Exposure, Metabolism, and Toxicity of Rare Earths and Related Compounds

Seishiro Hirano1 and Kazuo T. Suzuki2

1Regional Environment Division, National Institute for Environmental Studies, Tsukuba, Ibaraki, Japan; 2Faculty of Pharmaceutical Sciences, Chiba University, Inage, Chiba, Japan

For the past three decades, most attention in heavy metal toxicology has been paid to cadmium, mercury, lead, chromium, nickel, vanadium, and tin because these metals widely polluted the environment. However, with the development of new materials in the last decade, the need for toxicological studies on those new materials has been increasing. A group of rare earths (RE) is a good example. Although some RE have been used for superconductors, plastic magnets, and ceramics, few toxicological data are available compared to other heavy metals described above. Because chemical properties of RE are very similar, it is plausible that their binding affinities to biomolecules, metabolism, and toxicity in the living system are also very similar. In this report, we present an overview of the metabolism and health hazards of RE and related compounds, including our recent studies. — Environ Health Perspect 104(Suppl 1):85-95 (1996)

Key words: rare earth, lanthanoid, scandium, yttrium, exposure, distribution, retention, clearance, metabolism, toxicity, health hazard

Occurrence and Industrial Use of Rare Earths

A group of 15 transition metals in group III of the periodic table are called lanthanoids or rare earths (RE). They are lanthanum (La) and 14 lanthanides. The lanthanides consist of 14 elements: cerium (Ce), praseodymium (Pr), neodymium (Nd), promethium (Pm), samarium (Sm), europium (Eu), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), and lutetium (Lu). In this report, however, scandium (Sc) and yttrium (Y) are included in the group of RE because chemical and toxicological characteristics of these two transition metals in group III appear to be very similar to those of RE. The Clarke numbers (the ratio of the amount of a particular element mainly in the earth’s crust) of RE are shown in Table 1.

Although RE are not abundant in the earth’s crust, Ce, the most plentiful element of RE, is about 100 times more abundant than cadmium (Cd), one of the most well-known heavy metals in toxicology. The Clarke number of Ce is almost the same as those of cobalt, tin, zinc, and vanadium. Unlike all other RE, Pm, found as a decay product of uranium in 1947, has not been detected in the earth’s crust (3). The global annual demand of RE is estimated to be about 30,000 tons (4, 5). China has the world’s largest reserve, which is sufficient to meet the global needs of RE for 1000 years (4, 5).

Chemical Properties of Rare Earths

The chemical properties of RE and the detection limits of RE in atomic absorption, atomic emission, and mass spectrometry are summarized in Table 1 (1, 2). Although +2, +4, and +5 valences are possible for some of the RE, their valences are usually +3 when they are dissolved. One of the most prominent features of lanthanoids is what is called lanthanoid contraction (6). From La to Lu, the radius of lanthanoid ions (+3) decreases as the atomic number increases. This phenomenon is due to attraction of electrons of 4f orbitals by increasing positive charge of the nucleus with the atomic number. Because the radius of Ca2+ (0.99 Å) is very close to those of lanthanoids, lanthanoids have been used for Ca2+ probes in biochemical and physiological studies. The nitrates, chlorides, and sulfates of RE are soluble and their carbonates, phosphates, and hydroxides are insoluble (6). The differences in solubility among these ionic forms of RE seem to determine the metabolic fate of RE in the biological system. In general, the toxicity of lanthanoids decreases as the atomic number increases, probably due to greater solubility and ionic stability of heavier lanthanoids (7).

It is known that RE and organic ligands produce metal–ion complexes. The stability constants of RE3+-citrate, RE3+-nitritolactate (NTA), RE3+-ethylenediamine-N,N,N’,N’-tetraacetic acid (EDTA), and RE3+-diethylenetriaminepentacetic acid (DTPA) are 6.5 to 8.5, 10 to 13, 16 to 23, and 20 to 23, respectively (8, 9). These chelated RE have been used in toxicological studies (vide infra).

Exposure to Rare Earths

It was not until the nuclear era that attention was addressed to the health effects of RE. A fission product, 144Ce, was found in animal bones and clams (10) and in the lungs and lymph nodes obtained from deceased persons who had inhaled nuclear explosion aerosols (11).

Besides irradiation effects of radioactive nuclides, inhaled RE probably cause granulomatous lesions in the lung or pneumoconiosis (7). The concentration of La found in smoker’s lungs was 2 to 16 times higher than in normal lungs (12); La, Ce, Nd, Sm, Eu, Tb, Yb, and Lu were found in a deceased photoengraver’s lungs (13). These workers are at risk of pneumoconiosis; one worker, who had been exposed for only 18 months to dust containing 60% of RE (mainly Ce, La, and Nd), was reported to have radiologic evidence of pneumoconiosis (14). Industrial uses of RE are shown in Table 2. They have been used for ceramics, fluorescent materials, abrasives, magnets, etc. (15). To our knowledge, however, RE concentration in the air of work places has not been reported. There is no evidence of pneumoconiosis or chronic pulmonary
Table 1. Chemical properties of rare earths.

| Atomic number | Electron configuration | Valence | Radius of RE+\(\text{Å}\) | Clarke\(\text{a}\) number | Detection limit, ppb\(\text{b}\) | ICP-AES | ICP-MS | FAAS | GFAAS |
|---------------|-----------------------|---------|--------------------------|-------------------------|--------------------------|--------|--------|------|-------|
| Sc 21         | 3d\textsuperscript{4}4s\textsuperscript{2} | +3      | 0.83                     | 5 \times 10^{-4}       | 0.4                      | 0.015  | 100    | 0.74 |
| Y 39          | 3d\textsuperscript{5}4s\textsuperscript{2} | +3      | 1.06                     | 3 \times 10^{-3}       | 0.04                     | 0.004  | 300    | 8    |
| La 57         | 5d\textsuperscript{6}s\textsuperscript{2} | +3      | 1.22                     | 1.8 \times 10^{-3}     | 0.1                      | 0.002  | 2000   | 24   |
| Ce 58         | 4f\textsuperscript{4}5d\textsuperscript{1}6s\textsuperscript{2} | +3,+4   | 1.18                     | 4.5 \times 10^{-3}     | 0.4                      | 0.004  | –      | –    |
| Pr 59         | 4f\textsuperscript{1}5d\textsuperscript{1}6s\textsuperscript{2} | +3,+4   | 1.16                     | 5 \times 10^{-4}       | 10                       | 0.003  | 4000   | 80   |
| Nd 60         | 4f\textsuperscript{2}6s\textsuperscript{2} | +3,+5   | 1.15                     | 2.2 \times 10^{-3}     | 0.3                      | 0.007  | 2000   | 200  |
| Pm 61         | 4f\textsuperscript{2}6s\textsuperscript{2} | +3      | –                        | –                      | –                        | –      | –      | –    |
| Sm 62         | 4f\textsuperscript{3}6s\textsuperscript{2} | +2,+3   | 1.13                     | 6 \times 10^{-4}       | 30                       | 1.5    | 600    | –    |
| Eu 63         | 4f\textsuperscript{8}5d\textsuperscript{2}6s\textsuperscript{2} | +3      | 1.13                     | 1 \times 10^{-4}       | 0.06                     | 0.007  | 40     | 0.2  |
| Gd 64         | 4f\textsuperscript{14}6s\textsuperscript{2} | +3      | 1.11                     | 6 \times 10^{-4}       | 0.4                      | 0.009  | 4000   | 80   |
| Tb 65         | 4f\textsuperscript{15}6s\textsuperscript{2} | +3,+4   | 1.09                     | 8 \times 10^{-5}       | 0.1                      | 0.002  | 2000   | 100  |
| Dy 66         | 4f\textsuperscript{16}6s\textsuperscript{2} | +3,+4   | 1.07                     | 4 \times 10^{-4}       | 4                        | 0.007  | 200    | 3.4  |
| Ho 67         | 4f\textsuperscript{17}6s\textsuperscript{2} | +3      | 1.05                     | 1 \times 10^{-4}       | 3                        | 0.002  | 100    | 1.8  |
| Er 68         | 4f\textsuperscript{18}6s\textsuperscript{2} | +3      | 1.04                     | 2 \times 10^{-4}       | 1                        | 0.005  | 100    | 9    |
| Tm 69         | 4f\textsuperscript{19}6s\textsuperscript{2} | +3,+4   | 1.04                     | 2 \times 10^{-5}       | 0.2                      | 0.002  | 40     | 0.2  |
| Yb 70         | 4f\textsuperscript{20}6s\textsuperscript{2} | +3,+3   | 1.00                     | 2.5 \times 10^{-4}     | 0.02                     | 0.005  | 20     | 0.1  |
| Lu 71         | 4f\textsuperscript{21}6s\textsuperscript{2} | +3      | 0.99                     | 7 \times 10^{-5}       | 0.1                      | 0.002  | 2000   | 80   |

Abbreviations: ICP-AES, induced coupled plasma-atomic emission spectrometry; ICP-MS, induced coupled plasma-mass spectrometry; FAAS, flame atomic absorption spectrometry; GFAAS, graphite furnace atomic absorption spectrometry. \(\text{a}\) The ratio of the amount of a particular element mainly in the earth’s crust. \(\text{b}\) Data from Kawaguchi and Nakahara (1) and Date and Hutchison (2).

