Aus dem
Institut für Physiologie, Physiologische Chemie und Tierernährung
der Ludwig-Maximilians-Universität München

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RARE EARTH ELEMENTS IN AGRICULTURE

WITH EMPHASIS ON ANIMAL HUSBANDRY

Inaugural-Dissertation
zur Erlangung der tiermedizinischen Doktorwürde
der Tierärztlichen Fakultät
der Ludwig-Maximilians-Universität München

von

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München 2006

Gedruckt mit Genehmigung der
Tierärztlichen Fakultät der Ludwig-Maximilians-Universität München

Dekan: Prof. Dr. E. P. Märtlbauer
Referent: Prof. Dr. W. A. Rambeck
Korreferent: Prof. Dr. B. Kaspers

Tag der Promotion: 28. Juli 2006

For my Parents

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NOMENCLATURE

Greek Symbols

Symbol	**Definition**
μ	micro (10^{-6})
n	nano (10^{-9})
p	pico (10^{-12})

Physical Units

Symbol	**Definition**
a	year
Å	Ångstrom
°C	degree Celsius
cm	centimeter
cm^2	square centimeter
cm^3	cubic centimeter
d	day
eV	electron volt
g	gram
ha	hectare
IU	International Units
keV	kilo electron volt (10^3eV)
kg	kilogram (10^3g)
kt	kiloton (10^3t)
l	liter
m	meter
mm	millimeter (10^{-3}m)
m^2	square meters

Symbol	**Definition**
m^3	cubic meter
mg	milligram (10^{-3}g)
μg	microgram (10^{-6}g)
min	minute
ml	milliliter (10^{-3}l)
mmol	millimole (10^{-3}mol)
μmol	micromole (10^{-6} mol)
ng	nanogram (10^{-9}g)
pg	picogram (10^{-12}g)
ppm	parts per million 10^{-6} equals to μg/g
ppb	parts per billion 10^{-9} equals to ng/g
s	second
t	ton
[w/v]%	weight/volume percentage solution

Chemical Symbols

Symbol	**Definition**
Al	aluminium
As	arsenic
B	boron
Ba	barium
Be	beryllium
Br	bromine
Br^-	bromide ion
BrO_3^-	bromate ion
C	carbon
Ca	calcium
Ca^{2+}	calcium ion
$CaCO_3$	calcium carbonate
$CaSO_4$	calcium sulfate
Cd	cadmium
Ce	cerium
Ce^{3+}	trivalent cerium ion
Ce^{4+}	tetravalent cerium ion
^{144}Ce	radionuclide of cerium
$CeCl_3$	cerium chloride
$Ce(CH_3COO)_3$	cerium acetate
$Ce(C_6H_5O_7)$	cerium citrate
$Ce(C_6H_7O_6)_3$	cerium ascorbate
$Ce(NO_3)_3$	cerium nitrate
CeO_2	cerium oxide

Symbol	**Definition**
(Ce, La)$(CO_3)F$	rare earth fluorocarbonate
CH_3COO^-	acetate ion
Cl	chlorine
Cl^-	chloride ion
ClO_4^-	perchlorate ion
CO_2	carbon dioxide
$^{14}CO_2$	carbon dioxide
CO_3^{2-}	carbonate ion
$C_2O_4^{2-}$	oxalate ion
$COOH^-$	carboxyl group
Cr	chromium
Cu	copper
Dy	dysprosium
^{157}Dy	radionuclide of dysprosium
$DyCl_3$	dysprosium chloride
$Dy(NO_3)_3$	dysprosium nitrate
Dy_2O_3	dysprosium oxide
Er	erbium
$ErCl_3$	erbium chloride
Er_2O_3	erbium oxide
Eu	europium
Eu^{2+}	europium ion
^{171}Eu	radionuclide of europium
$EuCl_3$	europium chloride
$Eu(NO_3)_3$	europium nitrate
Eu_2O_3	europium oxide
F	fluorine
F^-	fluoride ion
Fe	iron
Gd	gadolinium
$GdCl_3$	gadolinium chloride
$Gd(NO_3)_3$	gadolinium nitrate
Gd_2O_3	gadolinium oxide
Ge	germanium
H	hydrogen
H^+	hydrogen ion
HCl	hydrochloric acid
$HClO_4$	perchloric acid
HNO_3	nitric acid
HCO_2^-	formate
HCO_3^-	hydrogen carbonate ion
H_2O	water
H_2O_2	hydrogen peroxide
Ho	holmium

Symbol	**Definition**
Ho_2O_3	holmium oxide
$HoCl_3$	holmium chloride
$Ho(NO_3)_3$	holmium nitrate
HPO_4^{2-}	hydrogen phosphate ion
I	iodine
I^-	iodide ion
K	potassium
KOH	potassium hydroxide
La	lanthanum
La^{3+}	lanthanum ion
$La(C_6H_5O_7)$	lanthanum citrate
$La(C_6H_7O_6)_3$	lanthanum ascorbate
$La(CH_3COO)_3$	lanthanum acetate
$LaCl_3$	lanthanum chloride
$La(NO_3)_3$	lanthanum nitrate
La_2O_3	lanthanum oxide
$La_2(SO_4)_3$	lanthanum sulfate
Ln	lanthanides
Ln^0	atomic lanthanide
Ln^{2+}	divalent lanthanide ion
Ln^{3+}	trivalent lanthanide ion
$Ln(ap)_6X_3$	lanthanide complexes with antipyrine (X = I or ClO_4)
$LnC_2O_4^+$	lanthanide oxalate ion
$LnC_2H_3O_2^{2+}$	lanthanide acetate ion
$Ln(C_6H_5O_7)_2^{3-}$	lanthanide citrate ion
$LnCl_3 \cdot xNH_3$	lanthanide chloride ammine complexes
$Ln(diket)_3 \cdot H_2O$	lanthanide 1,3 - diketonates
$Ln(EDTA)^-$	lanthanide aminepolycarboxylate ions
$Ln(NTA)_2{}^{3-}$	lanthanide aminepolycarboxylate ions
$Ln(OH)_3$	lanthanide hydroxide
$Ln(On)_3 \cdot nH_2O$	lanthanide 8-quinolinol
$LnPO_4$	lanthanide phosphate
$Ln_4(P_2O_7)^3$	lanthanide diphosphate
$Ln(R\text{-}CHOHCO_2)_6{}^{3-}$	lanthanide α - hydroxycarboxylate ion
$LnSO_3^+$	lanthanide sulfite ion
$LnSO_4^+$	lanthanide sulfate ion
$LnS_2O_3^+$	lanthanide thiosulfate ion
$LnX_3 \cdot yRNH_2$	lanthanide halide amine complexes
Lu	lutetium
Lu^{3+}	lutetium ion
^{177}Lu	radionuclide of lutetium
$LuCl_3$	lutetium chloride
Lu_2O_3	lutetium oxide
Mg	magnesium

Symbol	**Definition**
Mn	manganese
Mo	molybdenum
N	nitrogen
N_2	molecular nitrogen
Na	sodium
NaOH	caustic soda/ sodium hydroxide
NCS^-	thiocyanate ion
Nd	neodymium
Nd^{3+}	neodymium ion
$Nd(CH_3COO)_3$	neodymium acetate
$Nd(C_6H_5O_7)$	neodymium citrate
$NdCl_3$	neodymium chloride
$Nd(NO_3)_3$	neodymium nitrate
Nd_2O_3	neodymium oxide
NH_4^+	ammonium ion
Ni	nickel
NO_3^-	nitrate ion
O	oxygen
O_2	molecular oxygen
O_2^-	peroxide radical
OH	hydroxyl radical
OH^-	hydroxide ion
P	phosphorus
Pm	promethium
^{147}Pm	radionuclide of promethium
PO_4	phosphate
PO_4^{3-}	phosphate ion
Pr	praseodymium
$PrCl_3$	praseodymium chloride
$Pr(CH_3COO)_3$	praseodymium acetate
$Pr(C_6H_5O_7)$	praseodymium citrate
$Pr(NO_3)_3$	praseodymium nitrate
Pr_6O_{11}	praseodymium oxide
$RECl_3$	rare earth chlorides
S	sulfur
Sc	scandium
$ScCl_3$	scandium chloride
Si	silicon
Sm	samarium
^{153}Sm	radionuclide of samarium
$SmCl_3$	samarium chloride
$Sm(NO_3)_3$	samarium nitrate
Sm_2O_3	samarium oxide
SO_4^{2-}	sulfate ion

Symbol	**Definition**
Sr	strontium
Ta	tantalum
Tb	terbium
Tb^{3+}	terbium ion
$TbCl_3$	terbium chloride
$Tb(NO_3)_3$	terbium nitrate
Tb_4O_7	terbium oxide
Ti	titanium
Tl	thallium
Tm	thulium
$TmCl_3$	thulium chloride
Tm_2O_3	thulium oxide
TREO	total rare earth oxides
Y	yttrium
Y^{3+}	yttrium ion
^{90}Y	radionuclide of yttrium
^{169}Y	radionuclide of yttrium
$^{91}YCl_3$	radionuclide of yttrium chloride
Yb	ytterbium
$YbCl_3$	ytterbium chloride
$Yb(NO_3)_3$	ytterbium nitrate
Zn	zinc

Abbreviations

Symbol	**Definition**
AAS	atomic absorption spectroscopy
ACTH	adrenocorticotropic hormone
ADC	absorption capacity
ADI	acceptable daily intake
ADP	adenosine diphosphate
AES	atomic emission spectroscopy
AG	Aktien Gesellschaft
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
ATP	adenosine triphosphate
AUC	under the curve
BW	body weight
BWG	body weight gain
cAMP	cyclic adenosine monophosphate
CAT	catalase

Symbol	**Definition**
CEC	cationic exchange capacity
CF	crude fat
CFC	chlorofluorocarbon
CFU	colony forming units
CIS	Commonwealth of Independent States (former USSR)
CNNA	chemical neutron activation analysis
CP	crude protein
CR	concentration ratio in dry weight of plant per mass in dry weight of soil
CRT	cathode ray tube
DBWG	daily body weight gain
DFD	dark, firm and dry
DGGE	denaturing gradient gel electrophoresis
DLG	Deutsche Landwirtschafts-Gesellschaft (German Agriculture Society)
DM	dry matter
DNA	desoxyribonucleic acid
DPTA	diethylenetriaminopentaacetate
DW	air dried or oven dried weight
EC	European Community
EC_{50}	median effect concentrations
E. coli	Escherichia coli
Ed.	editor
ED_{50}	the median growth concentration
Eds.	editors
EDTA	ethylenediaminetetraacetic acid
EFSA	European Food Safety Authority
e.g.	for example
EMF	endomyocardial fibrose
ESRD	end-stage renal disease
ETH	Eidgenössische Technische Hochschule (Swiss Federal Institute of Technology)
EU	European Union
FAL	Forschungsanstalt für Landwirtschaft (Agriculture Research Institute)
FC	feed conversion
FCR	feed conversion rate
FI	feed intake
FIA	free ion activity model
Fig.	figure
GA_3	gibberellic acid
GABA	γ - aminobutyric acid
GH	growth hormone
GOT	glutamic oxaloacetic transaminase former AST
GPT	glutamic pyruvic transaminase former ALT

Symbol	**Definition**
HPGe	hyperpure germanium
HPLC	high performance liquid chromatography
IAA	indole-3-acetic acid
ICP - MS	inductively coupled plasma-mass spectrometry
Ig	or IG immunoglobulin
IgM	immunoglobulin M
IL	interleukin
i.m.	intra muscular
INAA	instrumental neutron activation analysis
incr.	increased
i.p.	intra peritoneal
IU	international units
i.v.	intra venous
LA - ICP - MS	laser ablation ICP - MS
LC_{50}	the median lethal concentration
LMWOAs	low molecular weight organic acids
LPC	lipid protein complex
ME	metabolic energy
MDA	malonyldialdehyde
MRI	magnetic resonance imaging
n	number of samples
NAA	neutron activation analysis
14C-NAA	α-naphthaleneacetic acid
NADH	reduced form of Nicotinamide adenine dinucleotide
NOEC	non observed effect concentration
NOEL	non observed effect level
NO(A)EL	non observed (adverse) effect-level
n.s.	not significant
OC	osteocalcin
OECD	Organization for Economic Co-operation and Development
OES	optical emission spectrometry
OVX	ovariectomized
p - value	significance
PCR	polymerase chain reaction amplification
PD	pyridinoline
pH_1	pH determined in meat one hour after slaughter
pH_{24}	pH determined in meat twenty four hours after slaughter
p.o.	per os
POD	peroxidase
PSE	pale, soft and exudative
PTH	parathyroid hormone
RE	rare earths
REE	rare earth elements
REO	rare earth oxides

Symbol	**Definition**
RE_2O_3	rare earth oxides
RNA	ribonucleic acid
RNAA	radiochemical neutron activation analysis
ROS	reactive oxygen species
RUSITEC	rumen simulation technique
s.c.	subcutaneous
SD	standard deviation
SOD	superoxide dismutase
SR	stomatal resistance
STH	somatotropin, equal to GH
T_3	triiodothyronine
T_4	thyroxine
TNF-α	tumor necrosis factor alpha
TREO	total rare earth oxides
TSH	thyrotropin, thyroid-stimulating hormone
UV	ultra violet
Vit.	vitamin
WHO	World Health Association
WUE	water use efficiency
YAG	yttrium aluminium garnet

ABSTRACT

CALCULATIONS performed in consideration of a continuously increasing world population have revealed that animal production needs to be enhanced worldwide by at least 2 % each year so as to provide sufficient feed. Yet, effective growth promoting agents, in terms of in-feed antibiotics, have been completely banned throughout Europe due to the possible development and spread of multiresistance in bacteria. New efficient, safe and inexpensive feed additives are therefore needed in order to maintain or even further improve performance levels in animal husbandry. Based upon this information, rare earth elements have been considered as promising natural feed additive. Thus, this study was designed to bring together the current research on rare earths in order to analyze the data obtained and to facilitate the discussion of its relevance to agricultural utilization.

The term *rare earth elements* comprises the elements scandium (21), yttrium (39), lanthanum (57) and the 14 chemical elements following lanthanum (58 - 71) called lanthanoids. Favoring the tripositive oxidation state, rare earths present a high affinity for ionic bonding, thus a large number of both organic and inorganic rare earth salts may be formed. Nevertheless, rare earths may also form complexes especially with chelating oxygen ligands. In nature, rare earths occur in multiple minerals, such as bastnaesite and monazite which are mainly used for industrial production. Today, rare earths are part of several daily used devices such as lighters, television sets and computers. Additionally they are found in medical technology, nuclear engineering, automobile industry, military devices and even in spacecraft. Furthermore, rare earth-containing drugs are used for the treatment of hyperphosphatemia in chronic renal failure patients and for burn treatment. Based upon their paramagnetic properties, rare earths, especially gadolinium, have also been arranged as contrast agents in magnetic resonance imaging and computer tomography. In the future, among other uses, rare earths might be involved in cancer therapy, treatment and prevention of osteoporosis and atherosclerosis as well as organ transplantation.

In China, rare earths have been successfully used at low concentrations as feed additives and fertilizers for decades. Yet, careful interpretation of Chinese data is recommended due to the fact that Chinese papers are often only available in native language and furthermore not up to standard with Western scientific research reports, hence lacking statistical treatment of data and details of experimental methods. However, in China, both yield increases and quality improvements were achieved in multiple plant species including cereals, fruits and vegetables after rare earth application. Recommended application rates vary with the crop species, the application technique (soil, foliar or seed dressing) as well as the timing.

As feed additives, rare earths were shown to improve body weight gain and feed conversion in nearly all categories of farming animals (chickens, pigs, ducks, cattle). Additionally, improvements in milk production in dairy cows, in egg production in laying hens and in output and survival rate of fish and egg hatching of shrimps were noticed. Feed additives used thereby predominantly contain light rare earths (La, Ce, Pr, Nd) but even though both organic (nitrates, chlorides etc.) and inorganic (ascorbates, citrates etc.) rare earth feed additives are commercially available, organic ones are claimed to provide better results.

Based on the effects reported in Chinese studies, experiments were initiated under Western conditions in order to investigate the action of rare earths on both plant and animal growth. Several Western feeding trials conducted on animals have been able to demonstrate significant performance enhancing effects after dietary rare earth application, while results obtained from experiments on the effects of rare earths on plant growth have been controversial. In pigs, improvements in body weight gain of up to 19 % and in feed conversion rate of 10 % were observed after their diets were supplemented with low-dosed rare earth chlorides. Even better effects were however noticed after rare earth citrates were added to the feed of pigs. Furthermore, under field conditions, rare earths were shown to increase body weight gain by up to 10 % and improve feed conversion by up to 9 % in pigs. Following these results, rare earth containing feed additives in terms of *Lancer*® have entered the market in Switzerland, where a temporary permission has been granted for their use in pig production.

In addition, in broilers, rare earths were also shown to increase final weights by 7 % and improve feed conversion by up to 3 %. Very recent studies also confirmed performance enhancing effects in broilers with increased body weight gain and feed intake of up to 6.6 % and 6.9 %, respectively. In rats, which were used as a small animal model, improvements in body weight gain and feed conversion of 4 - 7 % and 3 - 11 %, respectively, followed the application of rare earths. Thus, clear performance enhancing effects were achieved in Western studies on rats, pigs and poultry due to dietary rare earth supplementation. However, there are also studies in which positive effects of rare earths on animal performance were not as obvious or not observed at all.

A comparison between the results of these feeding experiments as to the mixture of rare earths, the concentration as well as the compound applied showed that these parameters are involved in the magnitude of performance enhancing effects of rare earths. At present, no definitive statement on optimum composition can be made. However, a dose-dependency was observed in several trials and better effects have been achieved when the mixture of rare earths was applied instead of single lanthanum. Additionally, it seems that organic rare earth compounds have a higher impact on animal performance than inorganic ones. This is probable ascribable to different chemical characteristics, which lead to variations in both absorption and bioavailability.

Generally, absorption of orally applied rare earths is very low, with more than 95 % being recovered in the feces of animals. According to minute gastrointestinal absorption of rare earths, oral toxicity is very low and comparable to usual table salt. LD_{50} values determined in various animal experiments rang from 830 mg/kg to 10 g/kg body weight. None of the feeding trials performed reported any effects on the state of health of the animals, which coincides with low oral toxicity and additionally supports the safe application of rare earth feed additives to animals. In addition, no effects on either meat or carcass quality were observed. Likewise, rare earth concentrations determined in organ samples were very low and similar or even lower than in control animals. This is attributed to the ubiquitous occurrence of rare earths, thus also in plants and soils. As a result they also appear in commercial diets and subsequently in animal and human tissue. It has also been shown that rare earth contents in usual vegetable foodstuff are still higher than those in meat obtained from animals additionally fed with rare earths. Therefore, the application of rare earths as feed additive is also considered to be safe for humans.

Furthermore, as to current knowledge, no damage is to be expected on the environment as a consequence of rare earth application to agriculture. In fact, as rare earths can improve feed conversion, they may support the efficient use of natural resources, while additionally reducing environmental loads in terms of animal excrements. Hence, with respect to animal, human and environmental safety, rare earths meet legal recommendations of the European Union for their registration as feed additive.

Although the mechanism underlying performance enhancing effects of rare earths is not completely understood, several proposals have been made. According to current research, rare earths might exert their action locally within the gastrointestinal tract, including effects on the bacterial micro-flora as well as on nutrient uptake, digestibility and utilization. Likewise, anti-inflammatory and anti-oxidative effects may also contribute to positive effects. Additionally, actions on the intermediate metabolism in terms of effects on cellular functions, growth- and digestibility-related hormones and enzymes or the immune system have also been considered. It might also be possible that rare earths are not yet identified essential elements.

Based on the information gained in this study, it has been concluded that rare earths are of high interest as possibly new, safe, inexpensive feed additive in Europe, especially in pig and poultry production.

KURZFASSUNG

Vor dem Hintergrund der stetig zunehmenden Weltbevölkerung, wurden Berechnungen angestellt, die ergaben, dass die Herstellung von tierischen Nahrungsmitteln weltweit jährlich um mindestens 2 % ansteigen muss, um eine ausreichende Lebensmittelversorgung gewährleisten zu können. In Europa wurden jedoch potente Leistungsförderer in Form von Fütterungsantibiotika verboten, um der Entstehung und der Verbreitung resistenter Bakterien vorzubeugen. Neue effektive, sichere und kostengünstige Futterzusatzstoffe werden daher benötigt, um das Leistungsniveau von Nutztieren aufrechterhalten zu können bzw. dieses nachhaltig zu verbessern. Aufgrund dieser Entwicklung werden Seltene Erden als vielversprechende natürliche Futterzusatzstoffe in Betracht gezogen. Diese Arbeit wurde daher mit dem Ziel angefertigt, einen Überblick über den gegenwärtigen Forschungsstand zur Anwendung Seltener Erden in der Landwirtschaft zu schaffen, sowie die aus der Literatur gewonnenen Daten zu analysieren und dadurch die Diskussion bezüglich ihrer Relevanz in der Landwirtschaft zu ermöglichen.

Die Gruppe der Seltenen Erden umfasst die Elemente Scandium (21), Yttrium (39), Lanthan und die 14 auf das Lanthan folgenden Elemente (58 - 71), die sogenannten Lanthanoide. Da die Seltenerdelemente bevorzugt im dreifach positiven Oxidationszustand vorkommen, sind sie in der Lage eine Vielzahl sowohl organischer als auch anorganischer Salze zu bilden. Seltene Erden können darüber hinaus auch Komplexe eingehen, besonders mit chelatbildenden Sauerstoffliganden. In der Natur kommen Seltene Erden in verschiedenen Mineralien vor. Für die industrielle Produktion werden vor allem Bastnäsite und Monazite verwendet. Heutzutage findet man Seltene Erden in einer Vielzahl täglicher Gebrauchsgegenstände, beispielsweise in Feuerzeugen, Fernsehern und Computern. Außerdem finden sie Anwendung in der Medizintechnik, der Kernkrafttechnik, der Automobilindustrie, der Rüstungstechnik sowie in der Raumfahrttechnik. Darüber hinaus werden Seltene Erden auch als Bestandteil von Medikamenten zur Behandlung der Hyperphosphatemie infolge chronischen Nierenversagens und in Salben zur Behandlung von Brandverletzungen eingesetzt. Aufgrund ihrer paramagnetischen Eigenschaften haben sich Seltene Erden, vor allem Gadolinium, als Kontrastmittel in der Kernspinresonanz- und der Computertomographie bewährt. Zukünftige Anwendungsgebiete könnten die Krebstherapie, die Therapie und Prävention von Osteoporose und Atherosklerose sowie Organtransplantationen umfassen.

In China werden Seltene Erden in geringer Dosierung seit Jahrzehnten erfolgreich als Futterzusatzstoffe und Düngemittel eingesetzt. Bei der Beurteilung chinesischer Daten ist jedoch Vorsicht geboten, da chinesische Artikel häufig nur in der Landessprache veröffentlicht werden und des Öfteren Angaben zu Statistik und Details des Versuchsaufbaus fehlen. Sie entsprechen daher oftmals nicht dem Standard wissenschaftlicher Forschungsberichte westlicher Länder. Es

ist jedoch unbestritten, dass durch die Anwendung Seltener Erden in China der Ertrag zahlreicher Pflanzenarten, darunter verschiedene Getreide-, Früchte- und Gemüsesorten, sowie deren Qualität verbessert werden konnte. Die empfohlene Art der Anwendung hängt von der Pflanzenart, der Anwendungstechnik (Boden-, Blatt- und Samenbehandlung) aber auch von der Jahreszeit ab.

Darüber hinaus konnte durch die Verfütterung Seltener Erden bei fast allen Nutztierarten (Hühner, Schweine, Enten, Rinder) eine Verbesserung der Körpergewichtszunahme und Futterwertung erzielt werden. Zusätzlich wurde eine Steigerung der Milchproduktion bei Milchkühen und der Eierproduktion bei Legehennen, sowie eine verbesserte Leistung und Überlebensrate bei Fischen und eine erhöhte Schlupfrate bei Garnelen beobachtet. Die dabei verwendeten Futterzusatzstoffe enthielten überwiegend leichte Seltenerdelemente (La, Ce, Pr, Nd). Es sind sowohl organische als auch anorganische Seltenerdfutterzusatzstoffe auf dem Markt erhältlich, bessere Resultate wurden jedoch mit organischen erzielt.

