood/organ barrier (especially in earlier pregnancy). No increase in markers' uptake was observed in the fetus, suggesting that there was no effect on the placental barrier.	Marciniak et al 1988
^{144}Ce citrate Mouse (female albino)	**IM.** Carrier free. 5 exposure groups (*n* = 24/group): (A) mothers injected 2 days before delivery; (B) mothers injected right before mating; (C) and (D) mothers injected 4 or 8 weeks before mating; (E) nonpregnant mice.	Uptake and distribution in litters. Distribution in mothers (whole body counts) immediately after delivery and at different times thereafter.	Uptake and distribution in litters: At birth, 0.23% of mother's activity was found in each pup of group A versus 0.01% or less in litters from other groups. Body burden of litters from all groups increased during suckling, reaching a maximum at PND 11 (about 11% of maternal burden in group A and 0.5–1.5% in other groups); afterward two-phase reduction (one rapid and one slower). In group A litters at PND 10, majority of radioactivity was in the digestive tract (60% of litter body burden), followed by carcass (35%) and liver (3.9%). Over time, radioactivity in digestive tract decreased and fraction in carcass increased up to 48% of litter burden (PND 16). Distribution in mothers: Radioactivity initially in liver, later also in skeleton. Example: 55% of total body burden in liver and 32% in skeleton 1 day after dosing and 11% and 85% 50 days after dosing. No difference in Ce retention between pregnant and nonpregnant mice.	Naharin et al 1969

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] Species Information	Route of Administration and Experimental Conditions	Endpoints	Findings	Reference
Ce chloride and other rare earth elements Rat (male Wistar-KY), weight 115–135 g	**IV (caudal vein).** 9–10 or 18–20 mg/kg, killed 2 hr or 1 day after exposure for Ce blood level and organ distribution, 3–5 animals/exposure/timepoint. 9 mg/kg, killed at day 1, 3, and 7 after exposure for other endpoints, 3–5 animals/exposure/timepoint.	Ce distribution by inductively coupled plasma atomic emission spectrometry (ICP-AES) in whole blood and in liver, spleen, kidney, lung, and femur. Ca level in liver, spleen, kidney, whole blood. Serum levels of GOT, GTP, total cholesterol, phospholipids, triglycerides, total bile acids, and bilirubins. Hepatic lipid content (triglycerides, cholesterol, phospholipids).	Distribution: Ce found in liver, bone, spleen, lungs, kidneys, and blood, but levels were not dose related. At 2 hr after dosing, serum contained 71–73% of initial dose. At day 1, liver contained about 70–75% of initial dose, spleen 3%, bone 12%, lungs 1%, kidneys 0.5%, and blood 2.3–4%. Ca level (at Ce low dose): increased in liver and spleen at day 1. Serum levels of compounds: (all at low dose) significantly increased in GOT, GTP, bilirubin, and bile acids at day 3; GOT and bile acids also increased at day 1. Hepatic lipid content: significantly increased at day 3 only.	Nakamura et al 1997
Ce oxide Mouse (male and female Swiss OF1)	**Oral.** 2000 mg/kg (suspended in carboxymethylcellulose). Cyclophosphamide 50 mg/kg as positive control. 20 animals/group for vehicle- and Ce-exposed, n = 10 for positive control. Killed at 24 and 48 hr after exposure.	Polynucleated polychromatic erythrocytes in femur bone marrow.	No increase in polychromatic erythrocytes in bone marrow from Ce-exposed mice relative to vehicle-exposed mice. Substantial increase in animals treated with cyclophosphamide.	Pichard 1993
Ce chloride Mouse (male C57BL/6 and DBA/2)	**IV (caudal vein).** 2 mg/kg; killed 6 hr after dosing and daily up to 1 week; n = 4–6/strain/timepoint.	Liver and kidney COH, EROD, TH activity in 9,000*g* supernatant (activity of these enzymes is mediated by cytochrome P450 1a-1); Synthesis of cytochrome P450 2a-4 and cytochrome P450 2a-5 (messenger RNA).	Enzyme activity: *DBA*: increase in COH by 2–3 fold at days 1 and 2, then decrease to about 10% of control in liver; also substantial decrease in EROD and TH. Increase of COH to 4.4-fold of control at day 4, then return to control values in kidney; slight reduction in EROD and TH at day 3 and 4. *C57BL*: moderate increase in COH at day 2, then return to control values in liver, no changes in other enzymes. Moderate increase in COH and TH in kidney, peaking at day 2 and 6; decrease in EROD. Cytochrome P450 2a-4/5 synthesis: marked increase at day 2 and 3 in liver (20 fold) and at 6 hr and 1 day in kidney (7 and 6 fold) in DBA. No changes in C57BL.	Salonpää et al 1992