Table 2. Industrial uses of rare earths.

| Element | Industrial use |
|---------|----------------|
| Sc      | Cathode-ray tubes, lasers, fluorescent materials |
| Y       | Superconductors, lasers, fluorescent materials, catalysts, ceramics |
| La      | Superconductors, lighters, catalysts, glass additives, ceramics, batteries |
| Ce      | Lighters, catalysts, glass additives, ceramics, magnets, abrasives |
| Pr      | Magnets, lighters, glass additives |
| Nd      | Magnets, lighters, lasers, glass additives, magneto-optical materials |
| Pm      | Magneto-optical materials |
| Sm      | Lighters, magnets, condensers, nuclear reactor control rods |
| Eu      | Fluorescent materials, imaging plates, nuclear reactor control rods |
| Gd      | Magnets, glass additives |
| Tb      | Fluorescent materials, magneto-optical materials |
| Dy      | Magnets, magneto-optical materials |
| Ho      | Electric materials |
| Er      | Glass additives |
| Tm      | Fluorescent materials, lasers |
| Yb      | Condensers |
| Lu      | Superconductors |

Data from Ito (4) and Ohmachi (5).

Reactions in laboratory animals, even though YCl\textsubscript{3} and LaCl\textsubscript{3} or oxides of Y, Nd, and Ce have been proven to cause bronchitis, pneumonitis, and granulomatous lesions (16–18).

Some radioactive RE nuclides have been used for cancer (19,20) and synovitis therapy (21,22). \(^{90}\)Y is a useful nuclide for clinical use because it has a moderate half-life (64 hr) and it is a pure \(\beta\)-emitter with high energy (2.28 MeV) (23). In addition, \(^{90}\)Y is easily separated by column chromatography from \(^{90}\)Sr, which has a very long half-life (28.8 years). It has been shown that Tb\textsuperscript{3+}, Tb\textsuperscript{4+}, and Yb\textsuperscript{3+} have a high affinity for tumor cells (24–27). It is interesting to note that Tb\textsuperscript{3+} was temperature-dependently taken up by tumor cells (MCF-7), and cisplatin, a well-known anticancer drug, reduced the binding of Tb\textsuperscript{3+} to those tumor cells (25). However, there is a contradictory report that has shown that La concentration in malignant laryngeal tissue was lower than in nonmalignant adjacent tissues, although serum La concentrations of laryngeal cancer patients were significantly higher than those of normal subjects (28).

Recently, DTPA-chelated Gd (gadopentetate dimeglumine), tetraazacyclododecane-tetraacetic acid (DOTA)-chelated Gd (gadoterate meglumine), and Gd-HP-D03A (gadoteriol) have been used as magnetic resonance imaging-contrast reagents (29,30). Although clearance of those intravenously (iv) injected imaging-contrast reagents have been reported to be rapid, it is possible that some ionic Gd is released from the complexes. Ionic RE are rapidly changed to colloidal RE (hydroxide and phosphates) in blood, and the colloidal RE are taken up by the reticuloendothelial system in the liver (30). Gd was found in the breast milk of a lactating patient who received an iv injection of gadopentetate dimeglumine (31).

It is also reported that Ce is a potent antiseptic drug for Gram-negative bacteria and fungi (32) and swabbing of La is effective in protecting teeth from caries (33,34). Thus, toxicological studies of RE are needed not only from the standpoint of environmental or industrial hygiene but also for medical treatment.

Interaction of Rare Earths with Cells or Biomolecules

Tb\textsuperscript{3+} binds to Ca\textsuperscript{2+} binding sites of the intestinal brush-border membrane (35) and surfaces of platelets (36) and vascular smooth muscle (37). When bound to membranes, the fluorescence of Tb\textsuperscript{3+} is increased probably by energy transfer to aromatic residues such as tyrosine (35). Tb\textsuperscript{3+} and Pm\textsuperscript{3+} are removable from the
surfaces of platelets and smooth muscle by both \( \text{Ca}^{2+} \) and \( \text{La}^3+ \) (36,37). Lanthanoids are also known to bind to \( \text{Ca}^{2+} \) or \( \text{Mg}^{2+} \) binding sites of calmodulin (38), ATPase of sarcoplasmic reticulum (39,40), cystatin (41), and phosphatidylserine (42). The binding mode to calmodulin, which has two high-affinity and two low-affinity \( \text{Ca}^{2+} \) binding sites, has been shown to be different among lanthanoids. \( \text{Lu}^{3+} \) and \( \text{Er}^{3+} \) bind like \( \text{Ca}^{2+} \), \( \text{Eu}^{3+} \) and \( \text{Tb}^{3+} \) bind in the opposite order from \( \text{Ca}^{2+} \), and \( \text{La}^{3+} \) and \( \text{Nd}^{3+} \) bind in a mode between them (38). \( \text{La}^{3+} \) has been shown to inhibit the \( \text{Ca}^{2+}\)-dependent release of chemical mediators such as catecholamine from the adrenal medulla and histamine from mast cells (43).

It has been reported that \( \text{Sc}^{3+} \), \( \text{Y}^{3+} \), and \( \text{La}^{3+} \) bind to globulin and DNA (44), and transferrin is a major \( \text{Sc}^{3+} \) or \( \text{Y}^{3+} \)-binding protein in blood plasma (45,46). \( \text{La}^{3+} \) and \( \text{Nd}^{3+} \) have anticoagulant action (47,48); inhibition of prothrombin–thrombin transformation or blood coagulant factors such as VII, IX, and X may be responsible for the anticoagulant effect of those ions.

**Deposition, Retention, Metabolism, and Clearance of Rare Earths**

**Inhalation or Intratracheal Instillation.**

As shown in Figure 1, inhaled or intratracheally instilled RE chlorides have been shown to accumulate in alveolar and tissue macrophages and alveolar walls (16,17,49,50). In macrophages RE have been shown to localize in lysosomes; it is proposed that RE are changed to insoluble phosphates in lysosomes according to Gomori (phosphatase) reaction (49). The transmission electron microscopy and X-ray microanalysis revealed intratracheally instilled Y and La deposits in basement membranes of pneumocytes (16,17).

Half-times of Y and La in the rat lung have been reported to be 168 (16) and 244 days (17), respectively, when these RE were instilled intratracheally as chlorides. Rhoads and Sanders (51) have reported a half-time of intratracheally instilled \( \text{Yb}_2\text{O}_3 \) in the rat lung of 21 days. In these intratracheal instillation studies, translocation of RE to extrapulmonary tissue was marginal or below the detection limit. On the other hand, it has been shown that significant amounts of inhaled \( \text{CeCl}_3 \) (52), \( \text{Ce(OH)}_3 \) (53), and Y (chemical form is unknown) (54) were translocated to the skeleton and liver in rats or hamsters. It has also been reported that a half-time of inhaled \( \text{Ce(OH)}_3 \) was 140 days following initial rapid clearance in the rat lung (53). The

![Figure 1](image_url)
The whole body retention of iv-injected chelated RE fits to a three-phase model shown by the following equation:

\[
\% \text{Retention} = \text{Ae}^{-0.693/Ta} + \text{Be}^{-0.693/Tb} + \text{Ce}^{-0.693/Tc}
\]

where A, B, and C are constants (A + B + C = 100), and Ta, Tb, and Tc denote half-times of fast, intermediate, and slow phases, respectively. Table 3 shows half-times of iv-injected RE in the three-phase model (64–67). Hiraki et al. (66) suggested that the fast, intermediate, and slow phases represent excretion via urine, from the soft tissues, and bone, respectively. These results indicate that although iv-injected chelated RE is excreted rapidly via urine, RE deposited in the bone is excreted very slowly.

It has been shown that accumulation of Sc3+-citrate (low stability) in the liver, spleen, and bone was much higher than that of Sc3+-EDTA (high stability) following iv injection in mice (68). Rosoff et al. (68) also showed that when Sc3+-NTA (intermediate stability) was injected, a relatively high concentration of Sc was accumulated in the bone compared to Sc3+-citrate or Sc3+-EDTA. Yb accumulated in rat offspring through milk following iv injection of YbCl3, Yb3+-EDTA, and Yb3+-DTPA into rat mothers, and the transfer of Yb to new-born babies increased in this order (69).

From a detoxication point of view, it is interesting to note that injection of Ca2+- or Zn2+-DTPA has been proven to be effective in removing Yb (70,71), Sc (72), and Ce (73) from the body. Liposome-encapsulated DTPA seems to be more effective than DTPA itself (70,71). Injection of either Na23+, Ca2+-EDTA or Na3, Ca2+-DTPA into Yb-exposed rat mothers has been proven to be effective in reducing the transfer of Yb to their offspring (69).