Die in der chinesischen Literatur beschriebenen Effekte veranlassten dazu, die Wirkung Seltener Erden auf das Pflanzen- und Tierwachstum unter westlichen Bedingungen zu untersuchen. Mehrere westliche Studien konnten zeigen, dass die Verfütterung Seltener Erden an Tiere zu einer signifikanten Verbesserung der Leistung führte, während Studien hinsichtlich ihrer Effekte auf das Pflanzenwachstum zu sehr unterschiedlichen Ergebnissen kamen. Bei Schweinen, deren Futter mit Seltenen Erden in Form von Chloriden in niedriger Dosierung ergänzt wurde, konnte eine um bis zu 19 % erhöhte Körpergewichtszunahme und eine um bis zu 10 % verbesserte Futterverwertung beobachtet werden. Weiter verbesserte Ergebnisse wurden erzielt, wenn Seltenerdcitrate dem Schweinefutter hinzugefügt wurden. Des Weiteren konnten Seltene Erden, die in Feldversuchen bei Schweinen eingesetzt wurden, die Körpergewichtzunahme um bis zu 10 % sowie die Futterverwertung um bis zu 9 % verbessern. Daraufhin sind seltenerdhaltige Futterzusatzstoffe als *Lancer*® in der Schweiz auf den Markt gekommen. Derzeit besteht in der Schweiz für die Anwendung Seltener Erden in der Schweineproduktion eine zeitlich begrenzte Genehmigung.

Zusätzlich konnten Seltene Erden bei Hühnern das Endgewicht um 7 % und die Futterverwertung um bis zu 3 % verbessern. Erst kürzlich durchgeführte Studien waren in der Lage, diese leistungsfördernden Effekte bei Hühnern zu bestätigen. Es wurde dabei von einer um bis zu 6,6 % erhöhten Körpergewichtszunahme und einer um 6,9 % verbesserten Futteraufnahme berichtet. Bei Ratten, die als Kleintiermodel verwendet wurden, verbesserten oral verabreichte Seltene Erden die Körpergewichtszunahme um 4 bis 7 % sowie die Futterverwertung um 3 bis 11 %. In westlichen Studien konnten demzufolge durch die zusätzliche Verfütterung Seltener Erden an Ratten, Schweine und Geflügel deutliche leistungsfördernde Effekte erzielt werden. Es wurde jedoch auch von Studien berichtet, in denen Seltene Erden nur schwache oder keine positiven Effekte auf die Leistung von Tieren ausübten.

Ein Vergleich der in Fütterungsexperimenten erzielten Ergebnisse hinsichtlich der verwendeten Mischungen, Konzentrationen und chemischen Verbindungen Seltener Erden hat ergeben, dass diese Parameter das Ausmaß der leistungsfördernden Effekte beeinflussen können. Eine abschließende Angabe zur optimalen Zusammensetzung kann derzeit noch nicht gemacht werden. Konzentrationsabhängige Effekte konnten jedoch in verschiedenen Studien festgestellt werden und bessere Effekte wurden erreicht, wenn eine Mischung Seltener Erden anstelle eines reinen Lanthans verwendet wurde. Des Weiteren haben organische Seltenerdverbindungen einen größeren Einfluss auf die Leistung als anorganische, was vermutlich auf chemische Unterschiede zurückzuführen ist, die ihrerseits zu Veränderungen in der Absorption und der Bioverfügbarkeit führen können.

Die Absorption oral verabreichter Seltener Erden ist generell sehr gering; mehr als 95 % wurden im Kot der Tiere wiedergefunden. Entsprechend der minimalen gastrointestinalen Aufnahme zeigen Seltene Erden eine sehr geringe orale Toxizität, die vergleichbar mit der von gewöhn-

lichem Kochsalz ist. LD_{50} Werte von 830 mg/kg bis 10 g/kg Körpergewicht wurden in mehreren Tierversuchen ermittelt. In Übereinstimmung mit der geringen oralen Toxizität, konnte in keinem der durchgeführten Fütterungsversuche eine Beeinträchtigung des Gesundheitszustandes der Versuchstiere festgestellt werden, was zusätzlich für eine sichere Anwendung Seltener Erden als Futterzusatzstoffe spricht. Außerdem konnten keine nachteiligen Effekte auf die Fleisch- oder die Schlachtkörperqualität beobachtet werden. Ebenso waren die Konzentrationen Seltener Erden in Organproben nur sehr gering und lagen in der gleichen Größenordnung wie die der Kontrolltiere oder sogar darunter. Die Begründung dafür liegt in dem ubiquitären Vorkommen Seltener Erden, also auch in Pflanzen und Böden und somit ebenfalls in kommerziellen Nahrungsmitteln. Sie sind daher auch in tierischem und menschlichem Gewebe zu finden. Es konnte gezeigt werden, dass der Gehalt Seltener Erden in pflanzlichen Lebensmitteln immer noch höher liegt als in Fleischprodukten, die von Tieren stammen deren Futter mit Seltenen Erden ergänzt wurde. Demnach ist der Einsatz Seltener Erden als Futterzusatzstoff für lebensmittelliefernde Nutztiere auch für den Menschen unbedenklich.

Darüber hinaus verursacht die Anwendung Seltener Erden in der Landwirtschaft nach heutigem Wissenstand auch keinerlei Umweltschäden. Vielmehr können Seltene Erden als Futterzusatzstoffe zu einer effizienteren Nutzung der natürlichen Ressourcen beitragen und zusätzlich die Umweltbelastung reduzieren, indem sie die Futterverwertung verbessern und dadurch die Ausscheidung tierischer Exkremente vermindern. Hinsichtlich der Sicherheit für Mensch, Tier und Umwelt erfüllen Seltene Erden hiermit die gesetzlichen Anforderungen der Europäischen Union für die Zulassung als Futterzusatzstoff.

Der den leistungsfördernden Effekten zugrundeliegende Mechanismus ist derzeit noch nicht vollständig geklärt, es wurden diesbezüglich jedoch einige Theorien aufgestellt. Entsprechend dem heutigen Stand der Forschung entfalten Seltene Erden ihre Wirkung vermutlich lokal im Magen-Darm-Trakt durch Einflussnahme auf die bakterielle Mikroflora oder auf die Aufnahme, Verdaulichkeit und Verwertung von Nährstoffen. Entzündungshemmende und antioxidative Effekte könnten ebenfalls positive Einflüsse haben. Zusätzlich wird eine Wirkung auf den intermediären Stoffwechsel, also auf zelluläre Funktionen und auf Hormone und Enzyme, die an Wachstums- und Verdauungsprozessen beteiligt sind, oder auf das Immunsystem in Betracht gezogen. Es besteht auch die Möglichkeit, dass es sich bei Seltenen Erden um derzeit noch nicht identifizierte essentielle Spurenelemente handelt.

Basierend auf den Erkenntnissen dieser Arbeit sind Seltene Erden auch für die europäische Landwirtschaft, besonders im Hinblick auf die Schweine- und Geflügelproduktion, als möglicher neuer, sicherer und kostengünstiger Futterzusatzstoff von großem Interesse.

CHAPTER 1

INTRODUCTION AND AIM OF THE THESIS

IN the past Chinese applications, especially medical treatments, were given a variable reception in the West. While some of them, like acupuncture, were keenly taken over and established because it can treat not only daily problems, like headaches and stress release, effectively but also more severe problems, such as pain relief in emergency medicine, other treatments favored by traditional Chinese medicine, such as the treatment of infertility in humans, are still considered to be ineffective and predominantly based upon placebo effects. However, it is strange that Chinese advances in agriculture with rare earths, which include enhanced plant and animal growth, were delayed so long from being transferred to the West. One explanation may be that the changeable reputation of Chinese medicine in the West was too easily led to a neglect of Chinese agricultural achievements in the application of rare earth elements, even though Chinese agricultural improvements are not in any way related to Chinese traditional medicine. However, ever since the valuable research on rare earth application to agriculture became known and Chinese achievements were acknowledged, the interest has greatly grown all over the world. Now it is well-known that the term rare earth elements refers to several elements in the periodic system: scandium, yttrium and lanthanum as well as the 14 elements following lanthanum (58 - 71) called lanthanoids. It is also known that applications of these elements can be made in various practical disciplines. Thus there is a real need to collect the research in China, as far as it is available, as well as in other countries, both in agriculture and in other disciplines.

This situation was the starting point for this thesis, which intends to assemble the current knowledge as it is presented in the various studies while emphasizing the application of rare earths to agriculture. Until now, only a few scientists have probed this enlarged field of Chinese rare earth application under Western conditions. Earlier studies were limited in number and pointed to the need for further studies. However, it was the complete ban on in-feed antibiotics from the European market as of the beginning of 2006, which accentuated the need of further investigations and temporary try-outs of rare earths, with a view to their potential use as new feed additives. Presently, there is no official authorization for the use of rare earths as either fertilizers in plant production or feed additives in animal husbandry within the European Union. Only Switzerland has been granted a temporary permission for the dietary application of rare earths in terms of *Lancer*® to pig production in 2003. The validity of this permission has just recently been extended until 2007. On this basis, it is the aim of this study to fill the need for more information on rare earths by presenting a comprehensive overview of current research on rare earths. Besides bringing together the available literature, this study additionally strives for an evaluation of this data. With respect to rare earth studies in Western countries, it is the objective of this thesis to assemble the basic information as well as available information on the increasing number of rare earth applications. Additionally the study will concentrate on the effectiveness of rare earths in terms of performance enhancements in agriculture with emphasis on animal production. Prospective future uses of rare earth elements, especially in Western agriculture, will also be considered and discussed by giving close attention to the potential function of rare earth elements as feed additives in animal husbandry. It is hoped that the information gained from these reports may pave the way for their registration as feed additive in Europe in addition to contributing to a comprehensive discussion of current views on the effectiveness of rare earth elements in agriculture.

The thesis will be divided in various chapters which move from theory to application. Thus, Chapter 2 briefly comments on the source materials that provide the basis for this study. It will be followed by a presentation of the theoretical background, including the discovery of rare earth elements, their occurrence, natural deposits and mining, the chemistry and physics of rare earths and their most important biochemical and pharmacological properties, which is provided in Chapters 3 to 5. The theoretical background will be carried on with information on the metabolism and toxicology of rare earths in Chapter 6. This will be followed by relevant information on the environmental impact of extensive rare earth use in industry, agriculture and animal husbandry in Chapter 7. Chapter 8 is then devoted to quantitative analytical methods for the determination of rare earth elements, because nearly all studies performed on rare earths depend on accurate and reliable methods of analysis. Two methods, inductively coupled plasma (ICP) - mass spectrometry and neutron activating analysis (NAA) will be treated with priority, since they are predominantly used in environmental (soil, rock and plant) analysis and animal experiments. Thus, it is hoped that a selection of theoretical areas that are directly relevant to the applications of rare earths will facilitate the explanation and evaluation of the research studies and avoid too much repetitiousness.

Chapter 9 starts with the report on rare earth applications. It briefly describes the uses of rare earths in technical and industrial areas including carbon-arc-lighting, lighter flints, coloring and decoloring of glass, television tubes, catalysts and lasers, while applications of rare earth elements to medicine are then outlined in Chapter 10. It will be shown that former uses of rare earths were limited to anti-vomiting agents in pregnancies and anticoagulation agents. But nowadays, drugs such as lanthanum carbonate, a newly registered phosphate binder, or cerium nitrate for the treatment of burns, are available, while, gadolinium chloride, a contrast agent, has been proven beneficial in several imaging studies.

Chapter 11 deals with the application of rare earths as fertilizer to agriculture in China, but also discusses experiments conducted under Western conditions in Australia and Europe, which aimed at investigating the yield enhancing effects of rare earths on different plant species. Furthermore information on the uptake and the bioavailability and on the concentrations of rare earths in plants is provided which leads into a description of the possible mechanism behind yield improving effects and ultimately into a discussion of future research needs.

Chapter 12 gives a detailed report on rare earth application to animal husbandry in China, including several feeding trials. It also specifically describes experiments carried out so far in Germany and Switzerland which were designed to investigate performance enhancing effects of rare earths on different animals, such as rats, pigs, Japanese quails, chickens, calves and fish. This leads into information on the safety of rare earth application, absorption and bioavailability as well as on the mode of action and ultimately into a discussion of their performance enhancing effects on animals. Based on the information gained from Chapters 3 to 12, Chapter 13 discusses the current views on the effectiveness of rare earth elements in animal production and provides perspectives for the future. This chapter particulary deals with potentially arising questions, such as: "Is the mixture of elements or one element itself responsible for growth enhancing effects? Is there a clear dose-dependency in effectiveness? Does it matter which anion is bound to rare earths?". These questions can give a perspective for further research. Finally, the thesis's conclusions for the adoption of rare earths in animal production will be delineated. The tables referred to within the report will be found in Appendices A to D in order to provide a concise design.

CHAPTER 2

RESEARCH SOURCES AND THEIR METHODOLOGY

THE search for sources of available studies within this thesis was extended to books, papers as well as to personal communication. This chapter therefore aims at presenting some overall information on currently available rare earth studies which were relevant to this report. In addition to information on their source and reliability research methods applied and problems revealing thereby are also described.

The literature on rare earth elements is fairly heterogeneous. First of all there are several hundred Chinese papers. Unfortunately a lot of these published papers originate from sources which are still hard to assess, because many of them, especially the older ones, are often completely written in Chinese or only attach an abstract in English. Also many Chinese papers, especially older ones, are not up to standard of Western scientific research reports due to a lack of information on their experimental methods and the absence of a rigorous statistical treatment of data. The lack of such essential information makes a critical evaluation of Chinese data rather difficult. Hence, a careful interpretation of data from China was necessary and has been attempted in this study. However, there are a few readily available Chinese papers, especially more recent ones which have either been partly or completely translated into English, meet Western criteria and have been treated on the basis of such criteria.

Besides literature from China, there is a number of studies in English which partly dates back to the first half of the last century, especially in regard to physical, chemical, biochemical and pharmacological features of rare earths. Some of that information has not yet been updated, thus current information on them is rare. The same applies to literature on their toxicological and metabolic behavior of rare earths. Even toxicological data presented on the home pages of rare earth producing companies mainly refers to papers dating back to the 1960s and 1970s. Only recently, that is with the introduction of new rare earth containing drugs, more information on their toxicity has become available.

However, there is also a good number of current papers from several Western countries, which clearly meet the scientific criteria in terms of statistical evaluation, material and methods and which were included in this thesis. Although many papers on rare earths are available, only a few monographs exist. Among them are mostly older ones such as Vickery (1953), Vickery (1960), Möller (1963), Trifonov (1963), Topp (1965), Evans (1990), Brown et al. (1990), Gmelin (1938 - 1993) and only few recent ones such as Sigel et al. (2003).

Additionally to books and papers, useful information has also been obtained through personal contact with M. L. He, a Chinese scientist, who works on rare earths through a research fellowship that is supported by the Humboldt Foundation (2005 - 2006), and from H. Richter, an expert in rare earth chemistry. M. L. He and his wife Shuyuan Li have provided several Chinese data, which they themselves translated into English.

A search in the internet has also produced information on rare earths which was made available in the websites of rare earth producing companies both in China and in Western countries. Their websites are listed below.

- `http://www.cre.net/english/index.asp`
- `http://www.brire.com`
- `http://www.beyondchem.com`
- `http://www.lanthanoide.de`
- `http://www.zehentmayer.ch`
- `http://www.sano-pharm.ch`
- `http://www.treibacher.com`
- `http://www.shire.com`
- `http://www.rhodia-ec.com`
- `http://www.molycorp.com`

In this thesis some recurring terms will be abbreviated, such as *rare earths* or *rare earth elements* as *RE* or *REE*. It is also worthy of note that the term "rare earths" is frequently used synonymously with *lanthanides*, shortened as Ln. Although, they are not identical in a strict sense, as further explained in Chapter 4; their equivalent use is often convenient not only in older literature but also in this study. It will also be noticed that rare earth studies conducted within the fields of physics, chemistry, biochemistry and pharmacology as well as in many medical studies, prefer the term lanthanide, whereas studies in agriculture predominantly use the term *rare earths*, in German *Seltene Erden* and in French *terres rares*, respectively.

The term *rare earths* refers to the elements scandium, yttrium and lanthanum as well as the 14 elements following lanthanum. Since they exhibit various useful chemical, physical, biochemical and pharmacological properties, the field of their application is enormous. On the one hand, they can be seen in common daily objects such as flints, carbon arc lights, glass additives, polishing agents, permanent magnets and liquid crystal display flat screens, and on the other hand, they can be used as medicinal agents. Lanthanum carbonate, for example (trade name *Fosrenol*®), has recently entered the European market. It is an important new drug for the treatment of hyperphosphatemia in patients suffering from chronic renal failure. Additionally, medical technology, including magnetic resonance tomography, has been greatly improved by the use of rare earth containing contrast agents (such as gadolinium chloride), which are applied intravenously. Extensive research has opened up even new areas of rare earth application. In China, for example, their utilization has already exceeded technical areas by breaking into the extensive field of agriculture. Almost none of the other elements in the periodic system has established a similar usefulness in so many different fields and modes of application. Thus, rare earth elements are somehow peculiar and special.

Nevertheless, in order to assess the usefulness of rare earths in different areas of application further aspects need to be considered. Therefore, Chapters 3 - 5 offer a gradual learning about their specific features. In addition, background information given in Chapters 9 - 12 will explain why rare earths can enter so many various fields and even conquer the area of agriculture including animal production. Potential adverse aspects, on the other hand, such as toxicological features and environmental hazards must not be neglected and are treated in detail in Chapters 6 and 7. Additionally, Chapter 8 provides information on rare earth analysis since a reliable method of qualitative and even more important quantitative detection is essential for the determination of rare earth contents in animal tissues, in environmental or food samples or in medical preparations.

However, the usefulness of rare earth properties for industrial production and commerce greatly depends on the accessiblility of rare earthes in the needed amounts. Therefore, some information on their occurrence and distribution will be added in Section 3.2. But generally speaking, it can be said that, despite their name, rare earth elements are quite abundant in the earths crust with Ce being the 25th most abundant element at 60 ppm, ahead of tin and lead and only a little less abundant than zinc (Calvert, 2003), (Brown et al., 1990), (Topp, 1965). For several applications, purified individual elements are more essential than a mixtures. Thus, a brief description on recovery and separation techniques of rare earths is also given in line with background information.

Concerning research emphases, it will be shown that research on the physics and chemistry of rare earths or on their biochemical and pharmacological features dates back to the first half of the last century. This is due to the fact that during that time the interest on rare earths had just started and there was a great interest in revealing the potential of rare earths. Since then, only little further research has been conducted in this field. Thus, several facts described in Chapters 3 to 6 are based on information obtained from older literature dating back to 1960s, 1950s or sometimes even further back. With increased research on their possible growth enhancing properties as well as with the introduction of new rare earth-containing drugs in human medicine, research on the metabolism and toxicity of rare earths has progressed. Therefore, new information has become available, while older one has been confirmed.

CHAPTER 3

DISCOVERY, OCCURRENCE AND SEPARATION TECHNIQUES OF RARE EARTH ELEMENTS

3.1 Discovery of Rare Earth Elements

THE history of the discovery of rare earth elements is one of the most complex and confusing areas in inorganic chemistry and has produced two hundred years of trial, error and false claims which reflect its peculiar nature within the periodic system.

First discovered, in 1788, by the Swedish army lieutenant Karl Axel Arrhenius, who collected the black mineral ytterbite, named after the nearby Swedish town, their special chemical structure was the reason for spending so much time on distinguishing the individual elements within the group of lanthanides. As rare earth elements could not be properly arranged into any table, no information on the number of existing elements was available. Thus, fractional crystallization was the only method used for the purification of elements at that time and multiple recrystallizations were necessary that in turn caused various false claims on the nature of rare earth elements (Holden, 2001). In 1794, Gadolin isolated ytterbia from the mineral ytterbite, containing mainly yttrium, middle and heavy earths. The discovery of ytterbia, shortened to yttria by Ekeberg 1797, aroused the interest of many scientists, particularly Berzelius, Vauquelin and Klaproth. Soon after, Berzelius and Hisinger and, independently of them, Klaproth, found a new oxide which was named ceria after the Latin goddess of agriculture. The mineral cerite predominantly contains light earths. Yttria and ceria presented similar properties and provided a basic mineral from which light and heavy earth groups could be subsequently isolated. Analyzing a cerite sample, Vauquelin found out that ceria has two degrees of oxidation. This was an important discovery which later established the presence of two valency states of cerium. In 1839, the chemist Mosander extracted lanthanum (meaning to lie hidden in Greek) from ceria, while two years later he separated another new earth called didymia (referring to the twin brother of lanthana; from Greek *dymium* - twin) from lanthanum oxide (1841). By fractional precipitation he obtained three oxides yttria, the pink terbia and the yellow erbia (1843).

After a relation between the chemical properties of the elements and their atomic weight was established and presented in line with the periodic law (Mendeleyev), further thorough studies on rare earth elements were conducted. The development of spectroscopic methods of analysis and the exploration of electrochemical separation led to the discovery of a new earth, ytterbia, from Mosander's erbium nitrate (C. Marignac 1878). A year later, Nilson (1879) isolated scandia and Cleve (1879) thulia (named after Thule, the roman name for the northernmost region of the inhabitable world) and holmia (Latin for Stockholm) from erbia (1879). In the same year, de Boisbaudran extracted samaria (named after an Russian engineer) and gadolina from didymium seven years later. He also discovered a third component of erbia, called dysprosia (Greek *dysprositos* - difficult to obtain), in 1886. Von Welsbach separated didymium into two constituents - neodymium (Greek *neo* - new) and praseodymium (Greek *prasios* - green) (1885) by using fractional crystallization. A similar procedure helped Demarcay to derive europium (from Europe) from samaria (1901). In 1907, Urbain extracted neo-ytterbia and lutetia (the Latin name of Paris) from ytterbia, earlier discovered by Marignac, while the same result was obtained by Von Welsbach in 1908. Apart from promethium, all elements had been discovered by 1907. It was not until 1947, that promethium (named after the Greek god) was chemically separated from fission fragments of uranium, which were produced by neutrons, through the use of ion exchange chromatography (Marinsky, Glendenin and Coryell) (Marinsky et al., 1947), (Möller, 1963), (Trifonov, 1963), (Topp, 1965), (Evans, 1990), (Holden, 2001), (Calvert, 2003), (Fachschaft Chemie, 2005), (Richter and Schermanz, 2006). Information on the discovery of the rare earth elements including the classifiers: element, year of discovery, discoverer and origin of the name given, are summarized in Table 3.1.

Considering the limitations of the techniques and efforts available, the early work on separation of rare earths was outstanding. Today, high purity isolates for commercial use are mainly obtained by solvent extraction while ion exchange resins are used in rather special cases.

	Discoverer	Year of discovery	Origin of name
Lanthanum	Mosander	1839	from Greek Lanthanein = to lie hidden
Cerium	1st Berzelius and Hisinger 2nd Klaproth	1803	Ceres, an asteroid discovered in 1801 which is named after the Latin goddess of agriculture
Praseodymium	Von Welsbach	1885	from Greek Prasios = green, dymium = twin
Neodymium	Von Welsbach	1885	from Greek Neo = new, dymium = twin
Promethium	Marinsky, Glendenin, Coryell	1947	Prometheus, the Greek god who stole fire from heaven for men’s use
Samarium	De Boisbaudran	1879	from its ore, samarskite, named after the Russian engineer Samarski
Europium	Crookes	1889	Europe
Gadolinium	Marignac	1880	after the Finnish chemist Gadolin
Terbium	Mosander	1843	after the town of Ytterby in Sweden
Dysprosium	De Boisbaudran	1886	from Greek Dysprositos = hard to get at
Holmium	1st Soret, 2nd Cleve	1879	from Latin Holmia = Stockholm
Erbium	Mosander	1843	after the town of Ytterby in Sweden
Thulium	Cleve	1878	after Thule, the Roman name for the nothernmost region of the inhabited world
Ytterbium	Marignac	1878	after the town of Ytterby in Sweden
Lutetium	1st Von Welsbach, 2nd Urbain	1908, 1907	from Latin Lutetia = Paris
Yttrium	Gadolin	1794	after the town of Ytterby in Sweden
Scandium	Nilson	1879	Scandinavia

Table 3.1: Discovery of rare earth elements.