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Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] **Species Information**	**Route of Administration and Experimental Conditions**	**Endpoints**	**Findings**	**Reference**
^{144}Ce chloride (also ^{95}Zr oxalate and ^{95}Nb) Rat (albino Wistar) age 0, 7, 14, 21 (pups); 100 days (adults)	**IG.** Dose not reported; *n* = 4–5 litters (40–50 pups)/group; *n* = 6 adult rats.	Absorption and retention (by whole body and organ radioactivity counting).	Absorption and retention. 0-, 7-, 14-day-old rats retained more radioactivity than adult rats up to 5 days after dosing, then rapid decrease; levels reached a plateau at weaning (around age 21 days), when about 11%, 6.5%, and 1.2% (depending on the age at administration) of dose was retained, and retention curves became similar for all age groups. Retention of 21-day-olds (weanlings) was similar to that of 100-day-olds (0.08–0.018% of dose administered retained 14 days after dosing). A small percentage of initial dose was still retained 70 days after dosing (0.04–0.08% in animals dosed at age 0–14 days and 0.008–0.02% in older animals). Most of radioactivity was found in intestinal tract. Patterns of Ce distribution in organs was similar in suckling and adult rats, but concentration was 2–3 orders of magnitude higher in suckling rats (90% of Ce absorbed in the body was present in skeleton, followed by liver, 4–8%, spleen, and kidney at 40 days after dosing 5-day-old pups).	Shiraishi and Ichikawa 1972
Ce oxide [MMAD 2 µm] Rat (Brown Norway)	**SC (foot pad).** 0.35, 3.5, 35 mg/kg (suspended in DMSO); *n* = 5/group (lymph node proliferation). **Intradermal (abdominal skin)**. 300 mg/kg. 7 days later **SC (foot pad)**. 150 mg/kg; *n* = 5 animals/group (IgE production and lymph node histopathology). Positive control: TMA. 35 mg/kg.	Lymph node proliferation: ^{3}H-thymidine incorporation (7 days after dosing) and popliteal lymph node weight. IgE production: IgE levels in blood (by ELISA) on days 14, 21, 28, and 35 after SC administration. Popliteal lymph node histopathology (after intradermal and SC).	Lymph node proliferation: No statistically significant increase in thymidine incorporation or lymph node weight among groups relative to control (DMSO alone). IgE production: No increase in IgE levels in animals treated with Ce, increased IgE levels after TMA treatment relative to control groups. Lymph node histopathology: No increase in lymph node weight in any of the groups exposed to Ce, increased weight in animals treated with TMA. Discoloration of lymph nodes and accumulation of fine granulated material in lymph nodes from animals exposed to Ce; lymph nodes of animals treated with TMA showed activation (increased germinal center development).	Spanhaak 1996