Rosoff et al. (68) have suggested that RE chlorides are changed into colloidal forms of hydroxide, phosphate, and carbonate in blood. We have shown that Y was distributed to a high molecular weight fraction (colloidal material containing proteins and some minerals such as calcium, phosphorus, and iron), transferrin, and a low molecular weight fraction (probably citrate) in the blood plasma; the percent of colloidal fraction of injected Y increased with dose of YCl3 as shown in Figure 2 (46). Uptake of Y by the liver and spleen also increased with the dose of YCl3 (46).

In Japanese quails, iv-injected LaCl3 and CeCl3 were deposited mainly in the liver and oocytes (74,75), and vitellogenin is a major lanthanoid-binding protein in these birds (75). At a dose of 15 µmol Gd/100 g body weight (bw), 80% of the dose was deposited in the liver; at doses below 0.15 µmol Gd/100 g bw, 80% of the dose was deposited in the oocytes (75).

Deposition of iv-injected GdCl3 in the liver, oocytes, and ova decreased as blood vitellogenin concentration was increased by intramuscular injection of estradiol in male Japanese quails (76).

### Intraperitoneal Injection

It is reported that intraperitoneally (ip) injected CeCl3 or Ce3+-citrate was deposited mainly in the liver and skeleton in hamsters (52) and rats (77). Electron microscope and ionic microanalysis revealed that ip-injected CeCl3 was localized in lysosomes of hepatocytes and Kupffer cells in lysosomes of bone marrow macrophages, and basement membranes of proximal convoluted tubules in the kidney of rats (50). Although Tb content in the liver was the largest among organs tested, tissue concentrations of Tb (µg Tb/g tissue) were higher in the seminal vesicles, pancreas, and spleen than in the liver of mice (78).

Following ip injection of La3+-citrate in mice, La was deposited in the skeleton, liver, kidney, spleen, and lung, in this order (79). However, the percent of deposition in the liver was increased as the dose of La3+-citrate increased, and the percent of deposition in the skeleton was decreased as the dose increased (79). As described above, Ca2+- or Zn2+-DTPA has been effective in removing RE deposited in the tissues following injection (77,80,81).

### Per Oral Administration

By oral intake through drinking water or per oral

---

**Table 3.** Half-times of intravenously injected chelated rare earths for fast, intermediate, and slow phases in the three-phase clearance model.

| Chelated RE | Animal | Ta (fast) | Tb (intermediate) | Tc (slow) | Reference |
|------------|--------|-----------|-------------------|-----------|-----------|
| Sc-EDTA    | Mouse  | 12.75 min | 40.2 min          | 5351 min  | (64)      |
| Sc-citrate | Rat    | 1.0 day   | 7.1 days          | 485 days  | (65)      |
| Tb-citrate | Rat    | 3.4 hr    | 95 hr             | 106 days  | (66)      |
| Yb-citrate | Rat    | 3.6 hr    | 194 hr            | 850 days  | (67)      |
(po) administration, ionic RE was absorbed mainly from the ileum (82–84) and deposited in the skeleton, teeth, and soft tissues such as the lung, liver, and kidney (33,85–87). Although swabbing of teeth with La(NO$_3$)$_3$ is known to replace Ca with La in the enamel in rats (33) and hamsters (88), La absorbed from the small intestine has also been shown to deposit in the teeth (33). It has been shown that 13.3% of po-administered CeCl$_3$ was excreted via bile during the first 4 hr in rats (89), suggesting that a significant amount of Ce was absorbed from the intestine. However, the intestinal absorption of RE seems to depend on the diet. Retention of Pm in the soft tissues in neonatal rats was two orders of magnitude higher than that in adult rats (82), probably because the neonates were on milk diet (84,90). Fasting significantly increased the absorption of RE from the gastrointestinal tract (90,91). This phenomenon is not hard to understand; it has been demonstrated that about 45% of po-administered CeCl$_3$ was present in the gastrointestinal content even 1 day after the administration in pigs (86). The po administration of Zn$^{2+}$-DTPA reduced the whole body retention of Ce to 1/20 to 1/30 of that in the untreated group by chelating Ce present in the gut and intestinal content (83,92).

**Exposure to RE via Other Routes.** Absorption of RE from the skin is known to be negligible (93); however, when the skin was stripped or wounded, RE seem to be absorbed into the body to some extent (93,94). Inaba and Yasumoto (93) reported that 4% of applied CeCl$_3$ was absorbed from the stripped guinea pig's skin while 89% of CoCl$_3$ and 79% of Co$_2$O$_4$ were absorbed from the skin under the same experimental conditions. It has been shown that Ce$^{3+}$ was deposited in the liver, spleen, and bone following subcutaneous (sc) injection of Ce$^{3+}$-citrate (95,96). Intramuscularly injected CeCl$_3$ has been reported to accumulate in the lysosomes of the liver in rats and hamsters (97). Allard et al. (98) reported that 6% of intracerebrally injected Gd$^{3+}$-DOTA was found in the brain at 0.5 hr postinjection, and 58% of the brain Gd was located in the soluble fraction, suggesting that even chelated Gd with high stability is taken up by the brain to some extent.

Because RE is known to deposit in the skeleton, it is interesting to know what cells in the bone marrow take up RE. Only macrophages take up ip-injected CeCl$_3$ in the bone marrow of rats (50); however, La was found in nuclear pores of marrow cells (especially erythroid cells) and the cell sap of light stromal cells when the rat bone marrow cells were exposed to La(NO$_3$)$_3$ in vitro under fixing conditions (99,100).

**Toxicity**

**Mortality.** As shown in Table 4, iv-, ip-, and po-administered ionic or chelated forms of RE are not highly toxic as far as the median lethal dose (LD$_{50}$) is concerned. However, is it really possible to determine LD$_{50}$ values for iv-injected RE? It has been shown that the percent mortality peaked at 20 to 40 mg Pr(NO$_3$)$_3$ /kg bw following iv injection in both mice and rats of both sexes; however, the lethality then decreased

| RE         | Route | Animal | LD$_{50}$ kg body weight | Reference |
|------------|-------|--------|--------------------------|-----------|
| La(NO$_3$)$_3$ | ip     | Mouse  | 150 mg La                | (34)      |
| CeCl$_3$   | iv     | Rat    | 10 mg Ce                 | (101)     |
| Ce(NO$_3$)$_3$ | po    | Mouse  | 1178 mg                  | (102)     |
| EuCl$_3$   | ip     | Mouse  | 550 mg Eu                | (103)     |
| EuCl$_3$   | po     | Mouse  | 5000 mg Eu               | (103)     |
| DyCl$_3$   | ip     | Mouse  | 585 mg                   | (104)     |
| DyCl$_3$   | po     | Mouse  | 7950 mg                  | (104)     |
| HoCl$_3$   | ip     | Mouse  | 560 mg HoCl$_3$          | (104)     |
| HoCl$_3$   | po     | Mouse  | 7200 mg HoCl$_3$         | (104)     |
| ErCl$_3$   | ip     | Mouse  | 535 mg HoCl$_3$          | (104)     |
| ErCl$_3$   | po     | Mouse  | 6200 mg HoCl$_3$         | (104)     |
| ScCl$_3$   | iv     | Mouse  | 24 mg Sc                 | (84)      |
| ScCl$_3$   | ip     | Mouse  | 440 mg Sc                | (84)      |
| Sc-EDTA    | iv     | Mouse  | 108 mg Sc                | (84)      |
| Sc-EDTA    | ip     | Mouse  | 702 mg Sc                | (84)      |
| RE(NO$_3$)$_3$ | po   | Mouse  | 1876 mg RE(NO$_3$)$_3$   | (102)     |
| RE(NO$_3$)$_3$ | po | Rat     | 1832 mg RE(NO$_3$)$_3$   | (102)     |
| RE(NO$_3$)$_3$ | po   | Guinea pig | 1397 mg RE(NO$_3$)$_3$ | (102)     |

* Mixture of La, Ce, Nd, Pr, and Sm.
as the dose increased. Even the lethality was abolished at 80 to 100 mg Pr(NO₃)₃/kg bw (105). In this bell-shaped dose–response mortality curve, mortality did not exceed 50% in male mice. Although more extensive study is required to answer the question about why the dose–response curve of the percent mortality is bell-shaped, the colloid formation of ionic RE in blood at higher doses of RE chlorides or nitrates might be responsible for the unusual dose–response curve in lethality. A marked increase in death due to pneumonia was found in mice when they were subacutely exposed to 30 mg/m³ of Gd₂O₃ dust (6 hr/day, 5 days/week, and up to 120 days) (106).