3.2 Occurrence and Distribution of Rare Earth Elements

Occurrence and distribution of rare earths are not only of interest because of their usefulness for industry but also because they have raised a discussion whether rare earths might be essential for plants, animals and even humans. As a group, rare earths constitute the fifteenth most abundant component of the earth's crust; thus they are not rare at all. The most plentiful rare earth elements, cerium and yttrium, occur more often in the earth's crust than lead, molybdenum or arsenic. Lanthanum and neodymium occur in similar quantities as lead. But even thulium, the *rarest* of the rare earth elements, can be found more often than gold, platinum or iodine (Reiners, 2001), (Brown et al., 1990), (Topp, 1965), (Fachschaft Chemie, 2005), (Richter and Schermanz, 2006). Table 3.2 provides the approximate average abundance values of the lanthanides in the earth's crust. Approximate values usually are in the range of 150 mg/kg. In addition, rare earths are also found in very small amounts in plant and animal tissues. Promethium, however, has only been found in very small amounts in uranium ore deposits (Richter, 2006).

	Evans (1990) and Möller (1963)	Taylor and McLennan (1985)
Lanthanum	18.0	16.0
Cerium	46.0	33.0
Praseodymium	5.5	3.9
Neodymium	24.0	16.0
Promethium	–	–
Samarium	6.5	3.5
Europium	1.1	1.1
Gadolinium	6.4	3.3
Terbium	0.9	0.6
Dysprosium	4.5	3.7
Holmium	1.2	0.8
Erbium	2.5	2.2
Thulium	0.2	0.3
Ytterbium	2.7	2.2
Lutetium	0.8	0.3
Yttrium	28.0	20.0
Scandium	–	30.0

Table 3.2: Average abundance of rare earth elements in the earth's crust (ppm).

The strong affinity for oxygen and phosphate explains the high incidence of rare earth occurrences as phosphate compounds. Under natural conditions, lanthanides exist as oxides, silicates, carbonates, phosphates and halogen compounds in minerals (Tyler, 2004). The amount of individual rare earths found in different mineral sources varies, yet the similarity in ionic radius, oxidation state and general properties results in their universal occurrence in all rare earth minerals. Apparently, nature is no better than chemists in separating them. Therefore, no known mineral contains only one lanthanide as a major constituent. However, the establishment of typical lanthanide contents in minerals enables scientists to determine their origin. This is also used for geochemical research on rock formations (Möller, 1963), (Trifonov, 1963).

Rare earth elements are obviously widely distributed, but usually occur in small amounts as shown in Table 3.2. The Oddo-Harkins rule can also be applied to members of the lanthanide series (Topp, 1965). According to that rule, elements with even atomic numbers appear more often than the neighboring element with an odd atomic number. In addition, studies show that the quantity of elements decreases with an increase in the atomic number in both even-numbered and odd-numbered sequences (Kabata-Pendias and Pendias, 2001), (Wei et al., 2001).

More than two hundred minerals are known to contain rare earth elements, yet only a few of them are useful for industrial production. Principal minerals, the abundance of rare earths in them and the geographical locations of their most important deposits are shown in Table 3.3.

	Composition		Location of significant deposits
	idealized	generalized	
Light Rare Earth - Cerium - containing Minerals			
Monazite	(light RE)PO_4	49 – 74% light RE 1 – 4% Y earths	China, Western Australia, India, Brazil, Zaire, South Africa, USA, USSR
Bastnaesite	(light RE)FCO_3	65 – 70% light RE $<$ 1% Y	China, USA, USSR
Heavy Rare Earth - Yttrium - containing Minerals			
Euxenite	$(Y)(Nd, Ta)TiO_6 \cdot H_2O$	13 – 35% Y earths 2 – 8% Ce earths	Australia, USA
Xenotime	$(Y)PO_4$	54 – 65% Y earths $\sim$ 0.1% Ce earths	Western Australia, Norway, Brazil
Gadolinite	$(Y)_2M_3^{II}Si_2O_{10})$	35 – 48% Y earths	Sweden, Norway, USA 2 – 17% Ce earths

Table 3.3: Important rare earth containing minerals; with M: Fe, Be (Möller, 1963).

Since rare earths are fractionated during weathering processes, ores tend to be rich in either heavy or light rare earth elements. Rare earth elements are mined from a great variety of ores, principally bastnasite and monazite (Zhang et al., 1995).

Presently, bastnaesite $(Ce, La)(CO_3)F$, a rare earth fluorocarbonate, constitutes the main source for industrial production of rare earths, it, therefore, is of high commercial importance (Tyler, 2004). Likewise, monazite, a thorium-rare earth phosphate, presents another important mineral source because it is readily highly available and contains about 50 % by weight rare earth elements. It can be found in Australia, China, South Africa and the United States, yet there are only a few places which offer enough quantity to permit vein mining. Therefore, secondary deposits, called monazite sands generated by natural weathering and gravity concentration processes are mainly used for industrial mining (Richter and Schermanz, 2006). Bastnaesite and monazite provide light rare earths and account for about 95 % of currently utilized rare earth elements. The composition of rare earth elements in monazite is shown in Table 3.4.

A further source for rare earths are aluminum silicates which are also known as ion absorption ores. They are produced by natural weathering processes, which enables them to absorb resolved lanthanides (Richter, 1996).

Monazite and xenotime naturally occur as accessory minerals in low-calcium granitoid rocks and pegmatites, while bastnaesite predominantly exists in calcium-silicate rich rocks and to a lesser extent in quartz veins, epithermal fluorite-bearing veins and breccia fillings (Trifonov, 1963), (Möller, 1963), (Evans, 1990), (Chengdu Beyond Chemicals, 2005).

However, the main fraction of rare earths on the earth's surface are not concentrated in previously mentioned enriched minerals but in abundant minerals of other elements such as apatite, a

	Composition of monazite (%)	Composition of gadolinite (%)
Lanthanum	23.0	1.0
Cerium	48.0	2.0
Praseodymium	6.0	2.0
Neodymium	20.0	5.0
Promethium	–	–
Samarium	2.0	5.0
Europium	0.02	< 0.1
Gadolinium	0.5	5.0
Terbium	0.04	0.05
Dysprosium	0.08	6.0
Holmium	0.01	1.0
Erbium	0.03	4.0
Thulium	0.003	0.6
Ytterbium	0.005	4.0
Lutetium	0.003	0.6
Yttrium	0.08	63.0

Table 3.4: Composition of rare earth minerals (Evans, 1990).

calcium phosphate which contains small amounts of F, Cl, Sr plus rare earth elements and corresponds approximately to $(Ca)_5(PO_4)_3(F, OH, Cl)$. The composition may, however, vary with its origin (Richter, 2006).

Since it possesses 80 % of the worldwide deposits, which is equal to 89 million tons of useable raw material, the People's Republic of China provides the greatest amounts, which makes it the largest producer of rare earths. China is followed by the Russian Federation, the United States, Australia, India, Canada, South Africa and Brazil. In addition, some deposits of rare earth elements without industrial significance are found in South Africa, Malaysia, Indonesia, Sri Lanka, Mongolia, North Korea, Afghanistan, Saudi Arabia, Turkey, Norway, Greece, Nigeria, Kenya, Tanzania, Burundi, Madagascar, Mozambique and Egypt. Producing mainly light rare earths, the mine Baiyuneba (Baiyuneba means "Mount of Riches") in Boutou Inner Mongolia is probably the most famous one. Another large deposit that might be of interest is located in the state of Minas Gerais of Brazil. It owns 100 000 t of rare earth elements (Evans, 1990), (Richter, 1996), (Hedrick, 2004), (Chengdu Beyond Chemicals, 2005).

In nature, rare earth elements become available to the soil and consequently to plants by leaching from mineral deposits and then entering groundwater. Various studies have reported significant differences in rare earth element concentrations among different types of Chinese soil. The sum of total rare earth elements ranges from 88,9 to 469 ppm, whereas light rare earth elements range from 76,2 to 447,7 ppm and heavy rare earth elements are in the range of 9,2 to 55,2 ppm, respectively (Kabata-Pendias and Pendias, 2001). Average contents of rare earth elements in soil are listed in Table 7.1. Comprehensive studies on the rare earth contents in different soils and plants were also conducted by Krafka (1999) and the reported values were in the range of ppm in soils and ppb in plants.

Even though rare earths present a slight mobility as well as low solubility and concentration in soil, they still provide an available pool to plants. Yet concentrations may considerably vary with the plant species. Contents of 10 ng/g dry matter, for example, were measured in spruce needles (Table 11.14) (Wyttenbach et al., 1996). In contrast, other plants including ferns (Ichihashi et al., 1992), (Wyttenbach et al., 1994), have been reported as being highly capable of absorbing lanthanides. Possessing concentrations of up to 2300 ppm DW (air dried or oven dried weight samples), hickory trees have been classified as lanthanide-accumulating plants (Robinson et al., 1958), (Evans, 1990). Thus, concentrations of rare earth elements in plants vary largely by ranging from below 1 ppm to above 15 000 ppb DW, while lanthanum, which exhibits maximum values from 88 to 15000 ppm DW represents the highest fraction (Kabata-Pendias and Pendias, 2001). In the past decade, many studies on the distribution and behavior of rare earths in soils and plants have been carried out and further details will be given in Chapters 7 and 11.

3.3 Mineral Sources and Separation Techniques

Recovering and separating rare earths from mineral sources constitutes the first step for their commercial applications in technical, medical and agricultural areas. As described above, rare earth elements are neither rare nor are they earths. Their first part of their name, the word *rare*, relates to the considerable difficulties in separating one rare earth element from another because of their close similarity in chemical and physical properties, the second part *earths*, an old chemical term for oxides, was applied to as they were first identified as rare earth oxides. As a consequence of their high resemblance to each other, several elements are found concentrated within individual minerals. Hence, it takes quite some effort to extract the individual rare earth elements from mineral sources.

First of all, rare earth mineral concentrates need to be cut-off from ores by using general mechanical and physical treatments with mineral dressing, such as gradual flotation and magnetic separation, or a combination of both methods before any chemical treatment can be applied. These methods usually provide > 60 % concentrates (Topp, 1965). Rare earth ions can be easily eroded from ion absorption ores by using saline or ammonium salts containing solutions. From this solution, rare earths are recovered by precipitation as oxalates. Concentrates of more than 90 % may be obtained by calcining the oxalates (Richter, 1996), (Richter and Schermanz, 2006).

Several methods of separating rare earths into the different elements are known, but none is considered to be universal. Since a detailed description of all methods available exceeds the limits of this thesis, the main points will be summed up briefly. Usually there is a choice between acidic (using sulphuric acid) or alkaline (using caustic soda) methods of breakdown, which use a variation of temperature. These processes will be exemplified for monazite and bastnaesite:

At first, both minerals are treated with concentrated sulphuric acids at 400 - 500 °C in rotary furnace before the pasty reaction product is diluted with water which creates a sulphate solution. For the separation of monazite, sodium saline or sulphate is added to the solution and a crystalline precipitate of the sodium lanthanide double-sulphates is obtained, which is boiled in a 10 % excess of caustic soda. The resulting rare earth hydroxides are filtered off. To obtain rare earth chlorides, hydrochloric acid is finally added. For the separation of bastnaesite, extracting agents are applied to the sulphate solution thereby receiving rare earth ions, which are further extracted with hydrochloric acid to rare earth chlorides.

To separate heavy rare earths from light rare earths, additional solvent extractions can be applied to the rare earth chloride-containing solution that could be obtained from either monazite or bastnaesite (Richter, 1996), (Topp, 1965). To isolate individual lanthanides from rare earth mixtures for industrial purposes, industry predominantly uses solvent solvent extraction, whereas ion exchange methods are only applied in certain special cases (Heyes, 1998). Extracting agents of industrial importance include Tri - n - butyl phosphate, Dimethyl heptyl methyl phosphonate, Di (2ethylhexyl) phosphoric acid, 2-Ethylhexyl phosphonic acid mono 2-ethyl hexyl ester, Tetra decyl phosphoric acid and Naphtenic acid (Richter, 1996). For further detailed description, the interested reader is referred to Vickery (1953), Ryabchikov et al. (1959), Topp (1965), Möller (1963), Trifonov (1963), Gschneidner and Eyring (1978 - 2003), Gmelin (1938 - 1993) and Richter and Schermanz (2006).

CHAPTER 4

CHEMICAL AND PHYSICAL PROPERTIES

THE introduction of the large group of elements known as rare earths will first require a definition of the group itself. The term *rare earth elements* literally refers to three members of group IIIB, namely scandium (atomic number 21), yttrium (atomic number 39), lanthanum (atomic number 57) and the 14 chemical elements found in group IIIA of the periodic table called lanthanoids with the serial numbers 58 - 71 cerium (atomic number 58), praseodymium (atomic number 59), neodymium (atomic number 60), promethium (atomic number 61), samarium (atomic number 62), europium (atomic number 63), gadolinium (atomic number 64), terbium (atomic number 65), dysprosium (atomic number 66), holmium (atomic number 67), erbium (atomic number 68), thulium (atomic number 69), ytterbium (atomic number 70) and lutetium (atomic number 71) (Trifonov, 1963), (Richter and Schermanz, 2006). This list does not distinguish between lanthanides and yttrium (atomic number 39) and scandium (atomic number 21). However, yttrium and scandium are included in the term rare earths due to similar chemical properties, which also accounts for the fact that these elements occur together in natural minerals (Osoon, 2005). While the term *lanthanoids*, meaning "lanthanum-like", embraces the elements 58 to 71 (cerium to lutetium), the term *lanthanides* includes lanthanum. In the periodic table, rare earth elements are represented by lanthanum while the other elements are found in a separate sub-table below the main groupings. Generally speaking, rare earth elements can be classified into two groups: the light or cerium subgroup, including the first seven elements (atomic numbers 57 - 63) and the heavy or yttrium subgroup, including yttrium as well as the elements within the range of atomic numbers 64 - 71. Since promethium is unstable and not well characterized, it will be described only marginally.

There are several major books which include detailed information on the topic of rare earths within the fields of physics and chemistry, such as (Gmelin, 1938 - 1993), (Möller, 1963), (Topp, 1965), (Cotton et al., 1999), (Evans, 1990), on which this general introduction of rare earth chemistry and physics is based. The selection of the information on properties will be governed by its relevance to applications of rare earth elements, for example, data on their electronic configuration, their ionic radius as well as their compounds, additionally on the chemical bonding behavior which is basic for the understanding of their biochemical and pharmacological behavior.

The introduction does not treat the structural chemistry of rare earth compounds whose relevance surpasses the realm of this study.

4.1 Chemistry of Rare Earths

4.1.1 General Information

Lanthanum is the first member of the third series of transition elements which are made of elements with unfilled f-orbitals. Lanthanides can only be distinguished by their 4f-electrons, hence they are often called f-elements, which explains their enormous similarity. In addition, their chemical properties are determined by the 3d-shell. With an increase atomic number, progressing from lanthanum to lutetium, a consecutively filling of the lower-energy 4f-orbitals instead of the 5d-orbital takes place while their oxidation states remain unchanged. Having 14 electrons in its f-shell, lutetium is fully occupied. This phenomenon is highly important for the understanding of rare earths, as many properties result from the shielding of the inner 4f-orbitals. The shielding of the 4f-electrons by electrons of higher orbitals moreover accounts for the fact that 4f-electronic behavior is neither influenced by ionization nor by complexation. Thus, their magnetic and spectroscopic properties are conserved upon binding. This successive addition of 14 electrons without exerting any influence on the chemical bonding is unique in the periodic table. The outer electronic configuration of the lanthanides is shown in Table 4.1.

	Atomic lanthanides Ln^0	Ionic lanthanides Ln^{3+}
La	$4s^2 4p^6 4d^{10} 5s^2 5p^6 5d^1 6s^2$	$5s^2 5p^6$
Ce	$4s^2 4p^6 4d^{10} 4f^2 5s^2 5p^6 6s^2$	$4f^1 5s^2 5p^6$
Pr	$4s^2 4p^6 4d^{10} 4f^3 5s^2 5p^6 6s^2$	$4f^2 5s^2 5p^6$
Nd	$4s^2 4p^6 4d^{10} 4f^4 5s^2 5p^6 6s^2$	$4f^3 5s^2 5p^6$
Pm	$4s^2 4p^6 4d^{10} 4f^5 5s^2 5p^6 6s^2$	$4f^4 5s^2 5p^6$
Sm	$4s^2 4p^6 4d^{10} 4f^6 5s^2 5p^6 6s^2$	$4f^5 5s^2 5p^6$
Eu	$4s^2 4p^6 4d^{10} 4f^7 5s^2 5p^6 6s^2$	$4f^6 5s^2 5p^6$
Gd	$4s^2 4p^6 4d^{10} 4f^8 5s^2 5p^6 5d^1 6s^2$	$4f^7 5s^2 5p^6$
Tb	$4s^2 4p^6 4d^{10} 4f^9 5s^2 5p^6 6s^2$	$4f^8 5s^2 5p^6$
Dy	$4s^2 4p^6 4d^{10} 4f^{10} 5s^2 5p^6 6s^2$	$4f^9 5s^2 5p^6$
Ho	$4s^2 4p^6 4d^{10} 4f^{11} 5s^2 5p^6 6s^2$	$4f^{10} 5s^2 5p^6$
Er	$4s^2 4p^6 4d^{10} 4f^{12} 5s^2 5p^6 6s^2$	$4f^{11} 5s^2 5p^6$
Tm	$4s^2 4p^6 4d^{10} 4f^{13} 5s^2 5p^6 6s^2$	$4f^{12} 5s^2 5p^6$
Yb	$4s^2 4p^6 4d^{10} 4f^{14} 5s^2 5p^6 6s^2$	$4f^{13} 5s^2 5p^6$
Lu	$4s^2 4p^6 4d^{10} 4f^{14} 5s^2 5p^6 5d^1 6s^2$	$4f^{14} 5s^2 5p^6$
Y	$4s^2 4p^6 4d^1 5s^2$	$4s^2 4p^6$

Table 4.1: Ground-state electronic configurations of atoms ; Ln: lanthanides (Evans, 1990).

Due to the fact that lanthanides generally favor tripositive oxidation state, thus being highly electropositive, their compounds are predominantly ionic in nature. Nevertheless, tetravalent and divalent forms exist as well, yet only Ce^{4+} and Eu^{2+} are stable enough to persist in aqueous solution, whereas their trivalent forms still present higher stability. The existence of further oxidation states besides 3+ is contributed to the special electronic configuration of $4f^0(Ce^{4+})$ which has an empty f-shell and $4f^7(Eu^{2+})$ and is half-filled (Cotton et al., 1999), (Evans, 1990), (Fachschaft Chemie, 2005). It has been argued that differences in oxidation states may distinguish rare earth elements as to their biochemical behavior in plants and animals, but this argument will be more closely looked into in Chapters 11 and 12.

The size of atoms and ions is determined by their nuclear charge, their number and the degree of occupied electronic shells. Hence, the actual radius of an ion is said to depend on its valency. Yet, rare earth ions display a unique physicochemical characteristic in which a decrease in ionic radii is associated with increasing atomic number (La 1.06 Å and Lu 0.85 Å) (Topp, 1965). This paradox called *lanthanide contraction* is ascribed to the shielded 4f-orbital, which cannot compensate the effect of increased nuclear charge. Thus enhanced nuclear attraction is exerted upon the whole electron cloud which finally shrinks and leads to the contraction of the entire ionic structure. With respect to ionic radius it is worth mentioning that the ionic radius of lanthanides largely resembles the one of Ca^{2+} at almost all coordination numbers because this is highly responsible for most of their biochemical behavior (Cotton et al., 1999), (Evans, 1990), (Richter and Schermanz, 2006). More detailed information on this topic will be given in Chapter 5. Additionally, Table 4.2 summarizes some of their chemical properties.

Element	Symbol	Atomic number	Atomic weight (g/mol)	Ionic radius (Å)
Lanthanum	La	57	138.91	1.061
Cerium	Ce	58	140.12	1.034, 0.92 (Ce^{4+})
Praseodymium	Pr	59	140.907	1.013
Neodymium	Nd	60	144.24	0.995
Promethium	Pm	61	Isotopes 141 - 151	0.979
Samarium	Sm	62	150.35	0.964
Europium	Eu	63	151.96	0.950, 1.09 (Eu^{2+})
Gadolinium	Gd	64	157.25	0.938
Terbium	Tb	65	158.924	0.923
Dysprosium	Dy	66	162.50	0.908
Holmium	Ho	67	164.930	0.894
Erbium	Er	68	167.26	0.881
Thulium	Tm	69	168.934	0.869
Ytterbium	Yb	70	173.04	0.858
Lutetium	Lu	71	174.97	0.848
Yttrium	Y	39	88.905	0.88
Scandium	Sc	21	44.956	0.68

Table 4.2: The chemical properties of rare earth elements (Möller, 1963).

4.1.2 Bonding and Chemical Compounds

Fundamental information on the chemical bonding behavior as well as on chemical compounds is essential for the prediction of the physiological behavior of rare earths in plants, animals or humans. This section will provide preliminary information which will be relevant in Chapters 11 and 12. In contrast to transition metals, rare earths do not exhibit significant covalent bonding or crystal field stabilization (Mikkelson, 1976). This is attributed to the high energy of the outer orbitals which hampers covalent bonding. Even though the extra d electron tends to increase the covalent character of bonding connections between rare earths and other molecules, rare earth compounds are usually based upon ionic binding. As a result, rare earths attract water molecules in aqueous solutions to form a hydration shell around them. Since the hydration of their tripositive ions is highly exothermic, rare earths are strong reducing agents under such conditions. In fact, reduction potentials of the Ln^{3+}/Ln^{2+} are reported to be between 0.43 and 1.35 V, respectively. By contrast, the potential of the couple Ce^{4+}/Ce^{3+} depends largely on the anion in solution. Hydration numbers ranging between 9 for La^{3+} to Nd^{3+} and 8 for Tb^{3+} to Lu^{3+} have been proven (Spedding et al., 1966). Lanthanide cations have a high affinity for bonding to fluorides, hydroxides and other oxygen-containing ligands (Bulman, 2003), (Fachschaft Chemie, 2005). The order of preference for donor atoms follows the sequence: $O > N > S$ and $F > Cl$, which indicates that lanthanides demonstrate an overwhelming affinity to oxygen donor atoms. Under physiological conditions, O donor atoms are supplied by either carboxyl or phosphate groups found in proteins, nucleotides and nucleic acids, respectively. Consequently, the great affection for ionic bonding leads to the formation of a large number of salts. The chemical term for *salt* refers to ionic compounds consisting of positively charged cations (mainly metallic ions) and negatively charged anions with the product being without a net charge. Thereby, anions can be either inorganic (Cl^-) or organic (CH_3COO^-) as well as mono-atomic (F^-) or poly-atomic (SO_4^{2-}) (Kurlansky, 2002).

Among inorganic rare earth salts, hydroxides, carbonates, phosphates, oxalates and fluorides formed by lanthanides are insoluble in water while their chlorides, nitrates and perchlorates remain soluble and their sulphates are hardly soluble. Hydrolysis generally increases forming insoluble precipitates of $Ln(OH)_3$ with an increasing pH and decreasing ionic radius from lanthanum to lutetium. Differences in solubility of many of these salts have been used to separate rare-earth metals from accompanying metals as well as to divide them into individual rare earth elements (Evans, 1990), (Trifonov, 1963). Furthermore, data on solubility (Table 4.3) is significant to predict the behavior of different rare earth salts under physiological conditions, the physiological pH being 7.4. It has been reported that in vivo many rare earth salts exhibit low solubility constants. Thus, crystalline lanthanum phosphates present solubility products of $10^{22.4}$ (Firsching and Brune, 1991).

Pharmacological properties as well as growth performance enhancing effects of rare earths have been proven to depend on the chemical compound that is applied. But this will be discussed in greater detail in Chapter 12. Due to the impact of different rare earth compounds regarding their growth promoting effects, further information on rare earth salts including their synthesis is given as follows.

