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

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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*).

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Abbreviations used: RE, rare earths; NTA, nitrilotriacetic acid; EDTA, ethylenediamine-*N,N,N′,N′*-tetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; EDTMP, ethylenediaminetetramethylene phosphonic acid; VLDL, very low density lipoprotein; HDL, high density lipoprotein; LD_{50}, median lethal dose; LC_{50}, median lethal concentration.

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 Ca^{2+} (0.99 Å) is very close to those of lanthanoids, lanthanoids have been used for Ca^{2+} 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 RE^{3+}-citrate, RE^{3+}-nitrilotriacetic acid (NTA), RE^{3+}-ethylenediamine-*N,N,N′,N′*-tetraacetic acid (EDTA), and RE^{3+}-diethylenetriaminepentaacetic 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, ^{144}Ce, 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 smelter'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^{3+} (Å)	Clarke[a] number	Detection limit, ppb[b]			
						ICP-AES	ICP-MS	FAAS	GFAAS
Sc	21	$3d^1 4s^2$	+3	0.83	5×10^{-4}	0.4	0.015	100	0.74
Y	39	$4d^1 5s^2$	+3	1.06	3×10^{-3}	0.04	0.004	300	8
La	57	$5d^1 6s^2$	+3	1.22	1.8×10^{-3}	0.1	0.002	2000	24
Ce	58	$4f^2 6s^2$	+3,+4	1.18	4.5×10^{-3}	0.4	0.004	–	–
Pr	59	$4f^3 6s^2$	+3,+4	1.16	5×10^{-4}	10	0.003	4000	80
Nd	60	$4f^4 6s^2$	+3,+5	1.15	2.2×10^{-3}	0.3	0.007	2000	200
Pm	61	$4f^5 6s^2$	+3	–	–				
Sm	62	$4f^6 6s^2$	+2,+3	1.13	6×10^{-4}	30	1.5	600	–
Eu	63	$4f^7 6s^2$	+2,+3	1.13	1×10^{-4}	0.06	0.007	40	0.2
Gd	64	$4f^7 5d^1 6s^2$	+3	1.11	6×10^{-4}	0.4	0.009	4000	80
Tb	65	$4f^9 6s^2$	+3,+4	1.09	8×10^{-5}	0.1	0.002	2000	100
Dy	66	$4f^{10} 6s^2$	+3,+4	1.07	4×10^{-4}	4	0.007	200	3.4
Ho	67	$4f^{11} 6s^2$	+3	1.05	1×10^{-4}	3	0.002	100	1.8
Er	68	$4f^{12} 6s^2$	+3	1.04	2×10^{-4}	1	0.005	100	9
Tm	69	$4f^{13} 6s^2$	+2,+3	1.04	2×10^{-5}	0.2	0.002	40	0.2
Yb	70	$4f^{14} 6s^2$	+2,+3	1.00	2.5×10^{-4}	0.02	0.005	20	0.1
Lu	71	$4f^{14} 5d^1 6s^2$	+3	0.99	7×10^{-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. [a]The ratio of the amount of a particular element mainly in the earth's crust. [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, fluorescente 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	(–)
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_3 and $LaCl_3$ 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 β-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 Tm^{3+}, Tb^{3+}, and Yb^{3+} have a high affinity for tumor cells (*24–27*). It is interesting to note that Tb^{3+} was temperature-dependently taken up by tumor cells (MCF-7), and cisplatin, a well-known anticancer drug, reduced the binding of Tb^{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), tetraazacyclododecanetetraacetic acid (DOTA)-chelated Gd (gadoterate meglumine), and Gd-HP-DO3A (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^{3+} binds to Ca^{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^{3+} is increased probably by energy transfer to aromatic residues such as tyrosine (*35*). Tb^{3+} and Pm^{3+} are removable from the