**Effects of Rare Earths on the Lung.** As we described earlier, chronic exposure to RE dust probably causes pneumonia in humans (14). It has been shown that intratracheal instillation of YCl₃ caused granulomatous changes in the rat lung (16). Inhalational exposure to high concentrations of Gd₂O₃ (106) and intratracheal instillation of YCl₃ (16), LaCl₃ (17), and GdCl₃ (107) have been shown to cause pneumonitis and acute inflammation in the lung, e.g., infiltration of neutrophils and leakage of enzymes and proteins into the alveolar space, in mice and rats. The acute toxicity of YCl₃ in the rat lung was between those of ZnO and Cd compounds, judging from dose-related changes in lactate dehydrogenase activity in the bronchoalveolar lavage fluid (16).

**Effects of Rare Earths on the Liver.** Intravenously injected RE chlorides increase vascular permeability for low molecular weight substances (108) and cause necrosis in the liver (109). Subcutaneous administration of Ce(NO₃)₃ has also been found to cause hepatic necrosis (96). Hepatic endoplasmic reticulum (ER) has been shown to be the primary target of iv-injected CeCl₃ in the rat liver, and dilation, disorganization, and degranulation of rough ER and proliferation of smooth ER occurred following the iv injection (110). Pretreatment of rats with pregnenolone 16α-carbonitrile, spironolactone, and phe-notharbitol, which are known to proliferate smooth ER, and estradiol, a putative stabilizer of smooth ER, have been shown to reduce hepatic damage caused by CeCl₃ in rats (101). It has also been demonstrated that pretreatment with pregnenolone 16α-carbonitrile or nefolpin increased the relative liver weight and significantly reduced mortality caused by iv injection of CeCl₃ in mice (58), suggesting that the liver is the primary target organ of iv-injected CeCl₃.

It has been shown that iv injection of CeCl₃ caused fatty liver in female rats (110,111) but not in male rats (111). Intravenous injection of YCl₃, TbCl₃, HoCl₃, and YbCl₃ caused focal necrosis with Ca deposition in rats but CeCl₃ did not (111). We have shown that patchy Ca deposition occurred in the focal necrotic area of the rat liver following iv injection of YCl₃ (~50 μg Y/g liver) (46). However, the reason that fatty liver was limited to female rats that received CeCl₃ remained unknown. It seems that iv injection of CeCl₃ produces lipid droplets in the liver of male mice (109).

There is a battery of reports about hepatic biochemical changes following iv injection of ionic RE; these reports are summarized in Table 5. There are differences in changes of RNA polymerase II activity among nitrates of Pr, Nd, Sm, Gd, Dy, and Er (120). The first three RE decreased RNA polymerase II activity while the latter three RE increased the activity; only Pr and Nd nitrates decreased RNA polymerase I activity while the other four did not change the RNA polymerase I activity. Otherwise, the biochemical changes are consistent among RE; these biochemical changes are increase in triglyceride in the liver (105,110,113,117) and increases in leakage of hepatic enzymes into blood (46,105,111–116). RE-induced hepatic injury seems to reduce P450 content and P450-related enzyme activities in rat (113) and mouse (109,119); however, the decreases in P450 activities (cumarin 7-hydroxylase and 7-ethoxyresorufin O-deethylase) at 3 to 4 days after iv injection of CeCl₃ were preceded by increases in these enzyme activities at 1 to 2 days postinjection in DBA/2 mice (109,119). Serum very low density lipoprotein (VLDL) and high density lipoprotein (HDL) have been shown to be decreased following iv injection of Pr(NO₃)₃ in rats; the decrease is probably due to a decrease in hepatic secretion of these lipoproteins (118). It has also been reported that iv injection of CeCl₃ causes lipid peroxidation and a decrease in glutathione reductase activity in the chick liver (121).

Although serum glutamic–oxaloacetic and glutamic–pyruvic transaminase activities, well-known markers for acute hepatic injury, were increased with doses of

---

**Table 5.** Hepatic and liver-associated biochemical changes following intravenous injection of rare earth.

| Effect | RE compound | Animal | Dose | Reference |
|--------|-------------|--------|------|-----------|
| s-GOT, s-GPT ↑ | CeCl₃, Ce(NO₃)₃, La(NO₃)₃, YCl₃ | Rat | 2–10 mg Ce/kg, 3–10 mg La/kg, 1 mg Y/rat | (46,112,113) |
| s-SDH ↑ | Pr(NO₃)₃, Ce(NO₃)₃, La(NO₃)₃ | Rat, mouse | 3–40 mg Pr(NO₃)₃/kg | (105,113–115) |
| s-OCT ↑ | Ce(NO₃)₃, Pr(NO₃)₃, La(NO₃)₃, CeCl₃ | Rat | 2–10 mg RE/kg | (113) |
| s-FFA ↑ | CeCl₃, Pr(NO₃)₃, LaCl₃, YCl₃, TbCl₃, HoCl₃, YbCl₃ | Rat | 1.5–3 mg Ce/kg, 3 mg Pr/kg, 0.75 mg La/kg | (111,116) |
| s-VLDL, s-HDL, s-triglyceride ↓ | Pr(NO₃)₃ | Rat | 9 mg Y/kg, 35 mg Tb/kg, 40 mg Ho/kg, 60 mg Yb/kg | (117) |
| Triglyceride (liver) ↑ | Pr(NO₃)₃ | Rat | 10 mg Pr(NO₃)₃/kg | (117) |
| ATP ↓ | Pr(NO₃)₃ | Rat | 10 mg Pr(NO₃)₃/kg | (118) |
| P450 | Pr(NO₃)₃ | Rat, mouse | 7 mg Pr/kg, 10–20 mg Pr(NO₃)₃/kg | (105,113,117) |
| COH, EROD, Cyto2a-4/5 mRNA ↑ | CeCl₃, Pr(NO₃)₃ | Rat | 10 mg CeCl₃/kg | (110) |
| RNA polymerase I ↓ | CeCl₃ | Rat | 7 mg Pr/kg | (113) |
| RNA polymerase II ↑ | CeCl₃ | Mouse | 2 mg CeCl₃/kg, 0.5–2 mg Ce/kg | (109,119) |
| RNA polymerase II ↓ | CeCl₃ | Rat | 35 μmol/kg | (120) |
| Lipoxygenase ↑ | Pr(NO₃)₃, Nd(NO₃)₃ | Rat | 35 μmol/kg | (120) |
| Lipoxygenase ↓ | Pr(NO₃)₃, Nd(NO₃)₃, Sm(NO₃)₃ | Rat | 35 μmol/kg | (120) |
| LPO ↑ | LaCl₃ | Chick (ip) | 250 mg LaCl₃/kg | (121) |
| LPO ↓ | LaCl₃ | Chick (ip) | 250 mg LaCl₃/kg | (121) |

Abbreviations: s-GOT, serum glutamic–oxaloacetic transaminase; s-GPT, serum glutamic–pyruvic transaminase; s-FFA, serum free fatty acid; s-VLDL, serum very low density lipoprotein; s-HDL, serum high density lipoprotein; ATP, adenosine 5'-triphosphate; AH, aniline hydroxylase; AD, aminophenazone demethylase; COH, coumarin 7-hydroxylase; EROD, 7-ethoxyresorufin O-deethylase; LPO, lipid peroxidation; GR, glutathione reductase.

---

90 Environmental Health Perspectives • Vol 104, Supplement 1 • March 1996
iv-injected Pr(NO$_3$)$_3$ up to 20 mg/kg bw, their activities were remarkably decreased at doses higher than 20 mg/kg bw in rats (105). Because formation of colloidal RE in blood significantly increased with doses of YCl$_3$ (46), it is reasonable to suppose that iv-injected RE was taken up by Kupffer cells rather than by hepatocytes at doses higher than a maximum lethality. The uptake of colloidal RE by Kupffer cells may have reduced the uptake of RE by hepatocytes, resulting in the reduced hepatic injury.

**Effects of Rare Earths on the Kidney, Spleen, and Gastrointestinal Tract.** When the rat kidney was perfused with Krebs-Henseleit bicarbonate buffer containing 3 to 5.5 mM of chelated Dy (tripolyphosphate or triethylenetetramine-hexaacetic acid) for 30 min, urinary concentrating ability was decreased and renal vascular resistance was increased (122). Ethoxyresorufin O-deethylation activity in the kidney was decreased following iv injection of CeCl$_3$ in mice (109). Lipid peroxidation was increased and glutathione content and antioxidant enzymes were decreased in the renal cortex following ip injection of LaCl$_3$ in chicks (123).

Intravenous injection of LaCl$_3$ or CeCl$_3$ increased vascular permeability of the spleen in mice (108), and both sc and po administration of Ce$_{5+}$-citrate caused hypertrophy, reticuloendothelial hyperplasia, and hyperactive lymphoid follicles in mice (96). Significant Ca deposition occurred in the spleen following ip injection of YCl$_3$ (46). Oral administration of Ce$_{5+}$-citrate has been shown to cause focal hemorrhage, necrosis of mucosa, and neutrophil infiltration in the stomach and duodenum (96).