Rare earth hydroxides $Ln(OH)_3$ are precipitated from a hot solution of a corresponding salt after the addition of ammonia or of diluted alkalis. Cerium remains the only exception since its hydroxide is unstable and can therefore only be only prepared by rigorously excluding air. Hydroxides are generally powdery and insoluble in water, but are soluble in acid. Rare earth hydroxides are soluble in acids and, when heated to 900 °C, they pyrolyse to oxides. The addition of ammonium carbonate to a diluted solution of a lanthanide salt leads to the precipitation of water insoluble rare earth carbonates. Having the compositions $LnPO_4$ and $Ln_4(P_2O_7)^3$ respectively, the rare earth phosphates precipitate when sodium phosphate is added to a lanthanide salt solution of pH 4.5. The normal oxalates precipitate from neutral solution by the hydrolysis of methyl oxalate, whereas in nitric solution, ammonium ion produces double salts. With solubility products in the range of 10^{-30}, all oxalates are very insoluble in water. Halides are prepared by treating the oxide with the appropriate halogen acid. Except for the insoluble fluorides, all halides are extremely

Anion	Light rare earth elements (atomic number 57 - 62)	Heavy rare earth elements (atomic number 39, 63 - 71)
Cl^-, Br^- I^-, NO_3^- ClO_4^-, BrO_3^- $C_2H_3O_2^-$	soluble	soluble
F^-	insoluble	insoluble
OH^-	insoluble	insoluble
HCO_2^-	slightly soluble	moderately soluble
$C_2O_4^{2-}$	insoluble, insoluble in $C_2O_4^{2-}$	insoluble, soluble in $C_2O_4^{2-}$
$(CO_3)^{2-}$	insoluble, insoluble in $(CO_3)^{2-}$	insoluble, soluble in $(CO_3)^{2-}$
basic NO_3^-	moderately soluble	slightly soluble
PO_4^{3-}	insoluble	insoluble
double M sulfate	insoluble in M_2SO_4 solution	soluble in M_2SO_4 solution

Table 4.3: General trends in the solubility of rare earth compounds in water; with M: Na, K or Tl (Möller, 1963).

soluble in water. Anhydrous and hydrous chlorides can be distinguished, yet both are hygroscopic. While hydrous chlorides can be simply prepared by heating the hydroxides with hydrochloric acid, anhydrous chlorides can be made by heating oxides with an excess of ammonium chloride. At high temperatures and in the presence of water vapor, the oxohalides are formed from halides. Rare earth nitrates are most soluble in water, but also soluble in some organic agents such as alcohol or acetone. They are prepared by the reaction of nitric acid with oxides. Anhydrous sulphates result from heating rare earth oxides and concentrated sulphuric acid at 400 - 500 °C. Beyond 1000 °C, the sulphates pyrolyse, thereby leaving the corresponding oxides. The solubility of sulphates varies with temperature. It decreases at elevated temperatures. This is an effect that can be exploited in separating light from heavy earths since the light earth sulphates are less soluble when heated (Topp, 1965), (Chengdu Beyond Chemicals, 2005), (Cotton et al., 1999), (Richter, 2006).

Organic salts composed of rare earth metal ions and organic acids, such as mono-, di- and tricarboxylic acids, can also be formed. Stability constants are reported to vary among different organic acid rare earth complexes. Complexes with dicarboxylic acids which offer two carboxyl groups, e.g., malonate, succinate, glutarate or fumarate, are more stable than those with monocarboxylic acids, e.g., acetate or lactate. For complexes containing citrate, a tricarboxylic acid, the stability constants range from $2.8 \cdot 10^9$ for La^{3+} to $6.3 \cdot 10^9$ for Eu^{3+}, and therefore provide higher stability than lanthanide dicarboxylates, which possess dissociation constants of $1.10 \cdot 10^4$ for La^{3+} - succinate. Despite their apparently higher stability, compared to competing biological ligands, citrates have a relatively low affinity to lanthanide ions and give them up easily (Evans, 1990). Rare earth citrates are of special interest as they have been used in recent research on performance enhancing effects of rare earths on animals (see Chapter 12). Organic acids are not only of interest because they are capable of modifying the physiological behavior of rare earths in animals, but also because they can influence the uptake of rare earths by plants from soil. Organic acids of low molecular weight, such as citric, malic and acetic, typically found in the rhizosphere, are considered important factors that influence the bioavailability of rare earths for plants (see Chapter 11).

Nevertheless, apart from ionic compounds, rare earths can also form complexes with coordination numbers ranging between 6 and 12 while preferring 8 and 9 (Table 4.4). Lanthanide complexes, predominantly chelation, present great geometrical flexibility due to absent participation of the f-electrons in compounds. This enables them to occupy various biological Ca^{2+} binding sites. By far the most stable and common lanthanide complexes are those with chelating oxygen ligands, such as the poly amino poly carboxylate chelators NTA (nitrilotriacetic acid), EDTA (ethylenediamine-N-N-N'-N'-tetraacetic acid), DTPA (diethylenetriamine-N-N-N'-N'-N"-pentaacetic acid) or DCTA (1,2-di-amino-cyclo hexane-N-N-N'-N'-tetra acetic acid). Regarding their physiological behavior after oral administration, lanthanide-DTPA complexes, which provide high stability, ensure gastrointestinal passage without interaction of lanthanide 3+ ions with physiological ligands, whereas weaker chelators, such as EDTA and NTA, permit physiological exchange to some extent. Since lanthanides with higher atomic numbers exert stronger electrostatic interaction, light rare earth chelates are weaker than those with heavy rare earths (Topp, 1965), (Evans, 1990), (Bulman, 2003), (Fachschaft Chemie, 2005). Structural changes in homologous rare earth compounds are contributed to *lanthanoide contraction*, because variations in cationic sizes have a major effect on the formation, coordination numbers and reactivity of their compounds (Kobayashi, 1999).

Type	Examples	Formula
Ion pair associations	Halo-LnF^{2+} Sulfito-$LnSO_3^+$ Sulfato-$LnSO_4^+$ Thiosulfato-$LnS_2O_3^+$ Oxalato-$LnC_2O_4^+$ Acetato-$LnC_2H_3O_2^{2+}$	
Isoable nonchelated species	Ammines Amine adducts Antipyrine adducts	$LnCl_3 \cdot xNH_3$ $LnX_3 \cdot yRNH_2$ $(Ln(ap)_6)X_3$ with X = I, ClO_4, NCS
Isoable chelated species		
1. Nonionic	8-Quinolinol 1,3 - Diketones	$Ln(On)_3 \cdot nH_2O$ $Ln(diket)_3 \cdot H_2O$
2. Ionic	Citrates α - Hydroxycarboxylates Aminepolycarboxylates	$[Ln(C_6H_5O_7)_2]^{3-}$ $[Ln(R\text{-}CHOHCO_2)_6]^{3-}$ $[Ln(EDTA)]^-$, $[Ln(NTA)_2]^{3-}$

Table 4.4: A classification of typical complex species derived from lanthanide 3+ ions (Möller, 1963).

Besides carboxyl groups of chelators, rare earth elements can also bind to unprotonated carboxyl groups of amino acids, hence forming complexes with biological ligands, such as amino acids, nucleotides or peptides. If two carboxyl groups are available in one molecule, as in thymopoietin, rare earths can bind both, hence forming a bidentate complex. Weak interactions with hydroxyl oxygen of certain peptides, including serine, thyreonine and tyrosine, and with carbonyl oxygens have also been reported (Prados et al., 1974), (Evans, 1990).

The coordination of cerium 3+ to nitrogen of porphyrin rings was demonstrated by using x-ray absorption fine structure methods with the coordination numbers of 8 and an average length of cerium-nitrogen bond of 0.251 nm (Fashui et al., 2002). However, possible binding to unprotonated amino groups remains to be debated, as coordination to the α - amino nitrogen atom and hydrolysis of lanthanide ions occur at the same pH. However, the complexation of rare earth elements with both amino and carboxyl components of amino acids could perhaps explain the fact that complexes with amino acids are stronger than those formed with monocarboxylic acids.

4.1.3 Rare Earth Oxides

Rare earth oxides are the most stable of various rare earth compounds, they are also the fundamental raw material of other compounds. Being the basic product of raw material in industrial production, they deserve a separate treatment within this introduction (Cotton et al., 1999), (Topp, 1965), (Chengdu Beyond Chemicals, 2005).

Rare earth oxides originally known as *rare earths* played an important role in the development of rare earth chemistry. The common formula RE_2O_3 is applied to oxides of the trivalent rare earth elements, whereas the dioxides CeO_2, with cerium being quadrivalent, is also characteristic member. A wide range of mixed oxides, many of commercial usefulness, are known. The ones containing La, Ba or Sr and Cu, and thus providing superconductivity at and even above liquid nitrogen temperature, are of great interest for industrial use. Furthermore, the amount of rare earth oxides is considered as a fundamental basis to compare the concentration of rare earths in different rare earth-products both in industry and agriculture (Richter, 2006). Rare earth oxides can be obtained through direct interaction of the metal with dry air (oxygen) or they can be produced by pyrolyzing corresponding hydroxide, oxalate and carbonate salts. Higher temperatures are required for nitrates and sulphates while halides are only converted by employing superheated steam. Rare earth oxides are very difficult to melt, e.g., the melting point of cerium rises up to 2500 °C (Trifonov, 1963).

4.2 Physics of Rare Earths

A short introduction into the physics of rare earth elements is considered to be essential and will complement the insights gained from the description of their chemical properties. But even though rare earths exhibit a great variety of physical characteristics, such as crystallographic, mechanical, thermal, electrical, magnetic and optical properties, only those of relevance to the applications described below in Chapters 9 and 10 will be treated here, including magnetic susceptibility, radiant energy absorption, luminescence behavior and superconductivity.

First it will be necessary to describe their physical appearance. Rare earth metals are soft, malleable, ductile and chemically very active. When freshly cut, their smooth surface has a silvery-white luster, which changes to chestnut and dark brown, respectively, as they form rare earth oxides in the presence of air. They all react directly with water, slowly at low temperatures and rapidly at elevated temperatures, by expelling hydrogen and thus producing the insoluble hydrous oxide or hydroxide. Reasonably fast reactions also take place with C, N_2, Si, P, S, halogens and other nonmetals at higher degrees of temperature. Their melting points and density increase with their atomic weight except for europium and yttrium, which might be due to differences in crystal structure. While being heated, many rare earths ignite and burn by forming oxides. This is why they must be kept in safe places. Nevertheless, since impure metals and cerium enriched alloys are pyrophoric, they have become useful in flints (Chapter 9).

The physical characteristics of rare earth elements, such as their magnetic susceptibility, radiant energy absorption and luminescence, result from their special electronic configuration. In general, magnetic properties are based on the fact that each moving electron itself is a micro-magnet. Having both unpaired spins and orbital motion around their nuclei, electrons like the 4f-electrons of the lanthanides can exhibit magnetic behavior in two ways. Within a magnetic field, substances may either align themselves in opposition (diamagnetic) or parallel (paramagnetic) to the field. While Y^{3+}, La^{3+}, Lu^{3+} and Ce^{3+} are diamagnetic all other lanthanides are paramagnetic. Paramagnetism is a feature that allows for their practical application to nuclear magnetic resonance spectroscopy (Chapter 10) but it is also important for industrial uses, e.g., as high-performance magnets (Chapter 9).

Absorption bands of 3+ lanthanides reflect the energy changes that result from electronic transitions within the 4f-orbitals. Since the 4f electrons are well shielded by filled 5s and 5p-orbitals, complex formation and external perturbations have no effect on the extremely sharply defined bands. Although characteristic absorption spectra of individual lanthanides can be obtained, absorption spectroscopy for analytical purpose is of limited sensitivity due to the low absorptivities of lanthanides. It still is a valuable property which is used in lighter filters, glass blower goggles or wavelength calibration in optical devices (Cotton et al., 1999), (Möller, 1963), (Topp, 1965), (Evans, 1990), (Fachschaft Chemie, 2005).

The transition of the f-electron is also responsible for the luminescent behavior of the lanthanides. The weak luminescence of lanthanides in solutions that have low oscillator strength ($\sim 10^{-6}$), can be overcome by energy transfer from organic chromophores, which will then produce highly luminescent lanthanide complexes. Luminescence can also follow excitation by ultraviolet irradiation, x-rays, fast electrons, neutrons and certain chemical and mechanical means which make lanthanides adaptable for commercial use in oxide phosphors, e.g., for color television tubes and related devices.

Although rare earths are very poor conductors of electricity since they possess an electrical conductivity of 10^{-8} Ohms, lanthanum can develop super-conducting abilities at temperatures close to absolute zero. This makes it highly useful for a number of technical applications (Trifonov, 1963), (Gmelin, 1938 - 1993), (Gschneidner and Eyring, 1978 - 2003). Disposing of sizable ionic radii, most of the rare earth elements possess high neutron capture profiles and high γ - emission probabilities for neutron activation products which are not only useful for their qualitative and quantitative analysis, but also for some medical applications (Horrocks and Sudnick, 1979) (Chapter 10). The physical properties of the rare earth elements, including melting points, density, number of unpaired 4f electrons and color of tripositive cations as well as magnetic moment and cross section for thermal neutron capture, are summarized in Table 4.5.

Element	Melting point °C [a]	Density (g/cm^3) [b]	Unpaired 4f-electrons of tripositive cations [c]	Color of tripositive cations [d]	Magnetic moment (Bohr/Magnetons) [e]	Cross section for thermal neutron capture (barns/atom) [f]
Lanthanum	920	6.174	0	colorless	0	9.3
Cerium	795	6.771	1	colorless	2,39	0.73
Praseodymium	935	6.782	2	yellow green	3,47	11.6
Neodymium	1024	7.004	3	reddish	3,62	46
Promethium	-	-	4	pink, yellow	2,83	-
Samarium	1072	7.536	5	yellow	1,54	5600
Europium	826	5.259	6	nearly colorless	3,61	4300
Gadolinium	1312	7.895	7	colorless	7,95	46 000
Terbium	1356	8.272	6	nearly colorless	9,6	46
Dysprosium	1407	8.536	5	yellow	10,5	950
Holmium	1461	8.803	4	pink, yellow	10,5	65
Erbium	1497	9.051	3	reddish	9,55	173
Thulium	1545	9.332	2	pale green	7,5	127
Ytterbium	824	6.977	1	colorless	4,4	37
Lutetium	1652	9.842	0	colorless	0	115
Yttrium	1509	4.478	0	colorless	0	1.31
Scandium	1539	2.992	-	-	24	-

Table 4.5: Physical properties of rare earth elements (Möller, 1963)[a,b,c,f], (Evans, 1990)[d,e].

CHAPTER 5

BIOCHEMICAL AND PHARMACOLOGICAL PROPERTIES

THE potential of rare earth elements for a great number of agricultural and medical applications principally relies on their biochemical and pharmacological actions which shall be introduced in this section. Furthermore, these actions are providing fundamental information regarding the use of rare earths as feed additives, hence they will be taken up again in Chapter 12. However, it must be noted that due to their enormous complexity, a detailed description including all of their biochemical and pharmacological properties would go beyond the scope of this thesis. Properties such as effects on smooth, striated and cardiac muscle, on the reticuloendothelial function or genetic effects are therefore just briefly mentioned or not discussed at all.

Some of them that are relevant to the application of rare earths to medicine, such as anticoagulation and antidiabetic properties, as well as effects on the calcium phosphate balance will be described in Chapter 10, and those of toxicological relevance, such as the induction of calcification, neurological actions, teratological effects and effects on the liver will be partly discussed in Chapter 6. For further explicit information, the interested reader is referred to Haley (1979), Evans (1990), Wang et al. (2003b).

5.1 The Biochemistry of Rare Earths

Their biochemical behavior will be described at first. In this connection, the ability of rare earth elements, mainly lanthanides, to substitute for a large number of metallic ions, such as Ca^{2+}, Mg^{2+}, Fe^{3+}, Fe^{2+} or Mn^{2+}, plays a major role (Evans, 1983). Among these metallic ions, Ca^{2+} is of particular interest. Given the importance of calcium in cellular metabolism and the efficient displacement by lanthanides, great biological activity of lanthanide ions is expected. Yet, their inability to normally penetrate the cellular membrane of living cells restricts the scope of their biological intervention.

Marked similarities in size, bonding but also in coordination geometry and donor atom preference – as shown in Table 5.1 – enables them to replace Ca^{2+} specifically in various physiological processes. Even though occurring isomorphously, the substitution of Ca^{2+} in enzymes and other molecules is not necessarily associated with a loss in functionality. Lanthanides have been shown to activate a number of proteins and enzymes, while in other cases, they inhibit Ca^{2+} or Mg^{2+} functions. There are also some Ca^{2+} binding sites that totally refuse Ln^{3+} (lanthanide ions) binding, e.g., in scallop myosin or concanavalin A.

Feature	Ca^{2+}	Ln^{3+}
Coordination number	reported 6 - 12 favored 6 or 7	reported 6 - 12 favored 8 or 9
Coordination geometry	highly flexible	highly flexible
Donor atom preference	O >> N >> S	O >> N >> S
Ionic radius (Å)	1.00 - 1.18	0.86 - 1.22 depending on species
Type of bonding	Ionic	Ionic
Hydration number	6	8 or 9
Water exchange rate constant (s^{-1})	$\approx 5 \cdot 10^8$	$\approx 5 \cdot 10^7$
Diffusion coefficient ($cm^2/(s \cdot 10^5)$)	1.34	1.30 for lanthanum

Table 5.1: Comparison of properties of calcium and rare earth elements, Ln: lanthanides (Evans, 1990).

Since larger Ln^{3+} ions are generally closer in ionic radius to Ca^{2+} ions, a relationship between ionic radius and activity has been described. Yet in some cases, e.g., the inhibition of α - amylase or of Ca^{2+} / Mg^{2+} - ATPase of skeletal muscle sarcoplasmic reticulum, the effect decreased with increasing atomic number. Even though Ca^{2+} and Ln^{3+} ions are reported to be quite similar, two major differences have been documented. Firstly, rare earth ions display a much higher charge to volume ratio which in turn leads to increased stability of lanthanide complexes preferring greater coordination numbers (Jakupec et al., 2005). Similarly, Horrocks (1982) reported K_d values to be smaller for Ln^{3+} than for Ca^{2+} explaining tighter bindings for lanthanides. The higher charge to volume ratio further contributes to greater affinity of lanthanides for given binding sites compared to Ca^{2+}. Secondly, in contrast to the spectroscopically silent Ca^{2+} ions, lanthanide ions (Ln^{3+}) exhibit spectroscopic signals. The use of lanthanides as ion probes has therefore become a valuable tool for the analysis of biomolecular functions and structures (Horrocks and Sudnick, 1979), (McCusker and Clemmons, 1997).

Most physiological effects of lanthanides on cells, tissues or organs are determined by interactions between Ln^{3+} and the external surfaces of plasmalemmae. Although lanthanides are generally unable to penetrate cellular membranes of healthy cells, they can still exert influence on transmembrane processes (Korenevskii et al., 1997), (Evans, 1990). Yet, it cannot be excluded that under certain circumstances entry may be permitted, since intracellular penetration has been reported for dead and damaged cells, that is cells that lost their cellular integrity. Nevertheless, binding of lanthanides to membrane proteins stabilizes the phospholipid membranes, increases their rigidity and alters their surface charge towards higher electropositivity. This effect further leads to increasing membrane potential and resistance and consequently to a dysfunction of the voltage-dependent transmembrane calcium currents. Yet in addition to voltage regulated calcium channels, calcium entrance may also be permitted by receptor operated calcium channels, Na^{+} - Ca^{2+} exchanger and Ca^{2+} - Ca^{2+} exchanger. All of them can also be inhibited by lanthanide ions

(Evans, 1990). In certain cells, e.g., erythrocytes or adrenal cells, Ca^{2+} efflux can also be inhibited, whereas Ca^{2+} influx is generally more susceptible, which indicates that the uptake of Ca^{2+} into the cells is usually blocked. As a result, those physiological processes depending on Ca^{2+} influx are antagonized, whereas those depending on intracellular calcium release or those that are mediated by an alternative source are not affected (Nachshen, 1984).

Among others, involved processes include the transmission of nervous impulses (Vaccari et al., 1999) and the release of neurotransmitter, the blood clotting cascade (Jakupec et al., 2005), the contraction of smooth, skeletal and cardiac muscle (Triggle and Triggle, 1976), the release of histamine form mast cells (Beaven et al., 1984), the reticuloendothelial function (Farkas and Karacsonyi, 1985), (Lazar et al., 1985) and a number of hormonal responses (Enyeart et al., 2002).

Since 1910, it has been known that lanthanides may inhibit the contraction of frog heart muscle reversibly (Mines, 1910). In addition, inhibitory effects have also been demonstrated on skeletal muscle (Hober and Späth, 1914). The precise biochemical nature of their binding sites remains unclear. Investigations on the identification of surface receptors for lanthanide ions were performed. Results obtained by El Fakahany et al. (1984), who studied lanthanide binding to murine neuroblastoma cells, suggested that lanthanides associate with calcium channels surrounding receptors, thus inhibiting calcium currents.

Furthermore processes influenced by lanthanides include the release of insulin or amylase from the pancreas. However, they do not depend on Ca^{2+} influx from the outside, but are triggered by intracellularly released Ca^{2+} (Evans, 1990). Yet, the mechanism behind it is thought to involve an exhaustion of the extracellular Ca^{2+} reservoir due to repeated activation of cellular functions by lanthanide ions. Since the maintenance of the intracellular Ca^{2+} pool strongly depends on the extracellular calcium concentration, further responses are prevented.

However, it has been assumed that rare earths can also exert their influence on cellular functions by other means than inhibiting calcium fluxes. Ghosh et al. (1991), for example, demonstrated that intraperitoneal administration of lanthanum and neodymium chloride to chicken caused an obvious reduction in enzymatic activity in the membrane of erythrocytes. Other studies also confirmed that their interactions are not restricted to Ca^{2+} channels. A dose-dependent increase of the gastric acid secretion by lanthanum in isolated mice stomach was demonstrated in in-vitro studies (Xu et al., 2004). It was suggested that the mechanism might involve either the release of gastrin and histamine or the activation of their receptors. Moreover, A-type potassium channels of adrenal cortical could be blocked by lanthanide binding to Ca^{2+} nonspecific sites (Enyeart et al., 1998), while γ - aminobutyric acid (GABA) - activated chloride channels of dorsal root ganglion neurons in rats could be enhanced (Narahashi et al., 1994). Additionally, rare earths have been shown to coordinate with further membrane structures such as receptors for acetylcholine (Rübsamen et al., 1976) or insulin (Williams and Turtle, 1984) as well as with adenylate-cyclase (Nathanson et al., 1976) and Na^{+} - K^{+} ATPase (David and Karlish, 1991). Activation of adenylate cyclase poses one possible explanation for their action on enhancing cAMP. As cAMP belongs to the intracellular signaling system lanthanides may also affected the signal transduction pathway. At the same time, lanthanides can also affect the cell signaling system via modulation of intracellular calcium ion concentrations or hydrolysis of phosphatidyl-inositol, another trigger substance in signal transduction pathways (Wang et al., 2003b).

Catalyzing hydrolysis has also been described in RNA molecules. According to Eichhorn and Butzow (1965) lanthanides have the ability to depolymerize RNA and nucleotides under experimental conditions. Besides destabilizing those molecules, it was shown that their hydrolysis was initiated. Binding to DNA generally induces conformational changes until final precipitation occurs. But the affinity of rare earths for RNA is even higher (Evans, 1990). Furthermore, Yajima et al. (1994) reported that, under physiological conditions, lanthanide ions are able to form adenosine 3',5'- cyclic monophosphate from adenosine triphosphate, thus to possess phosphatase activities and to provide a catalytic potential. The biological relevance of these actions is not yet clear. It has been suggested though that rare earths might exert an enormous impact on the total metabolism of organisms by the interaction with physiologically important phosphate compounds (Bamann et al., 1954), such as RNA. However, being capable catalysts for hydrolytic splitting of phosphate ester bonds including those of DNA, lanthanides might be clinically valuable for blocking gene-specific transcription for antibiotics or chemotherapeutic applications or for customized targeting of oncogenic mutations (Franklin, 2001).

Another biochemical feature of lanthanides involves phosphate. Wurm (1951) already described the formation of water-soluble compounds between lanthanides and phosphate in bacteria. Later studies have been able to confirm the phosphate binding property of rare earths (Evans, 1990), (Diatloff et al., 1995a), (Hutchison and Albaaj, 2005). The strong affinity of rare earths for phosphate has also been used to advantage commercially for the removal of phosphate from swimming pools to inhibit algae growth (Diatloff et al., 1995a), and it has been proposed that lanthanum could be useful in waste water treatment to precipitate and remove phosphorus (Recht et al., 1970). This property also accounts for the capability of orally applied lanthanum carbonate to decrease serum phosphorus levels and the calcium x phosphorus product in humans (Finn et al., 2004), which explains its current use in patients suffering from chronic renal failure. More detailed information on the phosphate binding properties of rare earths will be provided in Section 10.2.1 and Chapter 12. Phosphate binding ability of rare earths may provide a possible explanation for effects of rare earths on plants and animals.