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] **Species Information**	**Route of Administration and Experimental Conditions**	**Endpoints**	**Findings**	**Reference**
^{141}Ce chloride complexed with sodium citrate Mouse (male Swiss ICR)	**IG.** 1000 mg/kg (LD_5 at day 7) or 1163 mg/kg (LD_{25} at day 7). **SC.** 136 mg/kg (LD_5) or 173 mg/kg (LD_{25}). Controls treated with sodium citrate. Total n = 240 (for behavioral effects); n = 10/dose/time of observation.	Distribution to organs (by radioactivity counts) and Histopathology in tissue sections at day 7. Open field behavior at 4 hr, 1, 3, and 7 days postexposure: total ambulations and total rearings (rearing scored each time animal raised both forepaws). Exploratory behavior at 4 hr, 1, 3, and 7 days postexposure (number of times animal poked its nose in a hole in a 5-min period).	Distribution: after IG administration, highest levels (expressed as µg Ce/wet weight of tissue) in stomach and duodenum at 4 hr; after SC administration high levels in lung, spleen, and liver after 3 days. Example (after exposure to high concentration via each route): spleen level was 60 µg/g (IG) and 995 µg/g (SC) at 4 hr and 4.9 µg/g (IG) and 2,065 µg/g (SC) at day 3; lung level was 16.5 µg/g (IG) and 1,389 µg/g (SC) at 4 hr; and 1.1 µg/g (IG), 310 µg/g (SC) at day 3. Other organs that accumulated Ce included liver, kidney, muscle, pelt, and brain. Very little radioactivity in blood. Histopathology: *IG*: gastritis and enteritis at day 7 at both doses; stomach and duodenum showed focal hemorrhages and necrosis, polymorphonuclear cell infiltration. *SC*:. Focal midzonal liver necrosis and regenerative changes at both doses. After both routes: hypertrophy, reticuloendothelial hyperplasia, and hyperactive lymphoid follicles in spleen. Open field behavior: no effect after IG exposure; decreased activity in SC animals exposed 4 hr after high and low exposures and 1 day after high exposure. Measures were inversely correlated with brain concentrations followed by lung, stomach, blood, intestine, and kidney. Exploratory behavior: decreased exploratory behavior only after SC administration (at 4 hr at high dose).	Stineman et al 1978

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Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] **Species Information**	**Route of Administration and Experimental Conditions**	**Endpoints**	**Findings**	**Reference**
^{144}Ce chloride [MMAD 0.83 µm] (inhalation) ^{144}Ce citrate, pH 6.0, Ce chloride pH 6.0, or Ce chloride pH 3.0 (IP) Chinese hamster age 120 days	**Inhalation.** Nose-only, group A, for 20 min (concentration not indicated); total *n* = 40. **IP.** Group B, Ce citrate, *n* = 40; group C, Ce chloride pH 6.0, *n* = 10; group D, Ce chloride pH 3.0, *n* = 10.	Clearance (by whole body counts) daily for first 3 days, every other day for 2 weeks, and weekly thereafter. Distribution (by organ counts) after killings at days 2, 8, 16, 28, 64, 128, and 256 after exposure (groups A and B) and on day 16 and 256 (groups C and D).	Clearance. *Inhalation*: early loss from respiratory tract with 20% of IBB recovered in the lung on day 2; rate of loss decreased afterward with $T_{1/2}$ of 187 days; radioactivity in lung was 3.5% of IBB by day 64 and 0.27% by day 256. *IP*: greater overall body retention: 60% of IBB after 20 days in group B and 80% in groups C and D; long-term $T_{1/2}$ of 267 days for group B and 257 days for groups C and D. Distribution. *Inhalation*: uptake of radioactivity in liver and skeleton increased up to day 64, then remained constant (< 1% of IBB in each organ at day 2; 3.5% in liver and 1.3% in skeleton at day 256). *IP*: highest levels in liver followed by skeleton; fraction of radioactivity increased slightly at early times, then decreased with same halflife as in whole body; on day 256, 22% of IBB was in liver and 9.5% in skeleton in group B. Overall: although the portion of administered Ce retained was higher after injection than after inhalation, the fraction of retained activity in the liver and skeleton at 256 days was similar in the two groups and was about 70% in liver and 30% in skeleton.	Sturbaum et al 1970
^{144}Ce hydroxide [MMAD 1.4 µm] Rat (male and female Holtzman) age 4 months	**Inhalation in whole body plethysmograph.** 25-min exposure to low (*n* = 11) or high (*n* = 23) radiation dose (concentration not indicated). Animals maintained until time of death (47–607 days after exposure).	Deposition and distribution: whole-body counts and counts in feces and urine (up to 120 days) and organ counts at time of death.	Deposition and distribution: average whole-body deposition, 28% of inhaled aerosol. No substantial difference in deposition and retention at two concentrations. Initial rapid clearance of about 80% of IBB with fecal/urinary ratio of 50 decreasing to 10 by day 100; radioactivity distributed to lung, liver, and skeleton varied with day of death. Example: lung burden relative to IBB was 3–8% (day 101–103) and 2.7–1.9% (day 230–289), liver burden was 8–9% and 1–6%, and skeleton burden was 20–29% and 7–17% during same periods. Two animals surviving to day 528 and 607 had < 1% of IBB in lung and liver and 5% in skeleton. Radioactivity also detected in kidney and spleen.	Thomas et al 1972