**Effects of Rare Earths on the Eye and Skin.** Exposure to EuCl$_3$, DyCl$_3$, HoCl$_3$, and ErCl$_3$ caused conjunctivitis in rabbits when these RE chlorides were applied directly to their eyes (103,104). These RE chlorides have also been demonstrated to cause severe irritation when they are applied to abraded skin in rabbits and cause epilation and nodule formation when injected intradermally in guinea pigs (103,104). It has also been shown that sc injection of RE chlorides caused local calcification with mild fibrosis and accumulation of multinucleated giant cells, and the calcification area was increased with dose (up to 2 mg of RE chlorides) in mice (124).

**Effects of Rare Earths on the Blood, Bone Marrow and Other Cells/Tissues.** Intraperitoneal injection of LaCl$_3$ or NdCl$_3$ significantly decreased the contents of sulphydryl groups, cholesterol, phospholipid and lipid peroxides, and activities of galactosidase, glucuronidase, acetylcholinesterase, NADH dehydrogenase, ATPase, and p-nitrophenyl phosphatase in the red blood cell membrane in chicks. (125). It has also been shown that ip injection of LaCl$_3$ decreased contents of sulphydryl groups and lipid peroxides and increased activities of glutathione peroxidase, glutathione reductase, glutathione-S-transferase, and catalase in the bone marrow of chicks (126). Slight but significant aberration of bone marrow cells has been found following po administration of 1/10 of LD$_{50}$ dose of RE nitrates in mice (102); however, no aberration was observed in spermatogonia, spermatocytes, and sperm in those mice.

Basu et al. (127) have shown that the ip injection of LaCl$_3$ caused a marked depression in the activities of neural Ca$^{2+}$-ATPase, Mg$^{2+}$-ATPase, and cholinesterase in chicks. The depression of these enzyme activities may be related to inhibitory effects of La$^{3+}$ on binding of Ca$^{2+}$ to brain synapsosomal membrane.

The median lethal concentration (LC$_{50}$) for rat alveolar macrophages of CdO, CdCl$_3$, LaCl$_3$, CeCl$_3$, and Nd$_2$O$_3$ were 15, 28, 52, 29, and 101 μM, respectively, *in vitro*, and although La$_2$O$_3$ and Ce$_2$O$_3$ were less toxic than LaCl$_3$ and CeCl$_3$, respectively, Nd$_2$O$_3$ was more toxic than NdCl$_3$ (128). Cytotoxicity of superconducting particles (YBa$_2$Cu$_3$O$_{7-?}$) has been shown to be almost the same as that of quartz (DQ12) using bovine alveolar macrophages (129). These *in vitro* studies using macrophages have been carried out in culture medium without serum. Thus, it remains unanswered as to how addition of serum (fetal bovine serum) in the macrophage culture system affected the cytotoxicity of RE.

**Effects of Rare Earths on Behavior, Pregnancy, and Offspring.** Ce-exposed mice exhibited significantly reduced open field behavior; ambulations were depressed after 10 sc injections (at 3-day intervals) of Ce$_{5+}$-citrate at 20 mg Ce/kg body weight (95), and ambulation and rearing were depressed following sc injection of Ce$_{5+}$-citrate at doses of 136 to 173 mg Ce/kg body weight (96).

A single sc injection of Ce$_{3+}$-citrate at a dose of 80 mg Ce/kg bw during either pregnancy or the lactating period significantly reduced the body weight of offspring in mice (130). It has also been shown that ip injection of LaCl$_3$ (44 mg La/kg bw) increased the cessation of pregnancy and decreased the average litter size in pregnant mice (131). No malformation was observed in fetuses, even when the dams were administered po with a high dose of RE(NO$_3$)$_3$ (331 mg RE(NO$_3$)$_3$/kg bw) starting from the 16th day of gestation in rats (102).

**Effects of Rare Earths on Growth, Longevity, and Carcinogenicity.** The aortic contents of cholesterol, collagen, elastin, and Ca and urinary hydroxyproline excretion were increased in rabbits when they were kept on an atherogenic diet; intake of La (40 mg LaCl$_3$/kg bw/day) significantly reduced the increases of these atherosclerotic parameters (132). The growth of mice was depressed when they were given 5 ppm of Sc$^{3+}$ or Y$^{3+}$ in drinking water, and the longevity was increased in Y$^{3+}$-fed mice (133). However, no effect on growth was found in rats that had been fed a diet containing 0.1% to 1% of DyCl$_3$, HoCl$_3$, or ErCl$_3$ for 12 weeks (104).

No carcinogenicity of RE has been found in animals (102,113,133). In addition, at 0.5 to 50 mg/ml of RE(NO$_3$)$_3$ (a mixture of Ce, La, Nd, Pr, and Sm), Ames mutagenicity tests were negative (133).

**Rare Earths as Ca$^{2+}$ Antagonists.** The tonus and contractility of the rabbit ileum in response to acetylcholine or nicotine was decreased dose dependently by EuCl$_3$ (103), DyCl$_3$, HoCl$_3$, and ErCl$_3$ (104) *in vitro*. In the guinea pig, Tm$^{3+}$, La$^{3+}$, and Ce$^{3+}$ inhibited contractile responses to K$^+$ of longitudinal ileal muscle and the inhibitory effects increased in this order (134). The inhibitory effects of La$^{3+}$ and Tm$^{3+}$ on K$^+$- or noradrenaline-induced contractile responses have also been demonstrated using the vas deferens of rats (135). The inhibitory effects of RE$^{3+}$ on the contractility are due to displacement of membrane-bound Ca$^{2+}$ with RE$^{3+}$ (134) or modulation of the membrane stability by RE$^{3+}$ (135).

**Enzymatic Functions of Rare Earths.** Very recently it was found that RE ions hydrolyze RNA dinucleoside monophosphates (136) and phosphatidylinositol (137) *in vitro* under physiological conditions (pH 7.5 – 8.5, 30°C). Hydrolysis of phosphatidylinositol seems to be specific to RE because Fe$^{3+}$, Zn$^{2+}$, and Cu$^{2+}$ were found completely inactive (137). It has also been shown that RE ions catalyze cAMP production from ATP-like adenylyl cyclase (138), and Ce$^{4+}$ hydrolyzes cAMP (139) under physiological conditions. Although it is not clear whether those *in vitro* catalytic functions of RE ions are related to toxic effects of RE *in vivo*, those...
findings may shed light on the mechanism of toxicity of RE.

Summary and Implications

The chemical forms of RE compounds primarily determine deposition and retention of RE following iv, po, sc, intratracheal, and inhalational exposure. The clearance of chelated RE from the body depends on the stability of the complexes. The chelated RE are excreted rapidly via urine, while unchelated ionic RE easily form colloids in blood, and the colloidal material is taken up by phagocytic cells of the liver and spleen.

Although the bone is one of the target organs of RE, it is not clear what cells in the bone take up the most RE — macrophages, erythroid cells, or light reticular cells. It is important to investigate effects of RE on bone marrow cells because the clearance of RE from the bone is known to be very slow.

Inhalational or intratracheal exposure of animals to RE has been proven to cause acute pneumonitis with neutrophil infiltration in the lung; long-term exposure to RE dust seems to cause pneumoconiosis in human. However, the mechanism of neutrophil recruitment or interaction of RE with lung cells has not been fully investigated, except that intratracheally injected YCl3 and LaCl3 were deposited in the lysosomes of macrophages and basement membranes of pneumocytes.

Mortality studies reveal that RE are not highly toxic (LD50 values for iv-injected RE are 10 to 100 mg/kg/bw and those of ip-injected RE are 150 to 700 mg/kg bw); cytotoxicity of RE to macrophages is comparable to that of Cd or silica in vitro. These discrepancies in lethal toxicity between in vivo and in vitro studies seem to be due to chemical forms of RE in the experimental system because those cytotoxicity studies were carried out in culture medium without serum. It is of interest to study the toxicity of RE using macrophages and other cells in various culture conditions.

There is much evidence that lanthanoid ions function as Ca2+ antagonists in vitro; however, there are few in vivo studies that relate the toxicity of RE to Ca2+-displacement from cells or biomolecules.

Because RE have been used directly in humans for therapy of cancer and synovitis and for diagnosis by magnetic resonance imaging, more extensive studies, including chronic exposure experiments, are required.