surfaces of platelets and smooth muscle by both Ca^{2+} and La^{3+} (*36,37*). Lanthanoids are also known to bind to Ca^{2+} or 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 Ca^{2+} binding sites, has been shown to be different among lanthanoids. Lu^{3+} and Er^{3+} bind like Ca^{2+}, Eu^{3+} and Tb^{3+} bind in the opposite order from Ca^{2+}, and La^{3+} and Nd^{3+} bind in a mode between them (*38*). La^{3+} has been shown to inhibit the 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 Sc^{3+}, Y^{3+}, and La^{3+} bind to globulin and DNA (*44*), and transferrin is a major Sc^{3+}- or Y^{3+}-binding protein in blood plasma (*45,46*). La^{3+} and 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 Yb_2O_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 $CeCl_3$ (*52*), $Ce(OH)_3$ (*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 $Ce(OH)_3$ was 140 days following initial rapid clearance in the rat lung (*53*). The

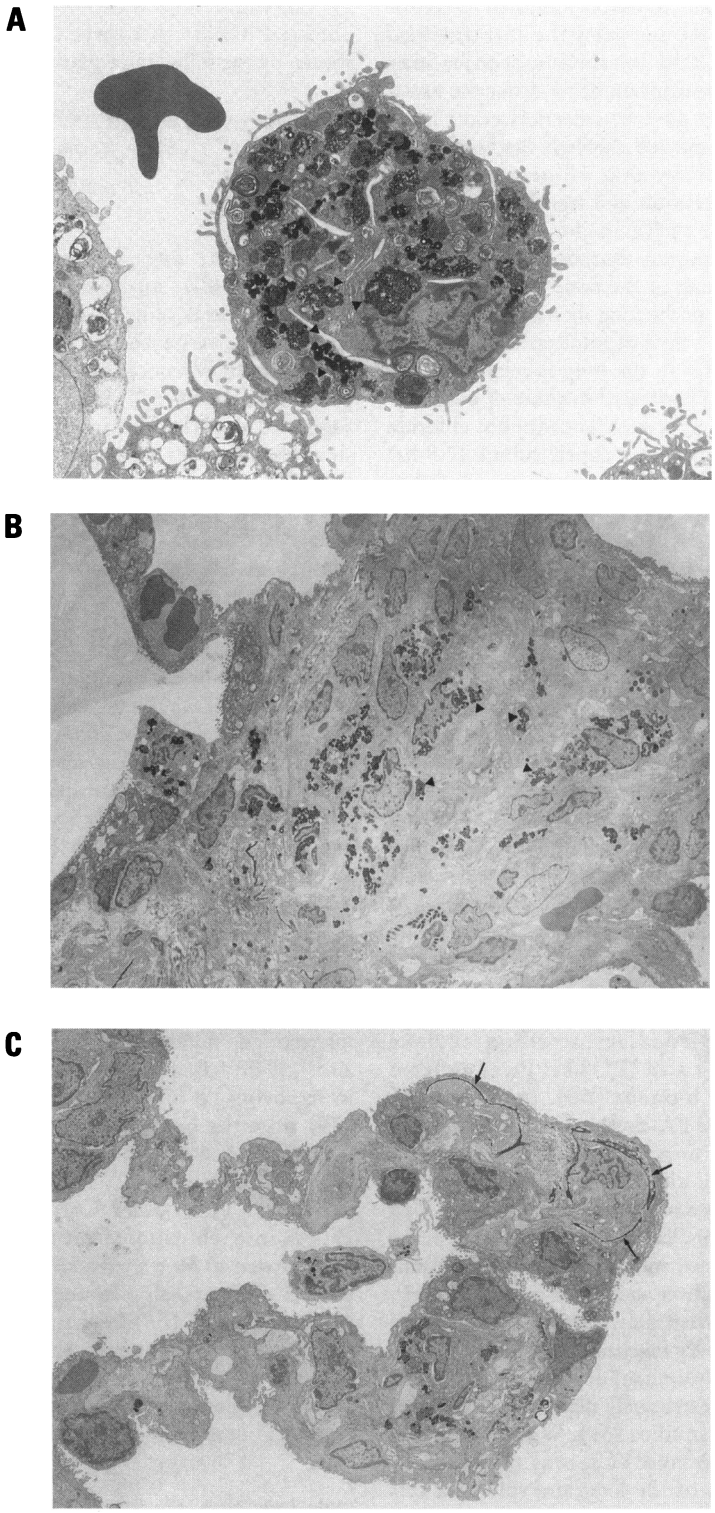

Figure 1. Transmission electron micrographs of alveolar macrophages retrieved in bronchoalveolar lavage fluid (*A*, ×3,640) and lung tissue (*B*, ×1,344; *C*, ×1,848). Male Wistar rats received intratracheal instillation of YCl_3 at a dose of 100 μg Y/rat and were killed at 7 days postinstillation. Yttrium was detected in lysosomes of macrophages (arrowheads) in both free (*A*) and granulomatous types (*B*), and in basement membranes (arrows, *C*) by X-ray microanalysis. Reproduced from Hirano et al. (*16*).

differences in the extrapulmonary translocation of RE between the intratracheal instillion and inhalation studies may be due to absorption of RE from the upper airways or gastrointestinal tract after being transported through the esophagus. Another factor that influences the pulmonary retention and translocation of RE is the dose of RE in the lung because it has been shown that translocation of Y from the lung to the bone decreased as the deposition in the lung increased (*54*).