Interactions between lanthanides and calcium specific or non - specific sites on proteins including ion channels, enzymes and receptors, are generally inhibitory. Yet enhanced insulin binding to its receptors induced by competitive antagonizing calcium from its site, illustrates one exception. As there is a number of G protein coupled receptors depending on calcium, it was suggested that lanthanide ions might also inhibit hormone binding to all of these receptors, as it has been shown for ACTH receptors (Enyeart et al., 2002). Interactions with the hormone system were also described by Haksar et al. (1976), Segal and Ingbar (1984), Lam et al. (1986).

5.2 The Pharmacology of Rare Earths

In the presence of agonists, it might occur that despite actually suppressing an action, lanthanides trigger an increase in activity as described for the release of serotonin from platelets, of catecholamines from the adrenal medulla and acetylcholine or other neurotransmitters from nerve ends (Evans, 1990). Such effects have been shown to depend on either the concentration or the ionic radius of lanthanides. This indicates that the so-called hormesis effect may also be applied to lanthanides. The hormesis effect describes a dose-dependent reversal effect that can occur in drugs. Accordingly, pharmacological effective substances, such as lanthanides, may exert contrary effects depending on their concentration. While stimulation may occur at low doses, no effects or even inverse effects may appear at high concentrations (Tripp, 2005), (Wang et al., 2003b).

It has been known for quite some time that lanthanides possess a great duality in biological events affecting them from opposite sides (Wang et al., 2003b), (Enyeart et al., 2002), (Wurm, 1951). Thus, Muroma (1958) already described dose-dependent effects of lanthanides on bacterial growth. At high concentrations of 10^{-4} - 10^{-2} mol/l, lanthanides have been shown to inhibit bacterial growth, whereas growth stimulating effects occurred at low concentrations of about 10^{-5} mol/l, and at supra-inhibitory doses the bacteriocidal potency was reduced. For cerium, concentrations ranging from 10^{-3} mol/l to 10^{-2} mol/l were required to inhibit the growth of several bacteria including E. coli, Bacillus pyocyaneus, Staphyloccous aureus, Leuconostoc and Streptococcus faecalis (Zhang et al., 2000b). While antibacterial properties of lanthanides have been widely reported (Burkes and McCloskey, 1947), (Wurm, 1951), (Muroma, 1958), (Zhang et al., 2000b) a couple of possible explanations for their mode of inhibition have been suggested. By binding to the surface of bacteria, lanthanides can change membrane structures and alter the surface charge, thus causing flocculation (Sobek and Talbut, 1968). Since lanthanides can form insoluble complexes with DNA and RNA, it is also possible that the combination with nucleoproteins of bacterial cells accounts for their bacteriostatic action. However, in 1921, Brooks (1921) described direct effects on bacterial metabolism, namely the ability of lanthanides to antagonize bacterial respiration processes. But Wurm (1951) attributed bacterial growth inhibition to phosphate deficiency caused by the formation of insoluble lanthanide phosphate complexes. Additionally, owing to a direct action upon the cell, lanthanides have been shown to also inhibit the resting, phosphate-independent metabolism. Finally, it is not known whether the antibacterial actions are due to morphological changes or metabolic disturbances.

Moreover, lanthanides can also inhibit the formation and germination of fungal spores. Thus, they may influence a large number of organisms (Burkes and McCloskey, 1947), (Muroma, 1958), (Talburt and Johnson, 1967), (Zhang et al., 2000c), (Zhang et al., 2000b) with bacteria, especially gram - negative (Drossbach, 1897), (Peng et al., 2004), which are more susceptible than yeast or fungi and heavy lanthanides that are more toxic than light ones (Muroma, 1958). This fact has already been reported in historical papers (Drossbach, 1897), (Dryfuss and Wolf, 1906). However, certain fungi species are capable of detoxifying lanthanides through incorporation into insoluble oxalate crystals (Talburt and Johnson, 1967). By using cerium nitrate for the topical treatment of wounds including burns, weeping eczema, intertrigo, impetigo contagiosa and other skin diseases, physicians have successfully capitalized on the antiseptic properties of rare earths (Böhm, 1915), (Deveci et al., 2000). Furthermore, anti-microbial actions are also considered as a possible explanation for the performance enhancing effects of rare earths observed in plants and animals.

Besides antibacterial effects, rare earths were also reported to affect viruses, too. Bjorkman and Horsfall (1948) were among the first to describe effects of lanthanides on viral organisms. Although no effects were found on infectivity, hemagglutinating capacity, antigenicity or immunological specificity, lanthanides demonstrated a certain potential to influence viruses. A single dose of stable lanthanum acetate was shown to alter the elution behavior of influenza B virus permanently in a similar manner as ultraviolet irradiation. Further investigations state that lanthanides indeed provide antiviral effects (Sedmak et al., 1986), (Liu et al., 1998), whereas intraperitoneal administration was shown to be more effective than oral application (Liu et al., 2000). Sedmak et al. (1986) contributed these effects to enhanced interferon activities, while Liu et al. (1998) gave an account of direct antiviral effects. The mode of action is still not well understood, and further research is required. Chinese scientists have even reported on anti-HIV activities caused by rare earths (Liu et al., 2002), (Liu, 1997), yet detailed information is lacking.

Further dose-dependent effects of lanthanides have been demonstrated on the immune system. Suppression of histamine secretion from mast cells was seen at high concentrations, while low-dose lanthanides acted stimulating (Foreman and Mongar, 1973). Thus, this is another example of the hormesis effect induced by lanthanides. After an intravenous administration at quite low concentration, lanthanides suppressed phagocytic activity of cells belonging to the reticuloendothelial system (e.g. Kupffer cells) (Husztik et al., 1980), (Lazar et al., 1985). Suppressing the immune system consequently increases susceptibility to bacterial and yeast infections (Farkas and Karacsonyi, 1985). At the same time, Lazar et al. (1985) reported increased survival rates from anaphylactic death in mice pretreated with lanthanides chlorides, especially $GdCl_3$. The stimulation of splenic lymphocyte transformation in mice after oral administration of lanthanum nitrate at low concentrations has also been reported (Wang et al., 2003b). It can therefore be concluded that lanthanides possess certain immunomodulating properties. Due to its Kupffer cell blocking ability, $GdCl_3$ supplies protecting action against ischemia and reperfusion injury as well as injury caused by xenobiotics in liver (Hamada et al., 1999), (Bailey and Reinke, 2000), (Wang et al., 2003b).

Lanthanides also exhibit reactive oxygen species modulating activity, a property which is to some extent related to the immune system. It is known that the formation of reactive oxygen species (ROS), such as free radicals and peroxides, is essential in the metabolism as well as in the immune system. Nevertheless, it can also cause severe cell injury up to cell death and impair cell function due to mutation. Depending on the species and concentration, lanthanides can either inhibit or promote ROS-mediated processes. Inhibition occurs with light rare earths and is further enhanced at increasing concentrations. In contrast, promotion happens with heavy rare earths, whereas decreased concentrations reinforce those effects. The underlying mechanism has been shown to be due to binding to hydroperoxides, thus inhibiting ROS-related lipid peroxidation and oxidation of membrane proteins, and to magnetic interaction with free radicals (Shimada et al., 1996), (Wang et al., 2003b).

Cell proliferation, differentiation and apoptosis are important features in both normal that is physiological and pathological processes. Effects of lanthanides on cellular proliferation have also been widely reported. A close relationship between cell injury and proliferation depending on concentration, but also on mechanism, was thereby noticed. Preeta and Nair (1999) demonstrated proliferative activities of low dose cerium on rat cardiac fibroblasts, while Gd^{3+} was able to enhance cell proliferation of hepatocytes (Rai et al., 1997). However, a dose-dependent inhibition was stated for bovine chrondrocytes proliferation after gadodiamide (gadolinium complex of diethylenetriamine pentaacetic acid bidmethylamide), a MRI contrast agent, was applied intraarticularly (Greisberg et al., 2001). Pretreatment of $GdCl_3$ prevented the proliferation of oval cells in a liver injured by bile duct ligation (Olynyk et al., 1998), whereas Ishiyama et al. (1995) reported that protecting effects of $GdCl_3$ on liver injury were followed by cell proliferation.

Although the exact mechanisms are still obscure, several hints have been provided. Cell proliferation induced by lanthanides is linked to increased DNA, RNA and protein synthesis (Wang et al., 2003b). As Sarkander and Brade (1976) have shown that different effects of lanthanides on RNA synthesis are due to variations in their ionic radii, it is generally agreed that those effects can change with species, cells and conditions. Since intracellular calcium has been proven to be a mediator of cell proliferation, lanthanides may exert their influence by increasing intracellular calcium concentrations, as seen in rat fibroblasts (Wang et al., 2003b). Liu et al. (1994) also contributed inhibitory effects of $GdCl_3$ on cell proliferation to the prevention of calcium influx. Rai et al. (1997) and Preeta and Nair (1999) both agreed on the fact that ROS-modulating properties of lanthanides account for cell proliferation. However, Weiss et al. (2001) reported calcium supply by store-operated calcium entry to be necessary for the proliferation of cancer cells. They further found lanthanide ions to be capable of inhibiting the store-operated calcium entry, therefore, blocking proliferation of human colon carcinoma cells, HRT-18. Sato et al. (1998) confirmed anti-cancer properties of lanthanides by demonstrating that the growth of cultured B 16 melanoma cells could be retarded by lanthanides at a concentration of 1 mmol/l as the transition from the G_0/G_1 to the S state was aborted.

Enhancing cell proliferation may account for growth promoting effects (hormetic effects) of lanthanides that have been observed in a number of plants and animals. Nevertheless, the opposite effect may also be beneficial with regard to the prevention of pathological processes as, for example, cancer development.

Although poorly documented, influence of lanthanides on cell differentiation is thought to be due to interference with calcium-depending processes. Lanthanide-induced cell death has been reported in rat alveolar macrophages associated with phagocytosis (Mizgerd et al., 1996), (Kubota et al., 2000), in rat skin fibroblasts and in HeLa and PC12 cells. After feeding mixed lanthanide nitrates at a concentration of $\geq$ 20 mg/kg to rats for 14 days, apoptosis has been observed in splenocytes and thymocytes (Wang et al., 2003b). In contrast to that, Wang et al. (2003c) found out that lanthanum chloride given at a dose of 10 mg/kg was able to decrease the apoptosis of thymocytes in endotoxemia in mice. The bulk results from studies on concentration dependency of cell growth suggest a growth promoting effect at low concentrations, but inhibitory up to lethal effects at high concentrations, which is in line with the previously described hormesis effect of rare earths. This conclusion should be kept in mind, as it may also explain the dose-dependent growth-enhancing effects in animal and plants, which will be presented in Chapters 11 and 12 in greater detail. Thus, it will be shown to be of great relevance as to the application of rare earths to agriculture.

A list of biological effects of lanthanides is provided in Table 5.2. The broad biological activity spectrum of lanthanides and the two-sidedness of their effects makes them highly attractive for medical purposes. However, clinical use of lanthanides strongly depends on the possible modulation of the opposing effects. A more detailed report on the therapeutic significance of their biological effects is given in Chapter 10 in conjunction with their former, present and future use in medicine.

Promotion and inhibition of growth of organisms
Promotion and inhibition of cell proliferation
Promotion and inhibition of apoptosis
Antioxidant activity and prooxidant activity
Stabilization and destabilization of cytoskeleton
Enhancement and inhibition of cell permeability
Positive and negative regulation of cell signaling system
Promotion and inhibition of bone growth
Increase and decrease of oxygen affinity of hemoglobin
Inhibition of muscle contraction
Blocking nervous transmission
Enhancement of mineralization and demineralization

Table 5.2: Biological effects of lanthanides (Wang et al., 2003b).

CHAPTER 6

TOXICOLOGY AND METABOLISM

THE wide-spread usage of rare earth elements within industry and agriculture as well as medicine has increased tremendously over the last years, and continual research has found new uses and applications. These facts explain the great need for detailed information on rare earth toxicology. Moreover, that information has become indispensable in view of the possible application of rare earths for growth enhancing purposes in animal husbandry and new medical applications.

At present, among other applications, rare earths are used as superconductors, glass additives, fluorescent materials, phosphate binding agents, magnetic resonance agents, fertilizers and feed additives in Chinese agriculture as well as in lasers, high-performance magnets and ointments for burn treatment. Under natural conditions, rare earths may only become available in small amounts via the groundwater and the atmosphere, increased use, however, has enhanced the amount of natural occurring rare earths, and has created several new routes for rare earth uptake. Assimilation might therefore occur by the inhalation of rare earth dusts at working sites (rare earths and coal mining, in the past: production of carbon arc lamps) and by intake of rare earth containing foodstuff, industrial rare earth products or medicinal agents (orally, intravenously, through burn wounds) (Evans, 1990), (Hirano and Suzuki, 1996), (Bulman, 2003). For humans, the inhalation of air-borne particles of lanthanides constitutes the most significant accidental exposure route. It is interesting to note that increased concentrations of cerium, praseodymium and samarium, which may be linked to the use of diesel fuel, have been measured next to motor-ways (Ward, 1988).

However, since this study deals with the use of rare earths in Chinese agriculture and their possible use as feed additives in Europe, the focus of this chapter is mainly on the oral intake of rare earths. Yet, gastrointestinal-absorbed amounts are expected to share the same fate as intravenously applied rare earths. The behavior of lanthanides after intravenous injection, which is reported to be the most toxic way of administration, will therefore be described as well, while other applications, such as subcutaneous, intramuscular and intra-peritoneally as well as inhalation, will be mentioned briefly for the sake of completeness. The accessible literature on rare earth metabolism and toxicity goes back to the 1960s and 1970s, but more recent studies are lacking. However, with the introduction of new drugs in medicine, some additional information has become available.

6.1 Metabolism of Rare Earths

To obtain a comprehensive understanding of rare earth toxicity, an account of their metabolic behavior is required. Their metabolism highly depends on the manner of administering rare earths as well as on the chemical form administered. Although strictly speaking, rare earths are not metabolized at all as their basic chemical nature remains unaffected, the term metabolism seems convenient to use (Bulman, 2003). Various studies performed on the metabolism of lanthanides used radionuclides as tracers (Arvela, 1977). It has to be considered that detailed biochemical analysis of lanthanide metabolism may be complicated by a variety of actions including the high affinity of lanthanides to form insoluble lanthanum hydroxides at physiological pH and the formation of so-called radio-colloids, which may take place prior to their precipitation. Further complications may be caused by the formation of insoluble phosphates and carbonates due to high physiological concentrations of phosphate and carbonate as well as by the presence of numerous organic ligands at different physiological sites (Chapter 5). Moreover, binding of lanthanides to insoluble carrier molecules may also cause their precipitation. Precipitated lanthanides constitute a main target for cells of the reticuloendothelial system and are therefore taken up by phagocytic cells, such as Kupffer cells in the liver. Yet, binding to soluble carrier ligands may enable lanthanides to travel from sites of extravascular injection (Evans, 1990). This is why the metabolic fate of soluble lanthanide salts, with respect to the type of application will be treated first.

Oral absorption of rare earths is of great relevance for their use as performance enhancer in animal husbandry. This section includes only some introductory information while a thorough description will be given in Chapter 12. It is generally agreed that in adults lanthanides are only poorly absorbed by the gastrointestinal tract (Baehr and Wessler, 1909), (Hamilton, 1949), (Cochran et al., 1950), (Haley, 1979), (Ji et al., 1985b), (Fiddler et al., 2003a), (D'Haese et al., 2003), (Rambeck et al., 2004), (Hutchison et al., 2006). In animal experiments using rats, retention values have been reported to be in the range of below 0.05 to 0.4 % of the orally administered dose (Hamilton, 1949). According to Norris et al. (1956), 90 % of a single oral dose of ^{91}YCl was found in the feces of rats during the first three days, while complete elimination occurred after one week. Similar results were obtained with dogs (Hutchison and Albaaj, 2005), chickens (Mraz et al., 1964) and quails (Robinson et al., 1978).

All lanthanides entering blood vessels, thus also trace amounts absorbed by the gastrointestinal tract, share the fate of intravenously injected lanthanides. Accumulation of lanthanides in liver, kidney, bone and teeth was reported in rats after oral application (Ji et al., 1985b), (Evans, 1990), (Harrison and Scott, 2004). Rare earth contents of up to 0.607 ppm were reported in liver, kidney, lungs, spleen and bone in rats fed rare earths at 1800 mg/kg over eight months (Ji et al., 1985b). Similar distribution patterns with slightly higher values were observed by Fleckenstein et al. (2004). After oral administration of rare earths to broilers, rare earth contents were in the range of 5 - 100 μg/kg and absorbed amounts were higher in liver, kidney and fat compared to muscle or heart. Highest values were obtained in fat tissue whereas concentrations in bones have not been measured. These results indicate minimal organ absorption of rare earths after oral administration. However, another experiment on rabbits, Kramsch et al. (1980) did not detect any lanthanum in bones after feeding lanthanum chloride for eight weeks, but an average concentration of 33 μg for lanthanum was measured in liver tissue. This might be explicable by the higher affinity of light rare earths for liver tissue (Haley, 1979).

In contrast to adults, it has been stated that newborns, assimilate lanthanides from the gastrointestinal tract to a much greater extent. 91 % of administered ^{144}Ce was absorbed from the digestive system by newborn pigs and presented later in the skeleton (Mraz and Eisele, 1977), (Haley, 1979). Further information will be given in Section 12.2.2.3. But Marciniak et al. (1996)

reported no absorption of rare earths from the gastrointestinal tract of suckling rats. Yet the transfer of lanthanides from the mother to the offspring via milk was evident and increased with atomic number following the order Ce $<$ Nd $<$ Sm $<$ Eu $<$ Tb. Accordingly, Feige et al. (1974) described rare earth transfer from mice previously injected with cerium^{144} to their sucklings. But no transfer through the placenta was seen, although higher liver contents have been noted in pregnant animals (Arvela, 1977). In contrast to those high values obtained in rats, only small amounts of intravenously injected yttrium transferred into milk with cows.

Intraperitoneal injected lanthanides are prone to stay within the abdominal cavity coating the surface of abdominal organs. Yet, transport of a small fraction of lanthanides to bone, liver and teeth has been reported (Evans, 1990). However, in guinea pigs unusually high absorption of yttrium by the pancreas was demonstrated (Graul and Hundeshagen, 1959). Greater transport may occur in the presence of chelating agents. After intrapleural injection, lanthanides have also been shown to remain primarily in the pleural space.

Absorption after intramuscular or subcutanous injections are reported to be negligible. Lanthanides predominately remain at the site of their injection (Evans, 1990), as is the case for wound contamination. No systemic absorption from burn wound could be found after local treatment with cerium nitrate ointment (Fox et al., 1977).

Although the same result has been reported for injections into the mammary glands, some transfer of lanthanides to the corresponding lymph node may occur due to phagocytosis by cells of the lymphatic system.

A biphasic removal from knee joints of rabbits was seen after intra-articular injection. While one third of the injected dose was removed with a half-life of less than one day, the remainder needed about 60 days to be fully cleared (Evans, 1990). Yet, only little transfer to other organs was observed. While excretion is usually mainly through feces, for intra-articular injection it has been shown to be via urine. It has therefore been speculated that lanthanides may bind to soluble physiological chelators found intra-articular thereby leaving the joint.

For intravenous injection, the formation of radio-colloids at low concentrations and of precipitates at high concentration as well as the extensive interaction with ligands in the blood has been of great concern. However, in vitro studies proved quite the contrary. No visible precipitates formed when lanthanides were added to blood or serum (Kyker, 1962), lanthanides have even shown to be more soluble in serum than in distilled water (Kanapilly, 1980). This might be ascribed to the formation of soluble complexes with ligands, such as phospholipids, amino acids, nucleotides, proteins etc., present in the plasma. Albumin has been shown to be a main complexing agent capable of preventing lanthanide precipitation. Clearance from the blood with circulating half-lives of 10 - 20 min, similar to those of chelators, and half-lives of one to three hours for smaller particles are reported. It might be concluded that the clearance of lanthanides strongly depends on the ligands to which they are bound (Evans, 1990). Nevertheless, at some point the complexing ability of the plasma may be exceeded. This may explain the fact that with increasing concentration of lanthanides, clearance from the blood decreases. According to extra-venous injections, liver and skeleton also seem to be the main sites of deposition, while other organs like spleen and kidney take up lanthanides only concur to a small extent with contents being below 2 % of the given dose (Li et al., 2002) (Haley, 1979), (Nakamura et al., 1991b), (Wassermann et al., 1996), (Nakamura et al., 1997). Some studies also reported the uptake of small amounts of lanthanides into the lung and certain endocrine glands. In contrast to previous findings, a recent study performed by Shimada et al. (2005) demonstrated deposition of terbium chloride in soft tissue, that is spleen, lung, and liver. Accordingly, Shinohara et al. (1997) reported that after intravenous injection of terbium chloride to mice, 80 % of the injected dose was mainly found in liver, lung and spleen along with increased tissue calcium concentrations.

The fact that a decrease in the ionic radius is, on the one hand, associated with increased solubility and chelate stability, and, on the other hand, with decreased basicity probably accounts for different distribution patterns among individual rare earths. Thus, the more basic light rare earths deposit mainly in liver and secondary in skeleton, whereas the more acidic heavy rare earths favor the skeleton (Durbin et al., 1956), (Arvela, 1977). Unlike adults, young animals have demonstrated far greater skeletal uptake (Mraz and Eisele, 1977). While the skeleton seems to be metabolically stable, over time lanthanides can be released from the liver (Evans, 1990). Liberalized material can be recaptured by the skeleton and thus after some time bone contains almost the entire body load of lanthanides.

It was expected that inhaled soluble lanthanide compounds show the same behavior as those that are intravenously injected (Norris et al., 1956). Evans (1990), on the one hand, stated that the major part of injected lanthanides is transferred from the respiratory tract and lung to the gastrointestinal tract, and thus excreted with the feces while the remaining part is gradually moved to liver and bone. However, several other studies reported the accumulation of inhaled lanthanide chlorides in alveolar and tissue macrophages and alveolar walls. Since rare earths have been localized in lysosomes of alveolar macrophages, it was suggested that they are changed into insoluble phosphates. Half-lives range between 168 to 244 days, whereas gadopentate dimeglumine (gadolinium chelate of diethylenetriaminepentaacetic acid) surprisingly presented a half-life time of just 2 hours (Suzuki et al., 1992), (Hirano et al., 1990). This is probably attributed to the compound composition, as gadopentate dimeglumine is considered to be stable in the alveolar space and hardly taken up by macrophages due to limited release of ionic gadolinium from the complex. Nevertheless, retention of inhaled insoluble species in the lung may last for several years (Bulman, 2003).

Except for intra-articular injections where the excretion was reported to be mainly via the urine, it is generally agreed that fecal excretion through both the bile and directly through the wall of the gastrointestinal tract, constitutes the main route of excretion. Early urinary excretion of less than 0.5 % is thought to be due to the formation of firm complexes with soluble ligands which are rapidly removed (Baehr and Wessler, 1909), (Durbin et al., 1956),(Arvela, 1977), (Haley, 1979), (Hirano and Suzuki, 1996), (Bulman, 2003),(D'Haese et al., 2003), (Harrison and Scott, 2004), (Hutchison and Albaaj, 2005).

Elimination from the liver was reported to be biphasic. 86 % are cleared within the first four days while it took between 10 and 37 days to remove the rest. In contrast, between two and a half and three years are needed for bone excretion (Hamilton, 1949), (Durbin et al., 1956), (Haley, 1979). In quails, half-life times of 3 hours hence considerably lower than in mammals, have been reported (Robinson et al., 1978), (Robinson et al., 1984). The liver was also shown to be the organ with the highest assimilation while quite a large amount was also found in the oocyctes and ovaries of females and in the testes of males. Furthermore, lanthanides accumulated in the intestine and cecum.

In sum, the systemic absorption of lanthanides administered as soluble salts increases in the following sequence per os $\ll$ subcutanous $<$ intramuscular $<$ intraperitonally $\ll$ intravenously. Though the absorption efficiency strongly varies ranging from less than 1 % for oral administration up to 100 % for intravenous injection, the distribution pattern for bioavailable lanthanides with liver and bone being the sites of highest accumulation is unchanged and independent of the way of administration. However, if insoluble lanthanides enter the body, they fall prey to phagocytosis in the presence of macrophages, and hence are quickly removed. Yet at sites with few phagocytes as in muscles slow removal occurs (Evans, 1990), (Hirano and Suzuki, 1996).