Table C.1 (*continued*). Summary of Animal Studies

Chemical Form [Particle Size] **Species Information**	**Route of Administration and Experimental Conditions**	**Endpoints**	**Findings**	**Reference**
Ce oxide [MMAD 1.8–2.2 µM; 25% of particles < 1.3–1.5 µm] Rat (male and female Sprague-Dawley CD)	**Inhalation (nose-only).** 4 exposure groups: group A, clean air; group B, 5 mg/m^3; group C, 50 mg/m^3; and group D, 500 mg/m^3; 6 hr/day; 5 days/week for 13 weeks; *n* = 15/sex/exposure group.	Clinical examination daily; Food consumption and body weight weekly; Organ weight, gross pathology, and histopathology after 13 weeks; Behavioral assessment (functional observation battery including grip strength and motor activity over a 1-hr period) at 4, 8, and 13 weeks; Clinical biochemistry, hematology, urine analyses at 6 and 13 weeks.	Clinical examination: transient signs after exposure in all groups (reddish stains of the muzzle, cranial, and periorbital regions). Food consumption and body weight: slight, nonsignificant reduction in body weight and food consumption in group D males. Organ weight: increased lung weight (absolute and relative to body and brain weight) in groups C and D (nonsignificant increase in group B), increased spleen weight in group 4 males (relative to body weight), increased thymus weight in group C males (not considered treatment related). Gross pathology: significant discoloration of the lungs in groups C and D and in group B females, and of bronchial, mediastinal, and pancreatic lymph nodes in all exposure groups. Histopathology: all Ce-treated groups accumulated pigment in lung, trachea, larynx, nasal cavity, liver, spleen, and in bronchial, mediastinal, and mandibular lymph nodes; all Ce-treated groups displayed lung, bronchial, mediastinal or pancreatic lymph node hyperplasia (degree of hyperplasia in lymph nodes correlated with pigment volume and with increased lymphocyte number in these tissues); pigment was within cytoplasm of alveolar macrophages in group B and both intra- and extracellular in groups C and D. Behavioral assessment: no behavioral effects observed with exception of significantly reduced forelimb grip strength in group D females at 13 weeks; no effect on total motor activity counts. Clinical biochemistry, hematology, urine analyses: only effect observed was increase in blood of segmented neutrophil counts in group B females and groups C and D of both sexes.	Viau 1994

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Table C.2. Acute Toxicity (LC_{50} or LD_{50}) for Various Forms of Ce Administered via Different Routes

Administration	**Nitrate**		**Chloride**		**Oxide**	
	Rats	Mice	Mice	Guinea pigs	Rats	Mice
Inhalation					> 50 mg/m^3 (M/F) (Rhône-Poulenc 1983b)	
Oral	4,200 mg/kg (F) (Bruce et al 1963)	1,178 mg/kg (F) (Ji and Cui 1988)			> 5,000 mg/kg (M/F) (Rhône-Poulenc 1983b) > 1,000 mg/kg (F) (Bruce et al 1963)	622 mg/kg (F) (Ji and Cui 1988)
IG			1,291 mg/kg (M) (Stineman et al 1978)			
IV	4.3 mg/kg (F) (Bruce et al 1963) 49.6 mg/kg (M) (Bruce et al 1963)					
IP	290 mg/kg (F) (Bruce et al 1963)	470 mg/kg (F) (Bruce et al 1963)	353 mg/kg (M/F) (Graca et al 1957)	103 mg/kg (M/F) (Graca et al 1957)	> 1,000 mg/kg (F) (Bruce et al 1963)	
SC			205 mg/kg (M) (Stineman et al 1978)		> 2,000 mg/kg (M/F) (Rhône-Poulenc 1983b)	

M = male; F = female.