The half-time of intratracheally instilled RE chlorides in the lung is relatively long (*vide supra*) compared to those of other soluble metal salts such as cadmium chloride (14 days) (*55*) and cupric sulfate (7.5 hr) (*56*). However, when rats were exposed to aerosols of gadopentate dimeglumine, a half-time of Gd in the lung was 2.16 hr (*57*). These results suggest that gadopentate dimeglumine was stable in the alveolar space and was hardly taken up by macrophages because of limited release of ionic Gd from the complex.

Intravenous Injection. Whole body retention and tissue distribution of iv-injected RE primarily depend on the stability of RE in blood. Urinary excretion of Ce during 14 days was less than 1% of the dose following injection of $CeCl_3$ in mice (*58*), and a half-time of iv-injected $CeCl_3$ was about 10 years in beagle dogs (*59*). On the other hand, chelated RE seems to be excreted rapidly; a whole body half-time of Tm^{3+}-citrate was about 2.5 hr in rats (*24*), and approximately 50% of iv-injected Sm^{3+}-ethylenediaminetetramethylene phosphonic acid (EDTMP) was excreted in 8 hr in humans (*60*). Intravenously injected DTPA-chelated Gd was excreted rapidly via urine after transient accumulation in the kidney, and only 2% of the injected dose remained in the body at 2 hr postinjection; $GdCl_3$ was taken up by reticuloendothelial cells, and 72% was accumulated in the liver and spleen in rats (*61–63*). It has also been shown that EDTA-chelated Sc was rapidly taken up by the kidney with subsequent elimination via the urine, while $ScCl_3$ was extensively deposited in the liver and spleen in mice (*64*). We have reported that iv-injected YCl_3 was taken up by phagocytes of the liver and spleen in rats and the half-time of Y in the liver was 144 days (*46*). Taken together, chelated RE are excreted mainly via urine after transient accumulation in the kidney and their whole body half-times are several hours; RE chlorides are taken up by the liver and spleen, and those RE are not easily excreted.