REFERENCES

1. Kawaguchi K, Nakahara T. ICP-MS Spectrometry [in Japanese]. Tokyo:Gakkaihuppan, 1994.
2. Date AR, Hutchison D. Determination of rare earth elements in geological samples by inductively coupled plasma source mass spectrometry. J Anal At Spectrom 2:269–274 (1987).
3. Vlasov KA Geochemistry of Rare Elements (Lerman Z, translation; Brenner Y, translation ed). Jerusalem:Israel Program for Scientific Translations, 1966.
4. Ito Y. Raw material of rare earths [in Japanese]. Bull Ceram Soc Jap 20:984–992 (1985).
5. Ohmachi R. Overview on resources and application of rare earths [in Japanese]. Bull Ceram Soc Jap 23:427–430 (1988).
6. Matsuura F, Fujisawa S, Nagashima H. Inorganic Chemistry [in Japanese]. Tokyo:Shokabo, 1975.
7. Halsey PJ. Pulmonary toxicity of stable and radioactive lanthanides. Health Phys 61:809–820 (1991).
8. Perrin DD. Stability Constants of Metal-ion Complexes. Part B. Organic Ligands. Oxford:Pergamon, 1979.
9. Dojindo Company (ed). Stability Constants of Chelates [in Japanese]. Kumamoto:Dojindo, 1994;219–223.
10. Nezu N, Asano M, Ouchi S. Cerium-144 in food. Science 135:102–103 (1962).
11. Liebscher K, Schonfeld T. Concentration of inhaled cerium-144 in pulmonary lymph nodes of human beings. Nature 192:1308 (1961).
12. Das T, Sharma A, Talukder G. Effects of lanthanum in cellular systems. Biol Trace Elem Res 18:201–228 (1988).
13. Sabbioni E, Pietra R, Gagliano P, Vocature G, Colombo F, Zanoni M, Rodi F. Long-term occupational exposure of rare-earth pneumoconiosis: a case report as investigated by neutron activation analysis. Sci Total Environ 26:19–32 (1982).
14. Husain MH, Dick JA, Kaplan YS. Rare earth pneumoconiosis. J Soc Occup Med 36:15–19 (1980).
15. Ohamachi R. Rare earth [in Japanese]. Ind Rare Metals 107:64–71 (1993).
16. Hirano S, Kodama N, Shibata K, Suzuki KT. Localization, localization, and pulmonary effects of yttrium chloride following intratracheal instillation into the rat. Toxicol Appl Pharmacol 104:301–311 (1990).
17. Suzuki KT, Kobayashi E, Ito Y, Ozawa H, Suzuki E. Localization and health effects of lanthanum chloride instilled intratracheally into rats. Toxicology 76:141–152 (1992).
18. Brooks SM. Lung disorders resulting from the inhalation of metals. Clin Chest Med 2:235–254 (1981).
19. Stewart JSW, Hird V, Snook D, Sullivan M, Myers MJ. Epenetos AA. Intraperitoneal 192H and 90Y-labelled monoclonal antibodies for ovarian cancer: pharmacokinetics and normal tissue dosimetry. Int J Cancer (Suppl. 3):71–76 (1988).
20. Washburn LC, Hwa Sun TT, Crook JE, Byrd BL, Carlton JE, Hung Y-W, Stepelowski ZS. 90Y-labelled monoclonal antibodies for cancer therapy. Nucl Med Biol 13:453–456 (1986).
21. Smith T, Shawe DJ, Crawley JCW, Gumpel JM. Use of single photon emission computed tomography (SPECT) to study the distribution of 90Y in patients with Baker's cysts and persistent synovitis of the knee. Ann Rheum Dis 47:553–558 (1988).
22. Kyle V, Hazleman BL, Wraight P. Yttrium-90 therapy and 99mTc pertechnetate kidney uptake measurements in the management of rheumatoid arthritis. Ann Rheum Dis 42:132–137 (1983).
23. Murakami Y, Danno H, Kobayashi M. Data Book on Radioisotopes [in Japanese]. Tokyo:Chishaku Shoin, 1982.
24. Beyer G-J, Franke W-G, Henking K, Johansen BA, Khalkin VA, Kretzschmar M, Lebedev NA, Münz R, Novgorodov AF, Thieme K. Comparative kinetic studies of simultaneously injected 169Yb and 75Ga-citrate in normal and tumour-bearing mice. Int J Appl Radiat Isotopes. 29:673–681 (1978).
25. Canada RG. Calcium receptor binding of cisplatin and terbium in human breast tumors after hyperthermia. Radiat Res 133:170–175 (1993).
26. Ando A, Takeshita M, Ando I, Hiraki T, Hisada K. Study of subcellular distribution of 169Yb and 111In in tumor and liver [in Japanese]. Radioisotopes 26:169–174 (1977).
27. Sudhira K, Sanada S, Ando I, Hiraki T, Hisada K, Takakura Y, Nagayama S, Immamura T. Study of distribution of 169Yb, 67Ga and 111In in tumor tissue by macroautoradiography. Radioisotopes 26:13–18 (1977).
28. Espósito M, Collecchi P, Brera S, Mora E, Mazucchetti A, Cátulo M, Oddone M. Plasma and tissue levels of some lanthanide elements in malignant and non-malignant human tissues. Sci Total Environ 56:55–63 (1986).
29. Cohen RH, Leder RA, Herzberg AJ, Hedlund LW, Wheeler CT, Beam CA, Nadel SN, Dunnick NR. Extravascular toxicity of two magnetic resonance contrast agents. Invest Radiol 26:224–226 (1991).
30. Öksenendal AN, Biodistribution and toxicity of MR imaging contrast media. J Magn Reson Imaging 3:157–165 (1993).
31. Roškový NM, Weinreb JC, Litt AW. Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. J Magn Reson Imaging 3:131–132 (1993).
32. Monafo WW, Tandon SN, Ayvazian VH, Tuchschmidt J, Skinner AM, Dietz F. Cerium nitrate: a new antiseptic for elective bowel surgery. Surgery 80:465–473 (1976).

33. Sakurai Y. Distribution and fate of lanthanum in the tissues of rats administered lanthanum salt solutions by means of swabbing the solution on the teeth and through stomach tube [in Japanese]. Aichi Gakuin Daigaku Gakusei Shi 20:1–17 (1982).

34. Ozeki M, Kobayashi Y, Takei M, Shimano Y. Inhibition of dental caries by lanthanum [in Japanese]. Koku Eisei Gakkai Zasshi 28:448–454 (1979).

35. Ohyabashi T, Ohtsuka T, Mohri T. Characterization of interaction between Tb\(^{3+}\) and porcine intestinal brush border membranes. Biochim Biophys Acta 817:181–186 (1985).

36. Loscalzo J, Rabbini D. The interaction of Tb\(^{3+}\) with the human platelet surface. Arch Biochem Biophys 249:237–242 (1986).

37. Weiss GB, Goodman FR. Distribution of a lanthanide (\(^{153}\)Pr) in vascular smooth muscle. J Pharmacol Exp Ther 198:366–374 (1976).

38. Buccigross JM, Nelson DJ. EPR studies show that all lanthanides do not have the same order of binding to calmodulin. Biochem Biophys Res Commun 136:1243–1249 (1986).

39. Fujimori T, Jencks WP. Lanthanin inhibits steady-state turnover of the sarcoplasmic reticulum calcium ATPase by replacing magnesium as the catalytic ion. J Biol Chem 265:16262–16270 (1990).

40. dos Remedios C. Lanthanide ions and skeletal muscle sarcoplasmic reticulum. J. Gaddolinium localization by electron microscopy. J Biochem 81:703–708 (1977).

41. Bell ET, Featherstone JD, Bell JE. Interaction of terbium and calcium with chicken cystatin. Arch Biochem Biophys 271:359–365 (1989).

42. Hammoudah MM, Nir S, Benz T, Mayhew E, Stewart TP, Hui SW, Kurland RJ. Interaction of La\(^{3+}\) with phosphatidylserine vesicles. Biochim Biophys Acta 645:102–114 (1981).

43. Weiss GB. Cellular pharmacology of lanthanum. Annu Rev Pharmacol 14:343–354 (1974).

44. Rosoff B, Spencer H. Binding of rare earths to serum proteins and DNA. Clin Chim Acta 93:311–319 (1979).

45. Ford-Hutchinson AW, Perkins DJ. Scandium metabolism; binding of metalloproteins in vivo and in vitro. Radiat. Res. 51:244–248 (1972).

46. Hirano S, Kodama N, Shibata K, Suzuki KT. Metabolism and toxicity of intravenously injected yttrium chloride in rats. Toxicol Appl Pharmacol 121:224–232 (1993).

47. Nagy I, Kadas I, Jobst K. Lanthanum trichloride induced blood coagulation defect and liver injury. Haematologia 103:353–359 (1976).

48. Hunter RB, Walker W. Anticoagulant action of neoodymium 3-sulpho-isonicotinate. Nature 178:47 (1956).

49. Galle P, Berry JP, Galle C. Role of alveolar macrophages in precipitation of mineral elements inhaled as soluble aerosols. Environ Health Perspect 97:145–147 (1992).

50. Berry JP, Masse R, Escaig F, Galle P. Intracellular localization of cerium. A microanalytical study using a electron microprobe and ionic microanalysis. Human Toxicol 8:511–520 (1989).

51. Rhoads K, Sanders CL. Lung clearance, translocation, and acute toxicity of arsenic, beryllium, cadmium, cobalt, lead, selenium, vanadium, and ytterbium oxides following deposition in the rat lung, Environ Res 36:359–378 (1985).

52. Sturuaon B, Brooks AL, McClellan RO. Tissue distribution and dosimetry of \(^{144}\)Ce in Chinese hamsters. Radiat Res 44:359–367 (1970).