Table C.3. Summary of In Vitro Studies

Compound	Tissue or Material	Experimental Conditions/Endpoints	Results	Reference
Ce chloride and other RECs	human plasma	Anticoagulant activity in human plasma: (1) intrinsic coagulation pathway, using kaolin induction of clotting with addition of Ce chloride at 0.05 mM; (2) extrinsic clotting, using thromboplastin and 0.05 M Ce chloride; (3) inhibition of clotting activity of plasma induced by factor Xa with 0.01 M Ce chloride. Amidolytic activity of thrombin and factor Xa with Ce chloride between 0.1 and 0.5 mM (increased activity would indicate anticoagulant effect).	Anticoagulant activity: Clotting time was prolonged (anticoagulant activity increased) by rare earth metals: Ce increased Kaolin-induced clotting time 2.2 fold, thromboplastin-induced clotting time 14.8 fold, and factor Xa-induced clotting time 4.2 fold. Amidolytic activity of thrombin and factor Xa was lowered to 40% of control at 0.1 mM Ce chloride and to 10% of control at 0.5 mM (possibly by Ce binding to enzyme functional sites).	Funakoshi et al 1992
Ce chloride and other RECs	alveolar macrophage from adult male Sprague-Dawley rats	Cells exposed to Ce chloride at 3 µM–50 µM for 3 days. Cell death (by staining with acridin orange and propidium iodide); measures of lethality were necrosis, apoptosis, post-apoptotic necrosis.	Cell death induction (by apoptosis) was seen at all concentrations tested (hypothesized to be interaction of Ce with cell membranes). Ce found as soluble metal in cells. LC_{50} estimated 50 µM.	Lizon and Fritsch 1999
Ce, La, and Cd chlorides and oxides	alveolar macrophage from lungs of adult male Sprague-Dawley rats	Cells exposed for 20 hr to concentrations of chlorides and oxides up to 1,000 µM; oxides were not soluble and in suspension (< 0.8 µM in diameter). Cell death (by staining with erythorin B); Release of lysozomal enzymes acid phosphatase and cathepsin D); Cell morphology: cell surface changes (by scanning electron microscopy).	Cell death: different salts exhibited different toxicity. The LC_{50} of Ce chloride (soluble form) was 29 µM; Ce oxide was minimally toxic (extrapolated LC_{50} was 4,740 µM). By comparison LC_{50} of Cd chloride was 28 µM and of Cd oxide was 15 µM; LC_{50} of La chloride was 52 µM and of La oxide 980 µM. Release of enzymes: no significant release with either Ce chloride or Ce oxide; small increase with Cd salts and La chloride. Cell morphology: generally, structure progressed toward a featureless surface with loss of pseudopodia and microvilli with increasing metal concentrations. More than 90% of cells were in this latter stage after treatment with 25 µM Cd salts, 13–18% with 20 µM La salts, and 15% with 1000 µM Ce oxide (not evaluated for Ce chloride).	Palmer et al 1987

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Table C.3 (*continued*). Summary of In Vitro Studies