The whole body retention of iv-injected chelated RE fits to a three-phase model shown by the following equation:

$$\% \text{ Retention} = Ae^{-(0.693/Ta)t} + Be^{-(0.693/Tb)t} + Ce^{-(0.693/Tc)t} \quad [1]$$

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 Sc^{3+}-citrate (low stability) in the liver, spleen, and bone was much higher than that of Sc^{3+}-EDTA (high stability) following iv injection in mice (*68*). Rosoff et al. (*68*) also have shown that when Sc^{3+}-NTA (intermediate stability) was injected, a relatively high concentration of Sc was accumulated in the bone compared to Sc^{3+}-citrate or Sc^{3+}-EDTA. Yb accumulated in rat offspring through milk following iv injection of $YbCl_3$, Yb^{3+}-EDTA, and Yb^{3+}-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 Ca^{2+}- or Zn^{2+}-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 Na^{+}_2, Ca^{2+}-EDTA or Na^{+}_3, Ca^{2+}-DTPA into Yb-exposed rat mothers has been proven to be effective in reducing the transfer of Yb to their offspring (*69*).

Rossoff 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 YCl_3 (*46*).

In Japanese quails, iv-injected $LaCl_3$ and $CeCl_3$ 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 $GdCl_3$ in the liver, oocytes, and ova decreased as blood vitelloginin concentration was increased by intramuscular injection of estradiol in male Japanese quails (*76*).

Intraperitoneal Injection. It is reported that intraperitoneally (ip) injected $CeCl_3$ or Ce^{3+}-citrate was deposited mainly in the liver and skeleton in hamsters (*52*) and rats (*77*). Electron microprobe and ionic microanalysis revealed that ip-injected $CeCl_3$ 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 Lu^{3+}-citrate in mice, Lu 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 Lu^{3+}-citrate increased, and the percent of deposition in the skeleton was decreased as the dose increased (*79*). As described above, Ca^{2+}- or Zn^{2+}-DTPA has been effective in removing RE deposited in the tissues following ip 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*)
Tm-citrate	Rat	3.4 hr	99 hr	106 days	(*66*)
Yb-citrate	Rat	3.6 hr	194 hr	850 days	(*67*)

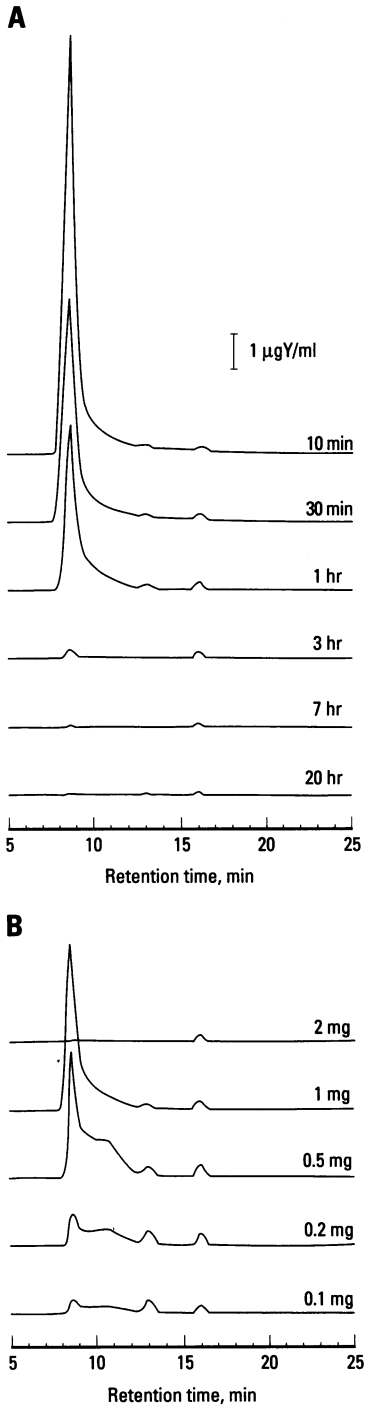

Figure 2. (*A*) Time-course and (*B*) dose-related changes in elution profile of Y in blood plasma on a gel filtration column (Asahipak GST-520). Blood samples were obtained from male Wistar rats at 10 and 30 min and 1, 3, 7, and 20 hr post iv injection of YCl_3 at a dose of 1 mg Y/rat (A) or at 1 hr post iv injection of YCl_3 at doses of 0.1, 0.2, 0.5, 1, and 2 mg Y/rat (B). The eluate was directly introduced to an atomizer of an inductively coupled argon plasma-atomic emission spectrophotometer. The atomic-emission intensity of Y was continuously monitored. Reproduced from Hirano et al. (*46*).