The introduction of chelated lanthanides into the body results in complete absorption, increased excretion rates, decreased plasma dwell times and alterations of the distribution pattern. Highly stable chelator-lanthanide complexes, on the one hand, pass quickly through the body and are excreted unchanged in the urine when applied intravenously and in the feces after being orally applied. On the other hand, weak chelator-lanthanide complexes permit the interaction with biological ligands and are therefore incompletely excreted. Chelators reduce the uptake of lanthanides by the liver, enhance the relative uptake by muscle and shift the main accumulation site from liver to bone (Arvela, 1977), (Haley, 1979). Chelating agents, such as diethylenetriaminopentaacetate (DPTA) may also be used in cases of intoxication to decrease liver and bone burdens and to remove lanthanides from mammalian tissue.

6.2 Toxicity of Rare Earths

According to the Hodge-Sterner classification system, rare earths are generally considered to be of low toxicity (Haley, 1979). As expected from prior information on rare earth metabolism, their toxicity varies with their chemical form and the route of administration. The acute oral lethal dose of several rare earth elements are given in Table 6.1. By comparing the effective doses, however, it should be kept in mind that these values have been collected from studies performed with lanthanides of different purity, hence discrepancy might have been occurred. Investigations on the acute and chronic toxicity of rare earths have started in 1950. In most studies, rare earths were administered at quite high levels. The low oral toxicity with LD_{50} values beyond 1 g/kg body weight (Venugopal and Luckey, 1975), (Ji et al., 1985b), (Richter, 2003), (Richter and Schermanz, 2006) is ascribed to their poor gastrointestinal absorption.

Administered substance	Animal	LD_{50} (mg/kg BW)	Reference
La^{3+} - acetate	rat	10000	Cochran et al. (1950)
La^{3+} - ammonium nitrate	rat	3400	Cochran et al. (1950)
$LaCl_3$	rat	4200	Cochran et al. (1950)
$LaCl_3$	mouse male	2354	Shimomura et al. (1980)
$La(NO_3)_3$	rat	4500	Cochran et al. (1950)
$La_2(SO_4)_3$	rat	> 5000	Cochran et al. (1950)
La_2O_3	rat	> 10000	Cochran et al. (1950)
$CeCl_3$	mouse male	1959	Shimomura et al. (1980)
$CeCl_3$	rat	2110	Rhodia (2005)
$CeCl_3$	mouse	5277	Rhodia (2005)
$Ce(NO_3)_3$	rat female	4200	Bruce et al. (1963)
CeO_2	rat	> 5000	Rhodia (2005)
$PrCl_3$	mouse male	4500 (4054 - 4995)	Haley (1979)
$Pr(NO_3)_3$	rat female	3500	Bruce et al. (1963)
Pr_6O_{11}	rat	> 1000	Rhodia (2005)

continued on next page

Administered substance	Animal	LD$_{50}$ (mg/kg BW)	Reference
$NdCl_3$	mouse male	5250 (4730 - 5830)	Haley (1979)
$Nd(NO_3)_3$	rat female	2750	Bruce et al. (1963)
Nd_2O_3	rat	$>$ 1000	Rhodia (2005)
$SmCl_3$	mouse male	$>$ 2000	Haley (1979)
$Sm(NO_3)_3$	rat female	2900	Bruce et al. (1963)
Sm_2O_3	rat	$>$ 1000	Rhodia (2005)
$EuCl_3$	mouse	5000	Rhodia (2005)
$Eu(NO_3)_3$	rat female	$>$ 5000	Bruce et al. (1963)
Eu_2O_3	rat	$>$ 1000	Rhodia (2005)
$GdCl_3$	mouse male	$>$ 2000	Haley (1979)
$Gd(NO_3)_3$	rat female	$>$ 5000	Bruce et al. (1963)
Gd_2O_3	rat	$>$ 1000	Rhodia (2005)
$TbCl_3$	mouse male	5100 (5049 - 5151)	Haley (1979)
$TbCl_3$	mouse male	2652	Shimomura et al. (1980)
$Tb(NO_3)_3$	rat female	$>$ 5000	Bruce et al. (1963)
Tb_4O_7	rat	$>$ 1000	Rhodia (2005)
$DyCl_3$	mouse male	7650 (7150 - 8186)	Haley (1979)
$Dy(NO_3)_3$	rat female	3100	Bruce et al. (1963)
Dy_2O_3	rat	$>$ 1000	Rhodia (2005)
$HoCl_3$	mouse male	7200 (6667 - 7776)	Haley (1979)
$HoCl_3$	mouse male	2568	Shimomura et al. (1980)
$Ho(NO_3)_3$	rat female	3000	Bruce et al. (1963)
Ho_2O_3	rat	$>$ 1000	Rhodia (2005)
$ErCl_3$	mouse male	6200 (5390 - 7140)	Haley (1979)
Er_2O_3	rat	$>$ 1000	Rhodia (2005)
$TmCl_3$	mouse male	6250 (5430 - 7190)	Haley (1979)
Tm_2O_3	rat	$>$ 1000	Rhodia (2005)
$YbCl_3$	mouse male	6700 (6374.9 - 7041.7)	Haley (1979)
$Yb(NO_3)_3$	rat female	3100	Bruce et al. (1963)
$LuCl_3$	mouse male	7100 (6630 - 7590)	Haley (1979)
Lu_2O_3	rat	$>$ 1000	Rhodia (2005)
$ScCl_3$	mouse male	4000 (3960 - 4040)	Haley (1979)

Table 6.1: Acute oral toxicity of lanthanides.

Numerous investigations have confirmed the minimal oral toxicity in different animal species such as Cochran et al. (1950), Durbin et al. (1956) and Ji et al. (1985b) in rats, Haley (1965), Ji et al. (1985b) in mice, Ji et al. (1985b) in guinea pigs and Hutcheson et al. (1975) in apes. Furthermore, in medicine several studies reported the oral intake of up to 3 g of lanthanum carbonate per person per day up to four years to be without toxic effects (Joy and Finn, 2003), (Harrison and

Scott, 2004), (Locatelli et al., 2003), (Ritz, 2004). For drinking water, safety levels of 2 μg/l were recommended (de Boer et al., 1996). As oral toxicity of rare earths is of special interest for the main topic of this thesis, more detailed information is provided in Chapter 12.

Due to slightly higher absorption of subcutanous or intramuscularly injected lanthanides, their acute toxicity is a little higher, as expected. For subcutanous injections, minimal lethal doses of 100 - 1000 mg/kg are reported. Providing LD_{50} values of 50 - 500 mg/kg body weight, intraperitoneal injected lanthanides are even more toxic, whereas guinea pigs have been shown to be more susceptible than rats and mice. Although inhalation produces only few immediate effects, due to accumulation of rare earth particles, chronic exposure is more toxic because it causes emphysema, pneumonitis, bronchitis and pulmonary fibrosis.

However, rare earths are most toxic when applied intravenously with LD_{50} values ranging between 3 and 100 mg/kg body weight for rats and mice (Haley, 1979), (Evans, 1990), (Hirano and Suzuki, 1996). Liver and spleen degeneration with yellow atrophy and central lobe necrosis may occur (Haley, 1965). A delayed lethality takes place following high doses of intravenously-injected lanthanides with peaks between 48 and 96 hours and acute toxic symptoms being writhing, ataxia, labored respiration, walking on toes with arched back and sedation. Those who survived for thirty days presented generalized granulomatous peritonitis and focal hepatic necrosis. Applied intravenously, all rare earth elements cause hypotension. In the end death occurs by cardiovascular collapse associated with respiratory paralysis (Haley, 1965), (Haley, 1979). While rabbits seem to be less sensitive, a sex-dependency with females being more susceptible was reported in mice and rats. In contrast to that, Robinson et al. (1978) detected higher resistance in female quails. The fact that the dose-response curve is bell-shaped, thus higher doses are of lower toxicity, is ascribed to possible precipitation of rare earths at higher doses. Given intravenously, the toxicity of rare earths increased with higher atomic numbers while for different neodymium salts, an increase in the following order was found: chloride $<$ proprionate $<$ acetate $<$ 3-sulfoisonicotinate $<$ sulfate $<$ nitrate Zimakov (1973) cited by Haley (1979). In general, with intraperitoneal and intravenous injection, low and frequent applications have been much better tolerated than single high ones. Besides using chelating agents, toxicity can be modified by further substances. Thus microsomal activity enhancing agents, drug-metabolizing enzymes, ATP, adenosine and tryptophan may reduce the toxicity of rare earths, whereas dexamethason and glucocorticoide provided lethality enhancing effects (Haley, 1979), (Evans, 1990), (Hirano and Suzuki, 1996), (Bulman, 2003).

Although binding of lanthanides to DNA, RNA and nucleotides has previously been reported in vitro (Eichhorn and Butzow, 1965), (Evans, 1990), in vitro and in vivo assays performed by Damment et al. (2004) demonstrated no genotoxicity after exposure to high tissue and plasma levels of lanthanum carbonate. Similarly, Ji et al. (1985b) reported negative mutagenicity tests. He further found no increase in chromosome abberation rates of marrow cells after oral application, but, when compared to low doses at high doses, chromosomal translocation of the spermatocytes increased significantly.

As far as carcinogenicity of rare earths is concerned, the majority of studies could not reveal any (Schroeder and Mitchener, 1971), (Strubelt et al., 1980), (Ji et al., 1985b), whereas a few older studies reported the formation of tumors in lung tissue after intratracheal application or inhalation and in liver, stomach or intestinal tract (Haley, 1979). However, as a consequence of chronically feeding rare earths at high concentrations growth depression was seen in rats (Haley, 1979), (Ji et al., 1985b), (Evans, 1990). In contrast to D’Agostino et al. (1982), who found reduced litter weight after subcutanous injection of cerium citrate, Ji et al. (1985a) reported neither changes of litter weights nor malformations of fetus or embryo after oral application.

In conclusion, regarding the oral application of rare earths, no genotoxic, carcinogenic or teratotoxic effects are to be expected, whereas for intravenous and other applications, the reported results are contrary. But in order to assess those effects further studies are required. With regard to the median lethal dose, rare earths administered orally, subcutanously, intra-peritoneally or intravenously are not regarded as highly toxic agents. Nevertheless, some toxicological changes may occur and shall therefore be briefly presented on the basis of the affected organ. As studies on the pathogenesis and mechanism of toxicity of rare earths are missing, explanations of their toxic properties are based upon their biochemical behavior (Chapter 5). It is therefore not always possible to differentiate toxic effects based on rare earths from nonspecific phenomena. Nor have specific target cells involved in pathological processes been reported. Hence some effects, such as the induction of neoplasms or the effects on spleen and gastrointestinal tract, might not be attributable to rare earths alone and should therefore be regarded critically.

6.2.1 Effects on Lung

Many studies on the toxic effects of rare earth elements after inhalation and intra-tracheal injection have been performed (Haley, 1979), (Evans, 1990). It was proven that pulmonary toxicity of stable rare earths is contributed to the development of progressive pulmonary fibrosis, also known as pneumoconiosis, which may be accelerated or enhanced by the contamination of radioactive materials. The significant pathogenic potential of inhaled lanthanides is related to type and physicochemical form of the materials as to dose and duration of exposure (Nemery, 1990), (Haley, 1991).

Rare earth pneumoconiosis is a long-term lung disease occasionally described in humans exposed to rare earth dusts, e.g., smoke of cored carbon arc lamps. The accumulation of fine granular dust particles containing rare earth elements, mainly cerium, may cause interstitial disorder, emphysema and severe obstructive impairment with a decrease of carbon monoxide diffusion capacity. These deposits are detectable for a long time (Vogt et al., 1986), (Sabbioni et al., 1982), (Nemery, 1990), (Porru et al., 2000). Although changes may be visible on x-ray, normally no symptoms or functional deteriorations are found (Kappenberger and Buehlmann, 1975), (Vogt and Rüegger, 2002). Compared to other well-documented fibrogenic dusts, such as quartz and silica, it can be stated that the toxic potential of rare earths displays only mild pathologic potential (Richter, 2003). Today, modern occupational exposure practices will severely restrict respiratory intake of rare earth particles at work sites and as rare earths are treated properly, health impairment is not expected. Maximum allowable concentrations at Russian work-sites have been reported by Neizvestnova et al. (1994) with maximum peaks of 2,5 mg/m^3 and average shift concentrations of 0,5 mg/m^3.

6.2.2 Effects on Liver

As liver tissue sequesters a considerable amount of bioavailable rare earths, especially light ones, hepatotoxic effects are to be expected and have already been reported in various studies. After the injection of rare earth elements, Magnusson (1963) and Tuchweber et al. (1976) demonstrated elevated activities of liver specific enzymes such as GPT and GOT, which, however, returned to normal after six to ten days. Furthermore hepatic necrosis was found after both intravenous and subcutaneous injection of rare earths (Robinson et al., 1986), (Salonpaa et al., 1992), while pretreatment with phenobarbital, spironolaction and prenenolon - α carbonitril was able to prevent hepatic damage (Tuchweber et al., 1976), (Salas and Tuchweber, 1976).

However, the induction of the fatty liver phenomenon by light rare earths is by far the most obvious hepatic lesion following intravenous injection of rare earths. This condition which is associated with a massive hepatic accumulation of neutral fat esters has not been described after oral application. Prior to producing the fatty liver, plasma concentrations of free fatty acids increased while cholesterol and phospholipid levels declined (Arvela, 1977). Though the exact mechanism is not fully understood, based on the biochemical properties of lanthanides, it is assumed that increased hepatic sequestration of triglycerides from the plasma, decreased oxidation of lipids by hepatic mitochondria as well as decreased hepatic synthesis and secretion of lipoproteins are involved (Evans, 1990) (Chapter 5). As lanthanides have been shown to accumulate in adrenal glands (Borowitz, 1972), it was suggested that the liberation of free fatty acids from adipose tissue is due to lanthanide induced adrenal stimulation (Renaud et al., 1980). In addition, Arvela and Karki (1971) found out that lanthanides also reduced the activity of hepatic microsomal enzymes which are responsible for metabolizing and detoxifying drugs. The induction of a fatty liver was reported in rats, mice and hamster, yet not in guinea pigs, chickens or dogs and furthermore, the effect was more consistent in females. Having its maximum after two to three days, all effects diminished after a week, even though rare earth concentrations in the liver remained high (Haley, 1965).

6.2.3 Effects on Spleen, Kidney and Gastrointestinal Tract

Further organs may also be affected. In spleen, Stineman et al. (1978) noted hypertrophy, reticuloendothelial hyperplasia and hyperactive lymphoid follicles in mice after both subcutaneous and oral administration of cerium citrate, while only after oral application focal gastric hemorrhages, necrosis of mucosa and neutrophil infiltration were seen.

6.2.4 Effects on Bone

In bone, lanthanides have been shown to associate to both the organic matrix and the inorganic mineral of the bone (Evans, 1990). Although the skeleton constitutes the second major deposition site of rare earth elements, no toxic effects on bone structure were found. Bone mineralization defects reported after high-dose lanthanum carbonate administration to rats which suffered from chronic renal failure are due to phosphate depletion rather than due to direct bone toxic effects (Damment and Shen, 2005), (Damment et al., 2003), (Freemont et al., 2004). Additional information will be given in Section 10.3.4.

6.2.5 Effects on Skin and Eye

Intact skin is generally resistant to lanthanide salts application in contrast to abraded skin which reacted severely with epilation and scar formation in rabbits (Haley, 1979). Furthermore, the production of granulomas and local calcification with mild fibrosis has been reported after intradermally injected rare earths (Haley, 1979), (Evans, 1990). Since pyrophosphate is considered to have a calcification-inhibitory function, it is hypothesized that precipitation of lanthanides with pyrophosphate is responsible for the induction of soft-tissue calcification. These precipitates are thought to form a crystallization nucleus on which calcium and phosphate may accumulate to form apatite (Boeckx et al., 1992).

Rare earth salts are also ocularly irritating after topical application. Haley (1965) reported ocular irritation with the formation of ulcera after the introduction of rare earth salt crystals or solutions into the conjunctival sac of rabbits. The corneal opacification which occurred later has also been contributed to calcergenic properties of rare earths. Interestingly, Swanson and Truesdale (1971) found out that cataractous human lenses contain more lanthanum than healthy ones. Lanthanides might therefore play a role in the development of catarractic diseases. Nevertheless, Ji et al. (1985b) presented only mild irritation of skin and eye mucosa in rabbits.

6.2.6 Effects on Brain

Lanthanides share a variety of actions on nerve cells and most of them, e.g., transmitter release are related to the interaction with Ca^{2+} involved transport processes. Because of the blood-brain barrier, lanthanides are unable to enter the central nervous system (Evans, 1990). Therefore, systemic administration does not cause severe neurological disturbances. Yet they can exert certain neurological effects. After direct injection into brain tissue, La^{3+} provoked analgetic effects similar to those of opiates. Since those effects could be antagonized by naloxone, and morphine-tolerant rats were cross-tolerant to lanthanum (Harris et al., 1975), it might be assumed that La^{3+} and opiates both operate by using the same mechanism. It has further been described that subarachnoidal injection of higher concentrations of gadolinium chloride, gadolinum-EDTA or gadolinium-DTPA may produce loss of motor function and epileptoid fits (Weinemann et al., 1984). Yet during long-term studies of orally applied lanthanum carbonate, no central nervous system adverse effects were found (Jones et al., 2004), (Joy and Finn, 2003).

Concerning the toxicity caused by rare earth applications, previous studies were able to demonstrate that the risk of oral intoxication is negligible. With an oral $LD_{50} > 1000$ mg/kg body weight, which equals to 70 000 mg per person (Wald, 1990), ingestion of such high amounts of rare earths without knowledge or without the ability to obtain medical care is highly unlikely to occur. Therefore, unless intravenously applied, intoxication by rare earths is not to be expected after oral application.

On this basis, the application of low concentrated rare earth feed additives, as described in Chapter 12, is not expected to harm either animals or humans who consume animal products. Experiments on the determination of rare earth contents in edibles even revealed higher concentrations in commercial vegetable feedstuff compared to those in the tissue of animals whose diet was supplemented with rare earths. This fact, which is ascribed to the ubiquitous occurrence of rare earths, additionally confirms the safe application of rare earth-containing feed additives to farming animals.

CHAPTER 7

ECOTOXICOLOGY – IMPACT ON THE ENVIRONMENT

MOST sources of environmental pollution are anthropogenic in origin with a great majority of pollutants originating from industrial discharges. Thus metals and metal species constitute a significant part in environmental contamination (Yusof et al., 2001). Rare earths also provide high industrial potential being important components of metal alloys, special glasses, superconductors (Fink, 2005), permanent magnets, fluorescent materials and solid-state laser areas. Along with the development of modern industries, the application of rare earth containing materials to many industrial fields (e.g. Eu in color television tube; La, Ce and Tb are in fluorescent light; Sm and Y in micro technology and superconductor) is growing rapidly (Zhang et al., 2001a), (Wei et al., 2001). It has been reported that the scattering of rare earths as residues in water and atmospheric environments may occur during extraction procedures from high-grad ores and subsequent refining by ion-exchange chromatography. In addition, rare earths may also enter the environment in terms of atmospheric airborne water droplets and particles bearing rare earths as a consequence of their use as fine chemical in modern industries (Ichihashi et al., 1992). Hence, these particles, which mainly originate from oil-fired power stations or transportation vehicles that use rare earths as catalysts (Huang et al., 1994) may enter the plants via their leaves.

However, rare earths are also directly applied to plants. Yield and quality improvements produced by rare earths led to a large-scale application of rare earth containing micro-fertilizers to agriculture in the Peoples Republic of China (Guo et al., 1988), (Diatloff, 1999), (Maheswaran et al., 2001). Micro-element fertilizers with lanthanum and cerium as their main components have been manufactured and used in Chinese plant production for over 20 years (Xiong, 1995), (Zhang et al., 2001a). The amount of rare earths applied to agricultural areas constantly increased. With an application rate of 750 - 1000 g/ha more than 3 million ha were covered in 1998 (Wang, 1998). Furthermore, based upon performance enhancing properties, rare earths have also been applied to animal husbandry in China and Switzerland and will eventually be used in further Western countries in the future. As a result, the amount of rare earths entering the environment may further increase since liquid manure is applied to agricultural crops as an organic fertilizer. It has already been predicted that industrial and agricultural utilization of rare earths will rapidly grow in the next few decades (Volokh et al., 1990), whereas in line with these human activities concentrations of rare earths will increase in the environmental system (Zhimang et al., 2001). However, Tyler (2004) stated that amounts of rare earths annually applied to soil are certainly much smaller compared to those already present. Hence, regarding currently recommended application rates, thousand of years may pass before the natural rare earth pool will be doubled.

Yet, rare earths originating from anthropogenic sources usually enter the environment in much more soluble and reactive forms, thus are biologically more available (Zhang and Shan, 2001). This is of particular concern as they may dislocate the balance of the biogeochemical cycle of rare earths (Shan et al., 2002), cause adverse effects on the integrity of the soil ecosystem (Ichihashi et al., 1992), (Wang et al., 1997b) or even exert toxic effects on the aquatic system (Boger et al., 1997). Finally, rare earths will find their way into the human food path through ingestion. Toxic effects of rare earths and several adverse health effects due to continuous occupational and environmental exposure have been reported and have been described in Chapter 6. Even though most of the ingested rare earths will be excreted, uptake of small amounts into the blood vessels and consequently into various organs cannot be excluded. Therefore, thorough investigations on environmental contamination of rare earths are highly recommended, and as to their use in agriculture, their chemical behavior in soil is of special interest. Yet, since in most countries rare earth utilization is currently restricted to industry, serious considerations on their environmental impact in general and in particular regarding their agricultural application have not been made (Li et al., 2001). Thus, at present only little information is available in this respect, which will be presented here.

7.1 Concentrations of Rare Earths in Soil

In order to assess environmental pollution due to excessive application to agriculture, reference values on their concentrations in soils but also in plants are indispensable. In multiple studies rare earth contents in the soils of different countries have been determined (Diatloff et al., 1996), (Yoshida et al., 1998), (Krafka, 1999), (Wyttenbach et al., 1998a), (Zhang and Shan, 2001) and their results are presented in Table 7.1. In most soils, rare earths were found in very small quantities which is consistent with an earlier report describing the total content of rare earths in soils to be of the order of mg/kg (Robinson et al., 1958).

For the determination of rare earths in various environmental samples, such as soil, accurate and precise analytical techniques are necessary, for which NAA and ICP-MS are most commonly used (Chapter 8). Among different types of Chinese soil, variations in rare earth concentrations have been reported (Kabata-Pendias and Pendias, 2001). The total amount of rare earths in soils gradually decrease from south to north and from east to west. They usually are in the range of 108 - 480 μg/g with an average of 196 μg/g. Similarly, mean values of 176.8 mg/kg (ranging from 85.0 - 522.7 mg/kg) were reported in another study. The content of light rare earths made up the main part with 83 - 95 %, while cerium accounted for 48 % (Liang et al., 2005).

	Diatloff et al. (1996) Australian soil ICP - MS	Yoshida et al. (1998) Japanese soil ICP - MS	Krafka (1999) German farmland NAA	Wyttenbach et al. (1998a) Swiss forest soil RNAA	Krafka (1999) German forest soil NAA	Zhang and Shan (2001) Chinese soil ICP-MS
La	2.7 - 24.3	1.20 - 51.1	14.5 - 40.1	17.8	4.8 - 46.6	1.20 - 51.1
Ce	21.0 - 120.3	2.46 - 116	27.3 - 79.5	36.1	10.4 - 100.8	2.46 - 116
Pr	0.8 - 6.8	0.28 - 11.7	-	-	0.28 - 11.7	-
Nd	2.8 - 24	1.08 - 43.5	12.9 - 32.6	15.0	4.2 - 41.5	1.08 - 43.5
Sm	0.4 - 4.6	0.21 - 8.73	2.46 - 6.8	2.82	0.81 - 8.49	0.21 - 8.73
Eu	0.1 - 1.6	0.05 - 2.57	0.5 - 1.29	0.513	0.15 - 1.75	0.05 - 2.57
Gd	0.6 - 4.3	0.23 - 8.71	-	-	-	0.23 - 8.71
Tb	0.1 - 0.7	0.03 - 1.40	0.34 - 0.95	0.381	0.1 - 1.18	0.03 - 1.40
Dy	0.3 - 3.2	0.19 - 8.21	1.97 - 5.44	-	0.56 - 8.63	0.19 - 8.21
Ho	0.1 - 0.4	0.04 - 1.80	0.35 - 1.1	-	1.14 - 1.54	0.04 - 1.80
Er	0.1 - 1.6	0.13 - 5.10	-	-	-	0.13 - 5.10
Tm	0.1 - 0.2	0.02 - 0.77	-	-	-	0.02 - 0.77
Yb	0.1 - 1.5	0.12 - 4.99	1.03 - 3.4	1.47	0.24 - 3.67	0.12 - 4.99
Lu	0.1 - 0.2	0.02 - 0.78	0.16 - 0.56	0.205	0.04 - 0.52	0.02 - 0.78

Table 7.1: Concentrations of lanthanides in various soil samples in ppm.