53. Thomas, R.L., Scott, J. K., and Chiffelle, T.L. Metabolism and Toxicity of inhaled \(^{144}\)Ce in rats. Radiat. Res. 49:589–610 (1972).

54. Wenzel WJ, Thomas RG, McClellan RO. Effect of stable yttrium concentration on the distribution and excretion of inhaled radioyttrium in the rat. Am Ind Hyg Assoc J 30:630–634 (1969).

55. Hirano S, Tsukamoto N, Kobayashi E, Suzuki KT. Toxicity of cadmium oxide instilled into the rat lung. I. Metabolism of cadmium oxide in the lung and its effects on essential elements. Toxicology 55:15–24 (1989).

56. Hisatsune S, Sakai E, Hiraoka H, Kodama N, Suzuki KT. Metabolism and pulmonary toxicity of intratracheally instilled cupric sulfate in rats. Toxicology 64:223–233 (1990).

57. Berthézène Y, Mühler A, Lang P, Shames DM, Clement O, Rosenau W, Kuwatsuru R, Brach RC. Safety aspects and pharmacokinetics of inhaled aerosolized gadolinium. J Magn Reson Imaging 3:125–130 (1993).

58. Biondahl K. Differences in liver weight, mortality in cerium-treated mice and \(^{144}\)Ce levels in blood, liver, urine and feces at various intervals after treatment with nafenopin and preg

59. Richmond CR, London JE. Long-term in vivo retention of cerium-144 by beagles. Nature 211:1179 (1966).

60. Singh A, Holmes RA, Farhangi M, Volkert WA, Williams A, Stringham LM, Kettering AR. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. J Nucl Med 30:1814–1818 (1989).

61. Wedeking P, Eaton S, Covell D.G., Nair S, Tweedle MF, Echelman WC. Pharmacokinetic analysis of blood distribution of intravenously administered \(^{153}\)Gd-labeled Gd(DTPA)\(^{2-}\) and \(^{99m}\)Tc(DTPA) in rats. Magn Reson Imaging 8:567–575 (1990).

62. Dean PB, Niemi P, Kivisaari L, Kormano M. Comparative pharmacokinetics of gadolinium DTPA and gadolinium chelate. Invest Radiol 23 (Suppl. 1):S258–S260 (1988).

63. Baltrukiewicz P, Kuhnt N, Bakun DA, Berk RN. Biodistribution of GdCl\(_3\) and Gd-DTPA and their influence on proton magnetic relaxation in rat tissue. Magn Reson Imaging 5:221–231 (1987).

64. Lachine EE, Noujaim AA, Ediss C, Wiebe LI. Toxicity, tissue distribution and excretion of \(^{46}\)ScI\(_2\) and \(^{46}\)Sc-EDTA in mice. Int J Appl Radiat Isotopes 27:373–377 (1976).

65. Byrd BL, Watson EE, Cloutier RJ, Hayes RL. Effect of stable scandium on the long-term whole body retention of intravenously administered \(^{46}\)Sc citrate in the rat. Health Phys 29:375–379 (1975).

66. Hiraki T, Ando A, Mori H, Ando I, Sakamoto K, Amano R, Kojima K, Hisada K. Whole-body retention studies of \(^{153}\)Tm-citrate. — Estimation of radiation dose to human from \(^{153}\)Tm-citrate [in Japanese]. Radioisotopes 27:85–89 (1978).

67. Ando A, Mori H, Ando I, Hiraki T, Hisada K. Whole-body retention studies of \(^{169}\)Yb-citrate. — Estimation of radiation dose to human from \(^{169}\)Yb-citrate [in Japanese]. Radioisotopes 26:602–605 (1977).

68. Rosoff B, Siegel E, Williams GL, Spencer H. Distribution and excretion of radiocative rare-earth compounds in mice. Int J Appl Radiat Isotopes 14:129–135 (1963).

69. Baltrukiewicz Z, Burakowski T, Derecki J. Effects of ethylene-diaminetetraacetic acid (EDTA) and diethylenetriaminopentaacetic acid (DTPA) derivatives on penetration of ytterbium-169 and cerium-144 into the rat offspring. Acta Physiol Pol 27:175–181 (1976).

70. Blank ML, Cress EA, Byrd BL, Washbaun LC, Snyder F. Liposomal encapsulated Zn-DTPA for removing intracellular \(^{169}\)Yb. Health Phys 39:913–920 (1980).

71. Blank ML, Byrd BL, Cress EA, Snyder F. Liposomal preparations of calcium- or zinc-DTPA have a high efficacy for removing colloidal ytterbium-169 from rat tissues. Toxicology 30:275–281 (1984).

72. Spencer H, Rosoff B. Removal of scandium-46 in man. Health Phys 11:1181–1185 (1965).

73. Gachaly A, Nameini J, Szegedi I, Varga PL. Effect of mixed ligand complex therapy on the retention of \(^{99m}\)Nb and \(^{144}\)Ce in mice. Radiat Res 120:177–181 (1989).

74. Robinson GA, Wastin DC, Floto F. Distribution of \(^{146}\)La and \(^{144}\)Ca in female Japanese quail and in the eggs laid. Poult Sci 57:190–196 (1978).

75. Robinson GA, Wastin DC, Floto F, Gibbins AM. \(^{153}\)Gadolinium as a useful radioiodanhanide for long-term labeling of tissues in Japanese quail. Poult Sci 60:861–866 (1981).
76. Robinson GA, Kupsh CC, Wasnidge DC, Floto F, Robinson BL. Increased deposition of uranium in the bones of vitellogenetic male Japanese quail: Effect of estradiol-17β on the distribution of uranium (VI), thorium (IV), gadolinium (III), and plutonium (IV) in adult birds. J. Inorg. Biochem. 65:1178–1183 (1996).

77. Kargačin B, Kostial K. Age-related efficiency of Ca-DTPA to reduce 141Ce retention in rats. Toxicol Lett 32:243–247 (1986).

78. Shinohara A, Chiba M. Distribution of terbium and increase in calcium concentrations in organs of mice administered with terbium chloride. Toxicology 66:93–103 (1991).

79. Muller WA, Linzner U, Schäffer EH. Organ distribution studies of lutetium-177 in mice. Int J Nucl Med Biol 5:29–31 (1978).

80. Kargačin B, Kostial K, Ciganovic M. The influence of age on the efficiency of delayed therapy with Ca-DTPA for cerium in rats. Arch Toxicol 58:276–277 (1986).

81. Kargačin B, Kostial K. Reduction of 85Sr, 137Cs, 131I and 141Ce retention in rats by simultaneous oral administration of calcium alginate, ferrichexacyanoferrate (II), KI and Zn-DTPA. Health Phys 49:859–864 (1985).

82. Sullivan MF, Miller BM, Goebel JE. Gastrointestinal absorption of metals (51Cr, 65Zn, 68Ga, 109Cd, 113Sn, 153Sm and 203Pm) by rats and guinea pigs. Environ Res 35:439–453 (1984).

83. Kostial K, Kargačin B, Landeka M. Gut retention of metals in rats. Biol Trace Elem Res 21:213–218 (1989).

84. Kostial K, Kargačin B, Lendeka M. Reduction of 141Ce absorption in sucking rats. Int J Radiat Biol Relat Stud Phys Chem Med 51:139–145 (1987).

85. Rabinowitz JL, Gavarron FF, Brand, J. Tissue uptake and intracellular distribution of 140lanthanum after oral intake by the rat. J Toxicol Environ Health 24:229–235 (1988).

86. Eisele GR, Mraz FR, Woody, MC. Gastrointestinal uptake of 144Ce in the neonatal mouse, rat and pig. Health Phys 39:185–192 (1980).

87. Menczel J, Rosoff B, Spencer H. Tissue distribution of orally administered 3H and 46Sc in mice. Health Phys 42:727–730 (1982).

88. Kobayashi Y, Ozeki M, Takei M, Shimano R. Absorption of lanthanum by the enamel surface of extracted human teeth in [Japanese]. Koku Eisei Gakkai Zasshi 29:276–290 (1979).

89. Kuri K, Morita Y, Kanai S. The effects of saponolactone on the biliary excretion of mercury, cadmium, zinc, and cerium in rats. Biochem Pharmacol 26:279–282 (1977).

90. Sagan CE, Lengemann FW. The retention and movement of cerium-141 in the gastrointestinal tract of adult rats irradiated with 800 R and fed grain-based or milk diets. Radiat Res 53:480–487 (1973).

91. Suzuki MF, Bonzler P, Ryan JL, Buschhorn RL. Influence of oxidizing or reducing agents on gastrointestinal absorption of U, Pu, Am, Cm, and Pm by rats. Health Phys 50:223–232 (1986).

92. Kostial K, Kargačin B, Landeka M. Oral Zn-DTPA therapy for reducing 141Ce retention in sucking rats. Int J Radiat Biol 52:501–504 (1987).

93. Inaba J, Yasumoto MS. A kinetic study of radionuclide absorption through damaged and undamaged skin of the guinea pig. Health Phys 37:592–595 (1979).