(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 CsCl and 79% of $CoCl_2$ 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 intracisternally 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

Table 4. LD_{50} of RE following intravenous, intraperitoneal, and per os administration.

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	7650 mg	(*104*)
$HoCl_3$	ip	Mouse	560 mg $DyCl_3$	(*104*)
$HoCl_3$	po	Mouse	7200 mg $DyCl_3$	(*104*)
$ErCl_3$	ip	Mouse	535 mg $DyCl_3$	(*104*)
$ErCl_3$	po	Mouse	6200 mg $DyCl_3$	(*104*)
$ScCl_3$	iv	Mouse	24 mg Sc	(*64*)
$ScCl_3$	ip	Mouse	440 mg Sc	(*64*)
Sc-EDTA	iv	Mouse	108 mg Sc	(*64*)
Sc-EDTA	ip	Mouse	702 mg Sc	(*64*)
$RE(NO_3)_3$[a]	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*)

[a]Mixture of La, Ce, Nd, Pr, and Sm.

as the dose increased. Even the lethality was abolished at 80 to 100 mg $Pr(NO_3)_3$/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 resposible 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/m^3 of Gd_2O_3 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 pneumoconiosis in humans (*14*). It has been shown that intratracheal instillation of YCl_3 caused granulomatous changes in the rat lung (*16*). Inhalational exposure to high concentrations of Gd_2O_3 (*106*) and intratracheal instillation of YCl_3 (*16*), $LaCl_3$ (*17*), and $GdCl_3$ (*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 YCl_3 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 $Ce(NO_3)_3$ has also been found to cause hepatic necrosis (*96*). Hepatic endoplasmic reticulum (ER) has been shown to be the primary target of iv-injected $CeCl_3$ 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 phenobarbital, which are known to proliferate smooth ER, and estradiol, a putative stabilizer of smooth ER, have been shown to reduce hepatic damage caused by $CeCl_3$ in rats (*101*). It has also been demonstrated that pretreatment with pregnenolone 16α-carbonitrile or nefolopin increased the relative liver weight and significantly reduced mortality caused by iv injection of $CeCl_3$ in mice (*58*), suggesting that the liver is the primary target organ of iv-injected $CeCl_3$.