In Australia, rare earth concentrations in soil solution from nineteen unamended soils ranged from below the limit of detection (0.007 μmol/l) to 0.064 μmol/l (Diatloff et al., 1996). The addition of $CaCO_3$ to the soil increased the solution pH and decreased the total concentration of rare earth elements, whereas inverse effects were seen after the addition of $CaSO_4$. Lanthanum and cerium constituted the greatest fraction with highest concentrations being 0.13 μmol/l for lanthanum and 0.51 μmol/l for cerium. The exchangeable rare earth elements however only accounted for 0.07 - 12.6 % of the total rare earths. Contents of 2.4 mg/kg EDTA - extractable lanthanum and 7.7 mg/kg total lanthanum were measured in Australian soil in other studies (Buckingham et al., 1995). Comparable higher concentrations of 30 - 40 μg/l of light rare earth elements (La, Ce, Nd) were also determined in other soil solution studies (Casartelli and Miekeley, 2003). Nevertheless, concentrations of rare earth elements determined in soils from various places have been shown to be very similar. Furthermore, the distribution patterns observed resemble the one found in the upper continental crust (Wyttenbach et al., 1996), and hence are equal to those of many other soils found worldwide (Kabata-Pendias and Pendias, 2001). A fact that has been ascribed to the nature of the parent rock.

7.2 The Accumulation of Rare Earths in Soil

Pollution from industry and agriculture has been reported to increase the soil's loading significantly usually through the addition of sewage sludge, mining waste and factory effluent (Jones, 1997). To evaluate the enrichment in the studied material, crust-normalized rare earth patterns are used since the abundance of rare earths in uncontaminated biological materials, such as plants, sewage sludge etc., reflects the one found in the earth's crust (Ichihashi et al., 1992).

It should also be noted that many phosphate fertilizers, if derived from apatite, contain appreciable amounts of rare earths as contaminants that may also influence the concentration of rare earths in soil and plants cultivated on it (Wyttenbach et al., 1998a), (Abdel Haleem et al., 2001). Potential accumulation of rare earths may therefore not only occur due to rare earth fertilizers or waste products, but also be expected as a consequence of long-term application of phosphate fertilizers. Russian scientists who analyzed phosphorus fertilizer production to evaluate the environmental pollution in soil found an increased storage of rare earths in agricultural plants (Volokh et al., 1990). Accordingly, enhanced contents of soil exchangeable rare earths, which however remained under 10 %, were reported after the treatment with rare earths (Ding et al., 2003). The composition of exchangeable rare earths in soil gradually approached that in extraneous rare earths while remaining constant over the treatment of rare earths at 200 mg/kg. The application of rare earths furthermore increased the contents of exchangeable heavy metals as well as of Fe, Mn and Zn with Mn responding the most. This indicates that continuous application of rare earths may lead to rare earth accumulation in agricultural soil. In addition, this may cause potential detrimental environmental issues followed by adverse health effects through bioaccumulation along the food chain.

Yet the contrary was demonstrated for foliar-dressing in a long-term in-situ experiment carried out over 11 years (Liu et al., 1997), (Liang et al., 2005). During the three-leaf stage of spring wheat, *Changle*, a rare earth-containing microfertilizer, was sprayed onto the leaves by 600 g per hectare (net content of rare earth elements was 204 g/ha), which is a relatively small amount compared to rare earth contents in soils themselves (Liu et al., 1997). After 11 years of foliage-dressing, contents as well as distribution patterns of rare earths in soil were still within the range of the soil background. This indicated that foliage-dressing with *Changle* fertilizer did not result in significant accumulation of rare earths in soils. Accordingly, studies on the determination of rare earth contents in atmospheric particles (36 ng/m^3), in rain water (5-7 μg/l soluble rare earths), soil water (1-4 μg/l soluble rare earths), surface runoff (5-7 μg/l soluble rare earths) and different parts of corn revealed that additional application has no influence on their concentration (Wang et al., 2001d).

Within the scope of another study, several waste ash samples were analyzed to assess their potential risk to soils. Total contents of rare earths ranged from 54 to 130 mg/kg with the following order: Ce > La = Y > Sc > Nd > Sm > Pr > Gd > Dy > Eu > Tb > Er > Yb > Ho > Lu > Tm. In contrast to animal and horticulture waste ashes, elevated values were observed for Sc, Sm, Eu, Gd, Tb in sewage sludge ashes and for Eu, Tb in incinerator bottom ashes. Both were slightly enriched in La and Ce. Food scrap ashes were only slightly enriched in Sm, Eu and Tb (Zhang et al., 2001a). Comparing the concentrations of rare earths in waste ashes with those determined in different agricultural soils indicated that continuous application of sewage sludge and incinerator bottom ashes may cause an accumulation of Sc, Sm or Eu in some of the soils. Phytotoxic or other adverse effects due to over-application of waste ash to agricultural land cannot be excluded. However, most of the rare earth elements in waste ashes were normally distributed and the pollution is therefore not regarded severe.

In this context, it may also be relevant that if rare earths improve feed-utilization, as reported with respect to animals (Chapter 12), they will consequently reduce the amount of faeces, thereby diminishing the environmental impact due to slurry disposal. Along with the restriction of antibiotic performance enhancers, application of copper and zinc to animal husbandry, especially to pigs, has increased tremendously. A recently conducted investigation observing the impact of heavy metal by economic fertilizers (slurry from pigs and cattle) over several years reported increased values of Cu and Zn since 1999, though in the period of 1986 - 1990, decreases were noticed (Müller, 2002). In accordance with that, increased copper and zinc contents were found in the liquid manure of pigs which will cause remarkable environmental loads. The use of rare earths as feed additives may therefore reduce the application of copper and zinc and decrease their environmental pollution.

Concerning the causes of rare earth accumulation in soil, further studies were performed in order to determine how rare earths may affect the soil-system as will be reported next.

7.3 Effects of Rare Earths on Soil Nitrification

Literature has shown that nitrogen transformation in soil can be affected by heavy metals such as Cu, Ni, Cd, Cr and As (Ladislav, 1995) and a few reports exist on the effects of rare earths on nitrogen transformation in soil (Zhu et al., 2002), (Liu and Wang, 2001). They have revealed that the effect of lanthanum on nitrification in soils was smaller than that of heavy metals. Nevertheless, interactions between rare earths and nitrogen in the soil plant system is considered very important for the safety assessment of agricultural used rare earths.

Rare earths applied at doses higher than 5 mg/kg dry soil were shown to affect the contents of soil available N and NH_4^+ - N significantly, whereas soil NO_3^- - N contents remained unchanged (Liu and Wang, 2001). A correlation was found between the decrease in soil-available nitrogen concentration and the inhibition of soil urease activity. The decrease of soil nitrogen may therefore be ascribed to inhibitory effects of rare earths on the enzymatic nitrogen mineralization. 5 mg of rare earths per kg dry soil were set up as no observed effect level (NOEL) as to the potential influence of rare earths on the chemical transformation and availability of soil available nitrogen. Inhibition of nitrification at high doses was also observed by Zhu et al. (2002). Yet at lower concentrations, soil nitrification was stimulated slightly by lanthanum with a stimulation rate of 20 % at 150 mg/kg dry soil in red soil and of 14 % at 300 mg/kg dry soil in fluvo-aquic soil. In red soil, ammonification was significantly reduced in doses of 900 and 1200 mg lanthanum per kilogram dry soil, whereas in fluvo-aquic soils, except at 600 mg/kg dry soil, lanthanum reduced soil ammonification in doses from 60 - 1200 mg/kg dry soil. In paddy soil however, ammonification was strongly stimulated by lanthanum. Based on those findings, it can be assumed that application of lanthanum accelerates the transformation of nitrogen in soils at low dosage. It was further concluded that the currently applied dosage in Chinese agriculture cannot inhibit soil nitrification and ammonification even after long term successive application.

7.4 Effects of Rare Earths on Soil Micro-flora

The fact that rare earths have been shown to influence a large variety of microorganism (Muroma, 1958), (Talburt and Johnson, 1967), (Zhang et al., 2000c), (Zhang et al., 2000b) (Chapter 5) has caused for concerns about the possible impact of rare earths on soil micro-flora. The soil micro-flora plays a major role in the living pool of soil organic matter and it is furthermore responsible for essential parts of the major nutrient cycles on Earth (Jenkinson and Ladd, 1981). Changes of the micro-flora due to rare earth application may therefore have great consequences. It has been reported that the functioning of soil-plant systems can be highly affected by agents which suppress or adversely affect soil organisms or change the quality or quantity of organic matter either in the short or long-term (Brookes, 1995). After entering the soil, heavy metal elements usually stimulate soil bacteria at low level while harming them at high level. Similarly, rare earths may change the population of microorganism found in the soil system to various extents (Ma et al., 1996), (Tang et al., 1998a), (Chu et al., 2001b), (Tang et al., 2004). It was reported that various microorganisms present a high capacity of absorbing rare earth ions, such as Gd^{3+} (Andres et al., 2000).

At moderate concentrations, lanthanum could increase the soil microbial biomass as well as the population of bacteria, actinomyces, azotobacter and nitrifying bacteria, whereas excessive application resulted in the inhibition of all microbial properties of the soil (Chu et al., 2001b), (Chu et al., 2001a). Inhibitory effects in association with increasing doses were also observed by Xu and Wang (2001), while stimulating effects of lanthanum on microbial biomass have however not been found. Non observed effect concentration (NOEC) were reported to be 432 mg lanthanum per kg soil. Consistent with Xu and Wang (2001), Chang (2006) observed inhibitory effects on the total number of soil bacteria after rare earths accumulated at 5 to 50 % of absorption capacity (ADC). Usually, there are two ways to express the amount of rare earths used in soil application. The amount may relate to the rare earth adsorption saturation (percentage of the maximum adsorption) or to the concentration used (mg/kg).

In further studies designed to evaluate the ecological effect of rare earths on soil micro-flora, different accumulative concentrations of lanthanum (Tang et al., 1998a) and cerium (Tang et al., 1997a) were applied to simulate the situation of long-term application of rare earths elements. For lanthanum, the results were as follows:

- La had inhibitory effects on the total number of soil bacteria at an accumulation of 5 to 50 % of adsorption capacity (ADC)

- La stimulated the growth of actinomycetes below 30 % ADC, highest effects at 20 % ADC
- La strongly stimulated the total number of fungi up to 50 % ADC, highest effects at 30 %
- La stimulated aerobic cellulolytic bacteria below 10 % ADC; while up to 50 % ADC La stimulated celluolytic fungi
- La slightly stimulated soil ammonifiers below 10 % ADC, while above 10 % La had inhibitory effects

In total, it has been shown that, from 5 to 10 % ADC, lanthanum had different stimulatory effects on aerobic cellulolytic bacteria, actinomycetes and ammonifiers, while inhibitory effects on the total number of soil bacteria were observed at all concentration levels (Tang et al., 1998b). Only slight differences were seen between lanthanum and cerium. Soil bacteria were inhibited by lanthanum above 5 % adsorption capacity (5 % ADC) and cerium above 10 % ADC, whereas actinomycetes were stimulated by both lanthanum and cerium between 5 and 20 % ADC but inhibited at high accumulation. At 5 to 50% ADC, lanthanum and cerium strongly stimulated soil fungi. In pure culture studies, some plant pathogenic bacteria as well as the activity of some enzymes related to pathogenesis were shown to be affected by rare earth elements (Tang et al., 1998c).

A recently conducted study on the ecological effects of low dosage mixed rare earth accumulation on major soil microbial groups revealed continuous stimulation of soil fungi and alternative effects of stimulation, inhibition and re-stimulation on soil bacteria and actinomycetes (Tang et al., 2004). Inhibitory effects of rare earths on the three groups of soil microorganisms were in the order of bacteria $>$ actinomycetes $>$ fungi. A remarkable change in the population structure of these soil microorganism was observed at an accumulation rate of 150 mg/kg of rare earths. But median effect concentrations (EC_{50}) of rare earths were 24.1 mg/kg for soil bacteria, 41.6 to 73.8 mg/kg for actinomycetes and 55.3 to 150 mg/kg for fungi. In contrast, no obvious influence of rare earths on soil bacteria was observed by Ma et al. (1996), whereas the biomass of soil fungi and actinomycetes increased by a factor of ten and two to three, respectively. Stimulation of fungi and actinomycetes at high levels of lanthanum was also observed by Xiong and Zhang (1997), while low accumulation levels inhibited bacteria. At 5 % ACD (0.354 mg/g/ soil), however, lanthanum had no obvious effect on soil microbial flora.

Based upon these results, it can be concluded that the ecological structure of microorganism in soil might be changed to various degrees under the stress of high concentrations of rare earths. However, according to current application rates of 750 - 1500 g/m^3 (Xiong and Zhang, 1997) or $<$ 0.23 kg/ha per year (Xu et al., 2002) in China, an accumulation of 5 % ADC or 30 mg/kg dry soil as critical limit (Tang et al., 2004) has been determined in order to assure safe long-term application of rare earths in Chinese agriculture.

7.5 Bioavailability of Rare Earths in Soil

A wide range of information on the bioavailability of rare earths in soil and their uptake by plants will be given in Chapter 11. However, as that information is indispensable in order to evaluate the potential health risk of rare earths in a contaminated environment, some of these aspects shall also be mentioned in this section.

It is generally agreed that the total concentration of metals in soil and water is neither a good indicator of bioavailability nor a good tool for potential risk assessment (Shan et al., 2003b). However, in extracted soil solution, rare earths can be found in different fractions: the water soluble fraction, the exchangeable fraction, the carbonate bound fraction, the sulfide bound fraction, the one bound to Fe-Mn oxide as well as the one bound to organic matter and the residual fraction (Li et al., 1998a), (Wang et al., 2001c). Several studies reported that the water soluble and exchangeable forms of rare earths are the ones most available to plants (Zhang and Shan, 2001), (Cao et al., 2000b), (Wen et al., 2001), (Xu et al., 2001). Yet the contents of various forms of rare earths as well as the transformation and distribution of rare earths in different fractions in soil are closely related to the physicochemical properties of soil itself (Liang et al., 2005) including soil pH, organic matter, cation exchange capacity (Li et al., 2001), (Jones, 1997), and organic acids (Davies, 1992), (Yang et al., 1999), (Shan et al., 2002), (Shan et al., 2003b).

Rare earth concentrations in the exchangeable faction range from trace amounts to 24 mg/kg, which equals to 10.5 % of the total rare earth concentrations (Zhu and Xi, 1992). Very small amounts of the water soluble and exchangeable fractions were also reported by Cao et al. (2000b), whereas the residual fraction accounts for the majority with 45.2 to 94.7 %. Residual forms of rare earths are stable under natural conditions, while other forms are unstable and may therefore be activated easily. Most of non-residual rare earths are bound to carbonates, Fe-Mn oxides and organic matter and the amount of rare earths in different fractions follows the order residual $\gg$ bound to organic matter $>$ bound to Fe-Mn oxides $>$ bound to carbonates $\gg$ exchangeable and water soluble (Zhang et al., 1996b). Hence, lowest amounts of rare earths are found in the most available fractions, which are considered of great importance as to environmental behavior. Studies on their contents, distribution and their ratio to total rare earth elements are therefore of high interest.

Average contents of water soluble rare earths were in the range of 10 - 20 mg/kg (Zhu et al., 1996). However, values may vary within soil-types and layers, which may be attributed to differences in rainfall, contents of organic matter and clay as well as soil pH. Acidity of the soil solution and the volume of acids may apparently cause the leaching of rare earths from soil. Yet, leaching property depends on soil-types and individual rare earth elements (Pang et al., 2002). The effect of soil pH on the bioavailability of rare earths will be further described in Chapter 11. Measuring the activity of glutamic oxaloacetic transaminase (GOT) may additionally provide useful information on the bioavailability and accumulation of rare earths, since a good correlation was observed between bioaccumulation values of rare earths in plants and the enzyme activity of GOT (Zhimang et al., 2001).

7.6 Rare Earth Transfer from Soil to Plants

Generally, low soil plant ratios (transfer factors) of 0.04 to 0.09 have been described for rare earths (Tyler, 2004), indicating low concentrations of rare earths in plants. Even lower transfer factors of 0.02 to 0.03 were reported by Krafka (1999). As described above, rare earth bioavailablility depends on their concentration in different fractions of the soil solution. For metals in general, concentrations in soil solution are most likely controlled by adsorption and desorption processes. Similarly, information on how rare earths are fixed and released as well as on the fixing and releasing rates have also been shown to be necessary for the prediction of bioavailability of rare earths (Wen et al., 2002). While desorption is generally reported to be very low, adsorption capacity of rare earth elements may vary with the clay type and the amount of amorphous iron and manganese oxides, the latter having the highest adsorption abilities (Peng et al., 1996). In China, rare earth adsorption was demonstrated to increase from South to North, thus correlates with the cation exchange capacity (Chang et al., 1998). Furthermore, it was shown that the migration distance of rare earths was very low, which coincides with low desorption reported for rare earths in soil. Depending on the soil pH, migrating distances of 1 cm/year were reported in acid soil with low absorption capacity; whereas in alkaline soil, the migrating distance was only 2 cm every 5 years.

Almost complete absorption of cerium III in soil occurred within 0.5 min in a study using the radioactive nuclide ^{141}Ce, whereas 1 to 30 min were necessary for cerium III desorption (Li et al., 2001). Thus, a fast reaction of rare earths with soils followed sorption from solution, whereas desorption took place at relatively slow rates. This leads to the conclusion that rare earth bioavailability decreases with time, which is further associated with reduced uptake by plants. Accordingly, applied rare earths (2 - 60 mg/l) were rapidly converted to other forms (Liu et al., 1999b). In addition, a time-dependent reduction in the soluble exchangeable fraction was observed. At the same time, rare earths complexed to organic matter remained unchanged at first but then increased, while Fe-Mn-oxide bounded rare earths initially increased, but later also decreased. Over the whole time, residual rare earths remained stable. Similar results were reported by Huang et al. (2002).

In accordance with Li et al. (2001), nearly complete absorption of lanthanum has also been observed in another study. Syha (2005) reported that the application of lanthanum at 10 mg/kg soil resulted in 80 % absorption by soil while smaller amounts were totally absorbed by soil. Based upon the incorporation of lanthanum ions into the soils matrix, the risk of increased toxicity using high amounts of lanthanum may therefore be considered minute. Furthermore, Syha (2005) demonstrated that even high-dose application of lanthanum only caused little accumulation in plants. Yet, higher values were obtained after foliar application of lanthanum chloride.

Studies on the dose-dependent accumulation of individual rare earth elements in different parts of crop plants upon addition of rare earths are very important for the safety assessment of agricultural rare earth application. Consistent with Syha (2005), no significant accumulation of rare earths in root and leaf was observed by Liang et al. (2005) after soil dressing. In contrast, compared to the control, foliage-dressing also caused higher accumulation of rare earths in root and leaf, but no significant difference in stem and crust. After foliage-dressing the contents of rare earths at the maturing stage of spring wheat were in the order of root $>$ leaf $>$ stem and crust. Yet after long-term foliage-dressing, no accumulation of rare earths was observed in spring wheat grains. Furthermore, no obvious accumulation was seen in grains of winter wheat when soil was treated with 2550 g/ha or three times higher amounts of rare earth elements (7650 g/ha) (Wang et al., 2001a). Thus, for both soil and foliar dressing methods, no distinct residues of rare earths were found in plant grains as can be seen in Tables 7.2 and 7.3.

According to Xu et al. (2002), at dosage of less than 10 kg rare earths per ha, no apparent accumulation was observed in maize grains. It was therefore concluded that even over a long period the dosage of rare earths ($<$ 0.23 kg/ha per year) currently applied in China can hardly affect the safety of maize grains. In wheat seed, rare earth contents ranged between 10^{-11} g/g and 10^{-8} g/g. Compared with the mean value of total rare earths in Chinese soil of 177 mg/kg, concentrations in seeds were three to four orders of magnitude lower than that in soil. However, its distribution pattern was similar to that in the soil (Liang et al., 2005). Similarly, pot experiments showed that after rare earths were sprayed on plants, their concentrations in the edible part of corn (grain) were below 0.09 mg/kg (Wang et al., 2001b). At an application rate below 32 mg/m^2, no dose-dependent accumulation was seen. Doses used in farming practices are reported to be in the range of 16 mg/m^2.

	Control (mg/kg)	Soil dressing (2550 g/ha)	Soil dressing (7650 g/ha)
La	0.0081	0.0079	0.0920
Ce	0.0182	0.0238	0.0197
Pr	0.0021	0.0028	0.0024
Nd	0.0079	0.0088	0.0086
Sm	0.0027	0.0038	0.0040
Eu	0.0017	0.0022	0.0002
Gd	0.0008	0.0012	0.0020
Tb	0.0002	0.0003	0.0002
Dy	0.0009	0.0016	0.0010
Ho	0.0004	0.0004	0.0008
Er	0.0009	0.0010	0.0018
Tm	0.0003	0.0002	0.0005
Yb	0.0009	0.0006	0.0008
Lu	0.0003	0.0006	0.0002
Σ REE	0.0458	0.0552	0.0514

Table 7.2: Concentrations of rare earths in winter wheat grains after soil dressing (Liang et al., 2005).

	La	Ce	Nd	Sm	Eu	Tb	Yb	Lu
Control	0.005	< 0.0075	< 0.04	0.0007	0.0006	< 0.0002	< 0.0008	< 0.0002
Application	0.004	< 0.0075	< 0.04	0.0007	0.0004	< 0.0002	< 0.0008	< 0.0002

Table 7.3: Concentrations of rare earths in grain of spring wheat after foliage-dressing with rare earths (Liang et al., 2005).

After long-term field studies performed over 12 years using foliar dressing of 16 mg/m^2 rare earths, no increase in rare earth concentrations in corn grain was observed while rare earth concentrations in other parts of corn were obviously higher in rare earth treated plants (Liu et al., 1997). It is therefore assumed that with regard to the concentration of rare earths of 0.04 - 0.3 mg/kg, observed in naturally grown corn grain (Wang et al., 2001b), application of rare earths at the present dose level in China should be safe for human and animal consumption. Certified reference values for rare earths in wheat flour are shown in Table 7.4.

Based on results from basin and field experiments using rare earth fertilizers, a safety interval of 25 days between spraying and picking was suggested for tea (Wang et al., 2003a). Concentrations in new shoots have been lower than those in other parts of tea plants and similar to those in control groups. In tea fusion, rare earths were mainly bound to polysaccharide and a decrease in the amount bound was observed with time.

In contrast to plant grains, there are a couple of reports on dose-dependent accumulation of rare earths in plant roots as well as in other plant parts due to agricultural application (Xu et al.,

	GBW08503 (wheat flour) certified value (ng/g)
La	15.1 ± 1.6
Ce	27.9 ± 3.09
Nd	14.8 ± 2.0

Table 7.4: Rare earth elements in certified reference material (wheat flour) by ICP - MS (Shan et al., 2003b).

2002), (Xu et al., 2003). Significant higher values were obtained in plant roots and stems after the application of 1 mg/kg rare earths. Although at low concentrations, contents of individual rare earths in overground plant samples were similar between control and treated group ranking in the order of Ce > La > Nd > Pr > Sm; another concentration order of La > Ce > Nd > Pr > Sm was noticed when rare earths were applied at higher doses, clearly indicating the incorporation of exogenous rare earths into plant tissues (Wang et al., 2001b). Increased rare earth concentration in root, leaf and stem following the application of rare earth fertilizers were also observed by (Wen et al., 2001). Even though rare earths accumulated in edible parts of vegetables, no significant accumulation was noticed in cereal grains.