94. Takada K. Comparison of the metabolic behavior of 144Ce injected intravenously with that absorbed from the wound site in rats. Health Phys 35:537–543 (1978).

95. Morganti JB, Hwang BA, Stinemans CH, Massaro EJ. Cerium tissue/organ distribution and alterations in open field and exploratory behavior following repeated exposure of the mouse to citrate complexed cerium. Gen Pharmacol 9:257–261 (1978).

96. Stinemans CH, Massaro EJ, Lown BA, Morganti JB, Al-Nakeeb S. Cerium tissue/organ distribution and alterations in open field and exploratory behavior following acute exposure of the mouse to cerium (citrate). J Exp Pathol Toxicol 2:553–570 (1978).

97. Seidel A, Wiener M, Krüger E, Wirth R, Haffner H. Studies on the lysosomal binding of 141Ce, 239Pu, 237Np and 241Am in rat and Syrian hamster liver using carrier-free electrophoresis. Nucl Med Biol 13:515–518 (1986).

98. Allard M, Kien P, Caille JM, Bonnemain B, Doucet D, Simonnet G. Subcellular localization of gadolinium in the rat brain. J Neuroradiology 14:159–162 (1987).

99. Shahkhi M, Tavassoli M. Preferential localization of lanthanum to nuclear-pore complexes. J Ultrastr Res 81:139–144 (1982).

100. Tavassoli M, Aoki M, Shahkhi MA novel stromal cell type in the rat marrow recognizable by its preferential uptake of lanthanum. Exp Hemat 8:568–577 (1980).

101. Salas M, Tuchweber B. Prevention by steroids of cerium hepatoxicity. Arch Toxicol 36:115–125 (1976).

102. Yi YJ, Cui MZ. Toxicological studies on safety of rare earths used in agriculture. Biomed Environ Sci 1:270–276 (1988).

103. Håley TJ, Komesu N, Colvin G, Koste L, Upham HC. Pharmacology and toxicity of europium chloride. J Pharmacol Sci 54:643–645 (1965).

104. Håley TJ, Koste L, Komesu N, Efros M, Upham HC. Pharmacology and toxicity of dysprosium, holmium, and erbium chlorides. Toxicol Appl Pharmacol 8:37–43 (1966).

105. Tuchweber B, Trost R, Salas M, Sieck W. Effect of praseodymium nitrate on hepatocytes and Kupffer cells in the rat. Can J Physiol Pharmacol 54:898–906 (1976).

106. Ball RA, Gelder GV. Effect of gadolinium oxide for mice following exposure by inhalation. Arch Environ Health 13:601–608 (1966).

107. Yoneda S, Emi N, Fujita Y, Omichi M, Hirano S, Suzuki KT. Effects of gadolinium chloride on the rat lung following intratracheal instillation. Fund Appl Toxicol 26:65–70 (1995).

108. Marciniaki M, Baltrukiewicz Z, Chas J. The effect of toxic doses of lanthanum and cerium on the placental barrier and blood/organ barrier in mice after intravenous injection of these elements. Acta Physiol Pol 39:294–299 (1988).

109. Salas M, Tuchweber B, Kovacs K, Garg BD. Effect of cerium on the rat liver. An ultrastructural and biochemical study. Beitr Pathol 157:23–44 (1976).

110. Murgunsson G. The behavior of certain lanthanoids in rats. Acta. Pharmacol Toxicol 20:1–95 (1963).

111. Arvela P, Reiniä M, Pelkonen O, Raunio H. Cerium-induced strain-dependent increase in Cyp2a-4/5 (cytochrome P450a-4/5) expression in the liver and kidneys of inbred mice. Biochem Pharmacol 44:1260–1274 (1992).

112. Salas M, Tuchweber B, Kovacs K, Garg BD. Effect of cerium on the rat liver. An ultrastructural and biochemical study. Beitr Pathol 157:23–44 (1976).

113. Marciniaki M, Baltrukiewicz Z. Serum ornithine carbamoyltransferase (OCT) in rats poisoned with lanthanum, cerium, and praseodymium. Acta Physiol Pol 28:589–594 (1977).

114. Oberdisse E, Arvela P, Gross U. Lanthanoid-induced hepatotoxicity and its prevention by pretreatment with the same lanthanoid. Arch Toxicol 45:105–114 (1979).

115. Gräswäski O, Volt- Lehmann B, Van H-R, Arvela P, Oberdisse E. Alterations of rat serum lipoproteins and lecithine-cholesterol-acyltransferase activity in praseodymium-induced liver damage. Naunyn-Schmiedeberg's Arch Pharmacol 301:65–73 (1977).

116. Arvela P, Kraul H, Stenbäck F, Pelkonen O. The cerium-induced liver injury and oxidative drug metabolism in DBA/2 mice. Toxicol Appl Pharmacol 37:199–208 (1977).

117. Sarkander H-I, Brade WP. On the mechanism of lanthanide-induced liver toxicity. Arch Toxicol 36:1–17 (1976).

118. Basu A, Haldar S, Chakrabarty K, Santra M, Chatterjee GC. Effect of cysteine supplementation on lanthanum chloride...
induced alterations in the antioxidant defence system of chick liver. Indian J Exp Biol 22:432–434 (1984).

122. Endre ZH, Allis JL, Radda GK. Toxicity of dysprosium shift reagents in the isolated perfused rat kidney. Mag Reson Med 11:267–274 (1989).

123. Maulik G, Ghosh N, Sengupta T, Chattopadhyay D, Charkraborty AK, Chatterjee GC. Curative effect of methionine on certain enzymes of chick kidney cortex under lanthanum toxicity situation. Indian J Exp Biol 30:1166–1169 (1992).

124. Garrett JR, McClure J. Lanthanide-induced calcergy. J Pathol 135:267–275 (1981).

125. Ghosh N, Chattopadhyay D, Chatterjee GC. Chicken erythrocyte membrane lipid profile and enzymatic activity under lanthanum chloride and neodymium chloride administration. Indian J Exp Biol 29:226–229 (1991).

126. Ghosh N, Chattopadhyay D, Mukhopadhyay S, Addya S, Chatterjee GC. Cellular defence mechanism under the influence of lanthanum intoxication in chick bone marrow. Indian J Exp Biol 26:374–376 (1988).

127. Basu A, Chakrabarty K, Chatterjee GC. Neurotoxicity of lanthanum chloride in newborn chicks. Toxicol Lett 14:21–25 (1982).

128. Palmer RJ, Butenhoff JL, Stevens JB. Cytotoxicity of rare earth metals cerium, lanthanum, and neodymium in vitro: comparisons with cadmium in a pulmonary macrophage primary culture system. Environ Res 43:142–156 (1987).

129. Wilczek W, Drosselmyer E, Seidel A. The in vitro effects of high-Tc superconducting particles (YBa2Cu3O7−x) and quartz (SiO2) on bovine alveolar macrophages. Exp Pathol 37:269–272 (1989).

130. D’Agostino RB, Lown BA, Morganti JB, Massaro EJ. Effects of in utero or suckling exposure to cerium (citrate) on the postnatal development of the mouse. J Toxicol Environ Health 10:449–458 (1982).

131. Abramczuk JW. The effects of lanthanum chloride on pregnancy in mice and on preimplantation mouse embryos in vivo. Toxicology 34:315–320 (1985).

132. Kramsch DM, Apsen AJ, Apstein CS. Suppression of experimental atherosclerosis by the Ca2+-antagonist lanthanum. J Clin Invest 65:967–981 (1980).

133. Schroeder, H.A., and Mitchener, M. Scandium, chromium (VI), gallium, yttrium, rhodium, palladium, indium in mice: effects on growth and life span. J Nutr 101:1431–1438 (1971).

134. Triggle CR, Triggle DJ. An analysis of the actions of cations of the lanthanide series on the mechanical responses of guinea pig ileal longitudinal muscle. J Physiol 254:39–54 (1976).

135. Swamy VC, Triggle CR, Triggle DJ. The effects of lanthanum and thulium on the mechanical responses of vas deferens. J Physiol 254:55–62 (1976).

136. Komiyama M, Matsumura K, Matsumoto Y. Unprecedentedly fast hydrolysis of the RNA dinucleoside monophosphates ApA and UpU by rare earth metal ions. J Chem Soc Chem Commun.:640–641 (1992).

137. Matsumura K, Komiyama, M. Hydrolysis of phosphatidylinositol by rare earth metal ion as a phospholipase C mimic. J Inorg Biochem 55:153–156 (1994).

138. Yajima H, Sumaoka J, Miyama S, Komiyama, M. Lanthanide ions for the first non-enzymatic formation of adenosine 3',5'-cyclic monophosphate from adenosine triphosphate under physiological conditions. J Biochem 115:1038–1039 (1994).

139. Sumaoka J, Miyama S, Komiyama M. Enormous acceleration by cerium (IV) for the hydrolysis of nucleotide 3',5'-cyclic monophosphates at pH 7. J Chem Soc Chem Commun:1755–1756 (1994).