It has been shown that iv injection of $CeCl_3$ caused fatty liver in female rats (*110,111*) but not in male rats (*111*). Intravenous injection of YCl_3, $TbCl_3$, $HoCl_3$ and $YbCl_3$ caused focal necrosis with Ca deposition in rats but $CeCl_3$ did not (*111*). We have shown that patchy Ca deposition occurred in the focal necrotic area of the rat liver following iv injection of YCl_3 (~50 μg Y/g liver) (*46*). However, the reason that fatty liver was limited to female rats that received $CeCl_3$ remained unknown. It seems that iv injection of $CeCl_3$ 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; those 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 (coumarin 7-hydroxylase and 7-ethoxyresorufin *O*-deethylase) at 3 to 4 days after iv injection of $CeCl_3$ 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 $Pr(NO_3)_3$ in rats; the decrease is probably due to a decrease in hepatic secretion of these lipoproteins (*118*). It has also been reported that ip injection of $CeCl_3$ causes lipid peroxidation and a decease 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 ↑	$CeCl_3$, $Ce(NO_3)_3$, $La(NO_3)_3$,YCl_3	Rat	2–10 mg Ce/kg, 3–10 mg La/kg, 1 mg Y/rat	(*46,112,113*)
	$Pr(NO_3)_3$	Rat, mouse	3–40 mg $Pr(NO_3)_3$/kg	(*105,113–115*)
s-SDH ↑	$Ce(NO_3)_3$, $Pr(NO_3)_3$, $La(NO_3)_3$	Rat	3–10 mg RE/kg	(*113*)
s-OCT ↑	$CeCl_3$, $PrCl_3$, $LaCl_3$	Rat	1.5–3 mg Ce/kg, 3 mg Pr/kg, 0.75 mg La/kg	(*111,116*)
	YCl_3, $TbCl_3$, $HoCl_3$, $YbCl_3$		9 mg Y/kg, 35 mg Tb/kg, 40 mg Ho/kg, 60 mg Yb/kg	
s-FFA ↑	$Pr(NO_3)_3$	Rat	10 mg $Pr(NO_3)_3$/kg	(*117*)
s-VLDL, s-HDL, s-triglyceride ↓	$Pr(NO_3)_3$	Rat	10 mg $Pr(NO_3)_3$/kg	(*118*)
Triglyceride (liver) ↑	$CeCl_3$,	Rat	10 mg $CeCl_3$/kg	(*110*)
	$Pr(NO_3)_3$	Rat, mouse	7 mg Pr/kg, 10–20 mg $Pr(NO_3)_3$/kg	(*105,113,117*)
ATP ↓	$CeCl_3$	Rat	10 mg $CeCl_3$/kg	(*110*)
P450, AH, AD ↓	$Pr(NO_3)_3$	Rat	7 mg Pr/kg	(*113*)
COH, EROD, Cyp2a-4/5-mRNA ↑↓	$CeCl_3$	Mouse	2 mg $CeCl_3$ /kg, 0.5–2 mg Ce/kg	(*109,119*)
RNA polymerase I ↓	$Pr(NO_3)_3$, $Nd(NO_3)_3$	Rat	35 μmol/kg	(*120*)
RNA polymerase II ↑	$Gd(NO_3)_3$, $Dy(NO_3)_3$, $Er(NO_3)_3$	Rat	35 μmol/kg	(*120*)
RNA polymerase II ↓	$Pr(NO_3)_3$, $Nd(NO_3)_3$, $Sm(NO_3)_3$	Rat	35 μmol/kg	(*120*)
LPO ↑	$LaCl_3$	Chick (ip)	250 mg $LaCl_3$/kg	(*121*)
GR ↓	$LaCl_3$	Chick (ip)	250 mg $LaCl_3$/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.

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 triethylenetriaminehexaacetic acid) for 30 min, urinary concentrating ability was decreased and renal vascular resistance was increased (*122*). Ethoxyresorufin *O*-deethylase 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^{3+}-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^{3+}-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 sulfhydryl 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 sulfhydryl 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 synaptosomal membrane.

The median lethal concentration (LC_{50}) for rat alveolar macrophages of CdO, $CdCl_2$, $LaCl_3$, $CeCl_3$, and Nd_2O_3 were 15, 28, 52, 29, and 101 μM, respectively, *in vitro*, and although La_2O_3 and Ce_2O_3 were less toxic than $LaCl_3$ and $CeCl_3$, respectively, Nd_2O_3 was more toxic than $NdCl_3$ (*128*). Cytotoxicity of superconducting particles ($YBa_2Cu_3O_{6-7}$) 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^{3+}-citrate at 20 mg Ce/kg body weight (*95*), and ambulation and rearing were depressed following sc injection of Ce^{3+}-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 adenylate 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 colloid 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 YCl_3 and $LaCl_3$ were deposited in the lysosomes of macrophages and basement membranes of pneumocytes.

Mortality studies reveal that RE are not highly toxic (LD_{50} 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 Ca^{2+} antagonists *in vitro*; however, there are few *in vivo* studies that relate the toxicity of RE to Ca^{2+}-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.

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