Compound	Tissue or Material	Experimental Conditions/Endpoints	Results	Reference
Ce (form not specified)	Neonatal rat heart cell and fetal human lung fibroblasts	Cells grown in medium with normal or low Mg in presence or absence of Ce (up to 20 µM) for 6 hr. Protein synthesis (measured as ^{3}H-tyrosine incorporation for 30 min after the 6-hr exposure), myofibrillar protein synthesis also measured.	Protein synthesis reduced by Ce by about 25% of control in cells grown in normal Mg and by 50% in cells grown in low Mg (low-Mg control cells synthesized only 70% of the protein in normal-Mg control cells). Ce did not affect tyrosine uptake inside the cells. Ce may reduce protein synthesis by acting on cell membranes and altering Mg availability, or by competing for critical metal cofactors.	Shivakumar and Nair 1991
Ce (form not specified)	Neonatal rat heart explant cultures and cardiac fibroblasts	Total protein and collagen synthesis: explants exposed to Ce for a total of 48 hr (last 24 hr in the presence of ^{3}H-proline and sodium ascorbate); fibroblasts exposed to Ce (10 and 100 µm) for 6 hr (in the presence of ^{3}H-proline and sodium ascorbate). DNA and RNA synthesis: fibroblasts exposed to Ce for 4 hr (in the presence of ^{3}H-thymidine or ^{3}H-uridine) or for 18 hr (with ^{3}H-thymidine added 14 hr after Ce addition). Ce concentrations were 0.1, 1, 10, and 100 µM.	Total protein and collagen synthesis: increased protein (80% and 35%) and collagen (75% and 58%) synthesis at two lowest Ce doses and decreased at higher doses in heart explants; increased collagen synthesis at 0.1 µM (only dose tested) in fibroblasts (+50%). DNA and RNA synthesis: no effect on DNA synthesis and increased RNA synthesis (+60%).	Shivakumar et al 1992

ABBREVIATIONS AND OTHER TERMS

AIB	aminoisobutyric acid
bhp-h	brake horsepower hour (0.7457 g/bhp-h = 1 kWh)
Ce	cerium
COH	coumarin 7-hydroxylase
$DeNO_x$ catalyst	catalyst that reduces NO_x emissions
DI	direct fuel injection in diesel engines
DMSO	diemethyl sulfoxide
DPG	diphosphoglyceric acid
DPX	see Eolys
EC	elemental carbon
ECE	Economic Commission of Europe test (also known as Urban Driving Cycle [UDC])
ECOD	ethoxycoumarin *O*-deethylase
EGR	exhaust gas recirculation
Eolys	trade name for a number of cerium-based organic additives (identified by DPX number)
EPA	US Environmental Protection Agency
EROD	ethoxyresorufin *O*-deethylase
ESC	European steady-state cycle
ETC	European transient cycle
EU	European Union
FTP	federal test procedure
GD	gestational day
GI	gastrointestinal
GOT	glutamic-oxaloacetic transaminase
GPT	glutamic-pyruvic transaminase
^3H	tritiated
H_2O_2	hydrogen peroxide
HC	hydrocarbon
HD	heavy duty
IBB	initial body burden
ICP-AES	inductively coupled plasma atomic emission spectrometry
IDI	indirect fuel injection in a diesel engine
IG	intragastric
IgE	immunoglobulin E
ILB	initial lung burden
IM	intramuscular
IP	intraperitoneal
ISO 8178	International Standards Organization test cycle
IV	intravenous
kW	kilowatt
kWh	kilowatt-hour
LC_{50}	lowest concentration that causes death in 50% of animals
LD	light duty
LD_5	lowest dose that causes death in 5% of animals
LD_{25}	lowest dose that causes death in 25% of animals
LD_{50}	lowest dose that causes death in 50% of animals
LOAEL	lowest observable adverse effect level
MMAD	mass median aerodynamic diameter
MMT	methylcyclo-pentadienyl manganese tricarbonyl
NCRP	National Council on Radiation Protection and Measurements
Nm	newton meter
NO_x	oxides of nitrogen
NOAEL	no observable adverse effect level
OC	organic carbon
PAHs	polynuclear aromatic hydrocarbons
PM	particulate matter
PM_{10}	particles with an aerodynamic diameter of 10 µm or less
PND	postnatal day
RECs	rare earth chlorides
SC	subcutaneous
$T_{½}$	halflife
TH	testosterone 15α-hydroxylase
TMA	trimellitic anhydride
TSP	total suspended particles
VERT	Verminderung der Emissionen von Realmaschinen im Tunnelbau (Reduction of Emissions from Construction Site Engines at Tunnel Sites)

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