In pot experiments conducted by Wang et al. (2001b), a dose-dependent accumulation of rare earths was observed in the roots of maize plants. Values were much higher in roots than in stem or leaves which was not only attributed to the assimilation of rare earths by roots, but also to their adsorption on the surface of the root system. Concentrations in stem were only one-sixth of those found in roots with a different dose-dependent behavior than the one observed in roots. Yet in leaves, a significant dose-dependent accumulation was not noticed at all and concentrations were much lower. Xu et al. (2002) however reported a significant dose-dependent accumulation of individual rare earth concentrations in both plant roots and tops of field grown maize after soil application. Yet, no obvious accumulation of individual rare earth elements was induced at concentrations below 10 mg/kg soil, whereas doses of 50 mg/kg soil resulted in a preferred accumulation of lighter rare earths in both roots and tops of corn (Xu et al., 2003). Compared to cerium, lanthanum was shown to be taken up selectively by a factor of two-thirds. In addition to concentration, accumulation also varied with both the method and timing, that is the plant growth stage at which rare earths were applied.

Further studies performed by Xu et al. (2002) showed that at high concentrations (2 kg rare earths per ha) accumulative concentrations of the light rare earths (La, Ce, Pr, Nd) and of gadolinium in the tops were even higher than in the roots of maize plants. Thus, under experimental conditions, a fast transport from the root to the tops occurred, which was particularly observed at low dose application. Easy (Wang et al., 2001c) and rapid (Ichihashi et al., 1992) translocation of rare earths to leaves have been reported before. Incorporation of exogenous rare earths in the plant, and a translocation process of rare earths from plant root to leaf or from leaf to root, respectively, when rare earths are applied to soil or to leaves, was highly assumed by Wang et al. (2001b). Yet, at the same time a homeostatic regulation mechanism for excessive uptake of rare earths by plants to control the rare earth concentrations in plant has also been suggested, which coincides with Diatloff et al. (1995b) and Chang (1991). Similarly, Xu et al. (2002) described an obvious reduction in their concentration in maize roots following rare earth application at very high doses of 100 kg rare earths per ha. Since this reduction was associated with decreased dry weight of the maize root and the presence of yellow spots in old leaves, it may be ascribed to certain plant protection mechanisms (Diatloff et al., 1995b). Reduced amounts of biomass in ryegrass plants were also observed after soil-dressing with 200 mg/kg rare earths, while additionally the average height of the plants decreased (Liang et al., 2005).

Toxic effects of high-dosed rare earth fertilizer were also demonstrated on root tip cells of Vivia faba, a field bean species thereby affecting its root growth (Qu et al., 2001). Within the scope of studies performed on the toxicity of rare earths on plants, which were based on methods recommended by the OECD (Organization for Economic Co-operation and Development), values ranging from 694 to 3916 mg/kg for the median growth concentration (EC_{50}) and from 967 to 4781 mg/kg for the median lethal concentration (LC_{50}) of rare earth oxides were reported. Additionally, it was shown that these values varied with crop species and soil types. For LC_{50} values, among the species tested lowest toxicity was seen in rice (Zhang et al., 2001c). However, values obtained have been lower than those of other heavy metals such as mercury (EC_{50} of 100.1 mg/kg), cadmium (EC_{50} 188.8 mg/kg), lead (EC_{50} 401.3 mg/kg), arsenic (EC_{50} 84.7 mg/kg) and aluminium (EC_{50} 810.2 mg/kg) (Chang, 2006), (Zhang et al., 2001b).

7.7 Accumulation in Plants

Concentrations in plants have generally been reported to be very low. However, the capacity of plants or agricultural crops to accumulate rare earths and thus the contents of rare earths may vary extremely depending on the plant species as well as on their growing conditions including rare earth contents in the substrate soils or rocks (Volokh et al., 1990), (Ichihashi et al., 1992), (Wyttenbach et al., 1998a), (Fu et al., 2001). Investigations on rare earth concentrations in corn and rice presented different results for both plant species (Li et al., 1998a). Higher values were found in rice which indicated that rice has a higher accumulation ability for rare earths than corn. Though much higher concentrations were observed in roots compared to other parts of the plants, in grains of both rice and corn, only Y, La, Ce, Pr and Nd could be determined quantitatively with values ranging from < 0.78 ng/g to 5.58 ng/g whereas other rare earth elements were close or below the limit of detection.

Usual rare earth contents are in the range of ng/g for ordinary plants (Wyttenbach et al., 1994). Concentrations of spruce needles, blackberry leaves and some other plants are presented in Chapter 11 (Tables 11.11, 11.12, 11.14). Nevertheless, higher rare earth contents have been reported for plants growing on high mineralized grounds (Miekeley et al., 1994). In addition, certain plants, including ferns and hickory trees, are capable of accumulating rare earths, thus being called hyperaccumulators (Robinson et al., 1958), (Koyoma et al., 1987), (Ichihashi et al., 1992), (Wei et al., 2001). Furthermore, Chua (1998) reported beet and apple to be among major biological stores of rare earths.

Researchers have suggested capitalizing on these hyperaccumulators, such as certain ferns, as indication plants to assess rare earth contamination, thus the environmental loads (Wei et al., 2001), while the safety of agricultural application of rare earth elements may additionally be assessed by determining gadolinium contents. Since both field (Xu et al., 2002) and experimental trials (Xu et al., 2003) demonstrated that increased application doses of rare earths result in positive gadolinium contents, which were more obvious in the plant tops than in the roots, the so-called gadolinium anomaly has been proposed as an important parameter.

7.8 Effects of Rare Earths on the Aquatic Environment

As a result of increased industrial and agricultural application, rare earths may also accumulate in the aquatic environment. This may not only impair the environment but also harm humans by getting into groundwater. There are two ways how rare earths may enter groundwater (de Boer et al., 1996). On the one hand, rare earths which are already present in soil may dissolve into the groundwater, while on the other hand, those brought onto the soil surface may migrate through different soil layers until reaching the groundwater. Despite this knowledge, only a few investigations have been performed on the effects of rare earths on the aquatic flora and fauna and on the contents of rare earths in natural or drinking waters.

Similarly to soil, an inverse correlation between the concentration of rare earths and the water pH was reported in river waters (Goldstein and Jacobsen, 1988), (Keasler and Loveland, 1982). Alkalinity was furthermore shown to correlate negatively with the uptake of lanthanides, indicating that increasing complexation reduced bioavailability. For dissolved lanthanum, which is mainly complexed to carbonates and dissolved organic matter, concentrations ranged from 0.82 μg/l to 23 μg/l. Accordingly, rare earth concentrations up to 1 μg/l were reported in surface waters. In the solution phase of river waters, a depletion of light and an enrichment in heavy rare earths has been found which might be ascribed to increased solution complexation with important ligands (F^-, CO_3^{2-}, OH^-, HPO_4^{2-}). Furthermore, cerium and europium anomalies were found in the water. According to soil solutions, different fractions of rare earths could be determined in five different streams in Finland. Among these was a cationic fraction, which was dominated in rare earth rich runoff from acid sulphate soils and depleted in heavy rare earths probably due to hydro-chemical and geochemical processes, an anionic fraction, a third fraction presumably consisting of colloidal rare earth elements and a minor particle-associated fraction.

Investigations on rare earth contents in raw and drink water samples of 18 groundwater stations and two surface water stations revealed dissolved rare earth concentrations of up to 30 μg/l in groundwater which is used for the preparation of drinking water. High concentrations were only determined when groundwater was won at moderate depths having low carbonate contents. Significant amounts of rare earths were measured in raw water samples of eight locations and in the drinking water of three locations. At two of the three locations, indicative admissible drinking water concentrations were exceeded for a number of rare earths by a factor of up to seven, thus possible health risks for humans could not be excluded (de Boer et al., 1996), (Moermond et al., 2001), (Astrom and Corin, 2003).

Results obtained from studies on the effects of rare earths on aquatic plants are quite similar to those reported for plants in general. Thus, environmental residues of rare earths could enter into the aquatic flora as demonstrated for Eichhornia crassipes, a water hyacinth (Chua, 1998). Consistent with reported conditions in soil, plants also assimilated rare earths via the root system in contaminated water while further distribution to various parts of the plant followed. Additionally to roots, accumulation also occurred in plant leaves. Moreover, leaves exposed to atmospheric contaminants have also been able to take up rare earths. Under testing conditions, both nil effects (Hu et al., 1996) as well as growth stimulation (Hu et al., 2003) of algae (Chlorella pyrenoidosa) have been reported at lower concentrations (2 mg/l). Yet with increasing concentrations, toxic effects in terms of inhibited growth and reproduction were observed. The order of toxicity EC_{50} 96 hours was $Nd > Ce > Pr > La >$ mixtures. Though the differences in toxicity were quite small, slightly higher values were obtained for Nd compared to the mixture of rare earths. On this basis, it was concluded that high concentrations of rare earths found in substrate water may impair the aquatic flora. Furthermore, due to accumulation in plants, rare earths may also enter the human food chain thus potentially endangering public health, especially in China, as water hyacinths are often fed to pigs (Chua, 1998).

Dissimilar to the typical distribution pattern of rare earths reported in plants with main accumulation in roots, in water hyacinths rare earth contents were found to be in the order leaves $>$ stem $>$ root. Furthermore, a dose-dependent accumulation was also observed. At concentrations of 0.4 ppm rare earths in the substrate water, accumulation of rare earths in plants was 8.8 times higher while especially the leaves accumulated rare earths up to a concentration ratio of 13.9. However, consistent with the suggested plant protection mechanism (Diatloff et al., 1995b), a decrease in these concentration ratios was observed at high rare earth concentrations until they approached constant values (Chua, 1998).

In contrast to rare earth accumulation behavior in aquatic plants, considerable low uptake was reported in fish under experimental conditions (Tu et al., 1994). After continuous exposure of carps (Cyprinus carpio L) to solutions containing 0.50 mg/l of lanthanum, gadolinum and yttrium respectively at a pH of 6.0 for 45 days, skeleton, muscle, gills and internal organs were analyzed for their rare earth contents. The bioaccumulation was reported to be in the order of internal organs $>$ gills $>$ skeleton $>$ muscle. Heavy rare earths generally presented lower concentrations than light rare earths. Besides very low accumulation, neither synergistic nor antagonistic effects were seen in carp after being exposed to rare earths. In tuna muscle, concentrations of rare earths were below the limit of detection (Riondato et al., 2001). Riondato et al. (2001) further reported that compared to low up to sub μg/g concentrations of rare earths in calcareous soil and river sediment, those in aquatic plants and mussel tissue were considerably lower (low to sub ng/g). On this basis, the risk of rare earth accumulation in the aquatic environment is suggested to be minute for both aquatic animals as well as humans. For Daphnia carinata (water fleas), the following chronic toxicity were reported (Barry and Meehan, 2000): 43 μg/l (soft tap water), 1180 μg/l (hard water) and 49 μg/l (diluted sea water). In addition, at concentration $\leq$ 57 μg/l no effects on growth were observed, yet, lanthanum caused a delayed maturation in Daphnia. Studies have also been performed on Tetrahymena shangaiensis (shrimps) in order to investigate the aquatic toxicity of rare earths. Results suggested a dual effect of rare earths with growth stimulation at low concentration and toxic effects at high concentrations (Wang et al., 2000c). The same was reported by Kong et al. (1998), with the sequence of toxicity being in the order $Gd^{3+} > Y^{3+} > Sm^{3+} > La^{3+}$.

7.9 Transfer into Human Beings through Foodstuffs

Besides raising environmental concerns following excessive rare earth application, it has also been objected that rare earths may enter the food chain though plant uptake, which might be deleterious to human health. Hence, this objection shall be more closely focused upon in this section. The risk of rare earths transferring into human beings via food originating from animals will be discussed along with animal product safety after rare earth application to animals in Section 12.2.2.

According to extremely small concentration ratios (CR) reported by Henkelmann et al. (1997) and Wyttenbach and Tobler (2002), transfer of rare earth elements from soil into plants is very low. Concentration ratios of rare earths expressed as mass of rare earths in dry weight of plant per mass in dry weight of soil were reported to be $0.8 \cdot 10^{-3}$ (Weimer et al., 1977), (Linsalata et al., 1989). A field study investigating the uptake of light rare earths in an area containing high amounts of rare earths in soil, reported mean concentration ratios ($\times 10^{-4}$) for edible vegetable samples of 22.5 for lanthanum, 16.8 for neodymium and 9 for cerium (Linsalata et al., 1989). Consequently, concentrations of rare earths have to be very low in plants. Several reports (Sun et al., 1994), (Li et al., 1998a), (Wang et al., 2001b), (Wen et al., 2001), (Wang et al., 2001a), (Xu et al., 2002), (Liang et al., 2005), as presented in Section 7.6, confirmed very low concentrations of rare earths in cereal grains and no significant accumulation due to rare earth fertilization. Thus grains and products made of them such as wheat flour are considered to be safe. Slightly higher concentrations were determined in other plant parts. Although concentrations are quite low (Syha, 2005), (Ichihashi et al., 1992), (Wyttenbach et al., 1994), transfer into humans cannot be fully excluded.

Analysis of several vegetable foodstuff (Ji et al., 1985b) showed rare earth concentrations to be in the range of 0.5 - 2 ppm (rice: 0.5 - 1 ppm, wheat: 1 - 2 ppm, vegetables, melons, fruits mostly: < 0.5 ppm). In addition, after rare earth application, no significant increase of residues was observed in wheat plants. Another study on the migration and transformation of rare earth elements in food chain (Gao, 1998) also reported very low rare earth concentrations in food (0.05 - 2.0 mg/kg). However, after treating plants with rare earths, a slight increase was observed in the residual level.

The acceptable daily intake (ADI) of rare earth nitrates for humans was reported to be 0.2 - 2 mg/kg (referring to rare earth oxides 0.1 - 1 mg/kg) (Ji et al., 1985b). Accordingly, a daily intake of 12 - 120 mg/person/day rare earth nitrates (referring to rare earth oxides 6 - 60 mg/person/day) was considered as safety standard (Henkelmann et al., 1997), (Ji et al., 1985b). This limited range exceeds the possible intake (2.10 - 2.50 mg/person/day) for people living in China, which was calculated from studies on rare earth contents in vegetable foodstuffs (Su et al., 1993). Consequently, it can be assumed that there is no risk for humans accumulating rare earths through vegetable food that is the food chain. Low transfer through the food chain may also be supported by low levels of rare earths determined in human tissues and fluids as shown in Tables 7.5 and 7.6.

	Liver^a	Ovary^a	Skin^a	Urine^a 24 h (μg)	Lymph-nodes^b	Cerebrospinal-fluid^b
La	0.08	0.002	0.072	0.28 - 0.71	61.4 ± 8.8	0.1 ± 0.06
Ce	0.08	0.006	-	36	158.3 ± 58	1.6 ± 0.08
Nd	-	-	-	-	51 ± 10.4	0.1 ± 0.06
Sm	-	-	0.07	-	9.8 ± 3.5	0.1 ± 0.06
Eu	-	-	-	-	61.4 ± 8.8	0.1 ± 0.06
Gd	-	-	-	-	-	-
Tb	-	-	-	1.6 ± 8.8	0.034 ± 0.03	-
Yb	-	-	-	-	5.7 ± 2.4	0.015 ± 0.05

Table 7.5: Concentrations of rare earths in human tissue and fluids for tissues in ng/g or for fluids in mg/l , no values reported for Dy, Ho, Er and Tm; (Iyengar et al., 1978)^a, (Sabbionia et al., 1992)^b.

Nevertheless, investigations on rare earth contents of people working in rare earth's mines demonstrated higher contents in the hair of workers (Pang et al., 2002). This was supposed to

	Total blood	Plasma	Serum	Lung	Bone	Brain	Heart
La	-	< 0.006	< 0.006	0.01	0.2	0.001 - 0.036	0.0012
Ce	< 0.002	-	-	0.05	-	-	-
Nd	< 0.001	< 0.002	< 0.03	0.0062	-	-	-
Sm	0.008	< 0.002	< 0.07	0.003	-	-	0.006
Eu	< 0.004	< 0.004	< 0.2	0.001	-	-	-
Gd	< 0.0086	< 0.002	< 0.1	0.02	-	-	-
Tb	-	< 0.0006	< 0.09	-	-	-	-
Dy	< 0.008	< 0.002	< 0.1	0.002	-	-	-
Ho	< 0.002	< 0.002	< 0.2	0.001	-	-	-
Er	< 0.008	< 0.006	< 0.03	0.002	-	-	-
Tm	< 0.002	< 0.0006	< 0.1	-	-	-	-
Yb	< 0.006	< 0.002	< 0.1	-	-	-	-

Table 7.6: Concentrations of rare earths in human tissue and fluids for tissues in ng/g and for fluids in mg/l (Iyengar et al., 1978).

reflect the transfer of rare earths from soil and plants to humans. Yet, concentrations of rare earths in the atmosphere were reported to be less than 0.62 mg/mg^3 at work sites, whereas CeO_2 was 0.33 mg/m^3. These values were only one-fifteenth of the maximum acceptable concentration (5 mg/m^3) defined in the former Soviet Union (Ji et al., 1985b). Higher values for rare earth dust (0.97 - 2.80 mg/m^3) were measured in another study. According to Chinese hygiene standards, they were still within the normal range (Guang-Li Zhao and Jun Tian, 1995). Furthermore, significant differences were neither observed during physical examinations nor in blood, urine, coagulation time or liver function tests (Ji et al., 1985b). In contrast to that, slight deviations of blood parameters, including decrease in total protein, albumin, β - globulin, glutamic pyruvic transaminase, serum triglycerides and immunoglobulins as well as increase in cholesterol, have been determined in human beings from regions containing high amounts of rare earths (Zhang et al., 2000a). It was suggested that these blood deviations might be attributed to prolonged intake of rare earths along with the food chains. While in women altered blood parameters went back to normal, this process was reported to be irreversible in males. Another study demonstrated no obvious differences between pregnant females working in a rare earth producing factory and the control group (Guang-Li Zhao and Jun Tian, 1995), whereas compared to the control, there was a higher tendency to low birth weights.

Effects of excessive rare earth intake on the central nervous, cardiovascular and immune system were also reported. In China, significant decreases in the intelligence quotient were observed in children living on high rare earth containing soil (Zhang et al., 1999a), whereas in adults, the conduction time from the median nerve to the thalamus was found to be reduced. Yet studies on long term application of rare earths reported that up to 4,2 mg rare earths did not cause any negative effects on the intelligence quotient of children, Zhang et al. (1999b) cited in (Richter, 2003). Normal uptake of rare earths was considered to be around 3.33 mg rare earths per day, whereas subchronic toxicity concentrations of 6 - 6.7 mg was determined. In addition, it was reported earlier that the presence of cerium in diets of poor people living in India may be a contributing factor for the development of endomyocardial fibrose (EMF) (Valiathan et al., 1989). This disease mainly affects children and young people and is especially found among those obtaining their carbohydrate intake from tropical tubers grown on high cerium soils. Cerium contents of 467 ng/g in yams, 466 ng/g in tapioca and 173 ng/g in taro were reported (Eapen, 1998). However, further studies indicated that EMF results from magnesium deficiency in association with excessive cerium intake.

Although it is very unlikely that excessive intake of rare earths may occur through edible vegetables, further research on possible effects of rare earths on humans after oral intake are recommended.

7.10 Conclusions and Research Needs

The application of rare earths to industry and agriculture is constantly increasing, which consequently leads to scattering and bioaccumulation of rare earths in the environment. Thus, rare earths may influence the plant and soil ecosystem including the aquatic environment. Furthermore rare earths may also affect animals, and last but not least, human beings through accumulation along the food chain. Until now, only little information is available on the impact of rare earths on the environment especially due to agricultural application, as in most countries rare earth elements are only used in industry. However, as to rare earth concentrations and their distribution patterns in soils it has been stated that they are quite similar among different soils tested. For Chinese soils, average values have been reported to be around 196 μg/g. Nevertheless, studies on the accumulation of rare earths in soil especially due to agricultural application of rare earths presented different results. While it is generally assumed that long-term application will result in bioaccumulation of rare earths in soil, a recent study demonstrated that foliage dressing over 11 years did not cause any significant accumulation of rare earths. Furthermore, quite normal distribution of rare earths was found in different waste ashes, which indicates only minor environmental pollution as a consequence of waste disposal.

Nevertheless studies were performed to reveal to which extent rare earth accumulation may influence the soil system. Although rare earths have been shown to affect soil nitrification, effects were smaller than those of heavy metals. Inhibition only occurred at high concentrations, whereas 5 mg/kg were considered as non observed effect level (NOEL). Compared to currently applied doses of rare earths to agriculture in China, no inhibitory effects on soil nitrification and ammonification are expected from long-term application. At high concentrations, rare earths have also been shown to change the ecological structure of microorganism in soil with inhibitory effects occurring in the following order: bacteria $>$ actinomycetes $>$ fungi. In addition, stimulation of fungi was reported at high rare earth concentrations. Therefore, a critical limit of 30 mg/kg was determined for accumulated rare earths in soil.

Even though rare earths may potentially accumulate in soil, it is assumed that after rare earth application only very little amounts are available, as the majority of rare earths has been found in the residual form. Furthermore among the non residual forms, lowest concentrations of rare earths were determined for the most bioavailable forms which are found in the water soluble and exchangeable fraction. Moreover, adsorption of rare earths to soil happens very fast thereby additionally reducing their bioavailable forms. Consistent with that desorption and migration of rare earths are reported to occur at very low rates.

With respect to rare earth accumulation in plants following additional rare earth supplementation, results obtained are controversial. However, it was shown that dose-dependent accumulation varied with the method of application. Higher accumulation was reported after foliar dressing whereas the inverse was seen with soil application. Yet, for both methods no residues were reported in grains. In addition, application of rare earths at very high doses caused a reduction in rare earth uptake by plants. Along with that, adverse effects such as decreased biomass occurred. Studying the toxicity of rare earths to plants revealed EC_{50} values of 694 - 3916 mg/kg and LC_{50} values of 967 - 4781 mg/kg, which varied with plant species and soil types. These values were far exceeding the currently applied dosage of $<$ 0.23 kg/ha rare earths per year in China thus indicating that long-term application of rare earths to agriculture in this respect is safe.

The effects of rare earths on the aquatic environment are variable. On the one hand, algae presented a strong ability to accumulate rare earths even if their concentration was quite low in substrate water. Generally low bioaccumulation of rare earths, on the other hand, was observed in carps and tuna muscle.

Investigations on the migration and transfer of rare earths along with the food chain into humans are still very rare. Yet, concentrations of rare earths determined in vegetable (0.05 - 2 mg/kg) were very low. In China, acceptable daily intake of rare earth nitrates of 0.2 - 2 mg/kg was reported to exceed the daily intake of 1.75 - 2.25 mg/person/day of vegetable edibles. Consequently, the risk for humans to accumulate rare earths through consuming vegetable comestible may be considered negligible.

In conclusion, it seems unlikely that rare earths may cause any severe environmental pollution in the near future, as, compared to their ecotoxicity, concentrations are too low. In addition, their use as feed additives might even have positive effects on the environment. Regarding improved feed conversion, rare earths can reduce the amount of feces produced in animal husbandry and thus the environment load associated. Notwithstanding, it might be possible that rare earth contents in soil and water may reach unfavorable levels around strong point sources. Yet, currently recommended application levels for the agricultural use of rare earths in China do not seem to be of great environmental concern. However, systematic research into the environmental biogeochemical behavior of rare earth elements in soil-plant systems is not satisfactory at present and information on the fundamental mechanisms in plant metabolism as well as on the effects of rare earths in humans after oral uptake is still lacking. Thus, until now, the ecological consequences of extensive fertilization using rare earths may not be predictable sufficiently. Further research might be advised prior to the application of rare earths as either fertilizers to plants or feed additives to animals. Research needs include:

- Thorough investigations on the dynamic changes and fates of rare earths used as fertilizers
- Estimation of indirect effects of rare earths on human health and ecosystem due to their use in agriculture
- Assessments of rare earths as hazards in their use in agriculture
- Development of standards for soil and water quality
- Consequence of the transfer of rare earths to water and plants

An international association for the research on rare earth eco-physiology has already been created (Fink, 2005). Participating countries are Germany, China, Brazil, Argentina and Austria. Research will be focused on the metabolism of rare earths while background information on natural rare earth concentrations, solubility of rare earths and biological transfer will also be provided.

CHAPTER 8

METHODS OF ANALYSIS

INCREASING interest in the use of rare earth elements in agriculture, animal production and medicine requires an accurate determination of rare earths in various samples. Furthermore, the determination of rare earths becomes more and more important with respect to environmental issues and food safety. Therefore, this chapter will be dedicated to the establishment of authoritative and accurate methods of analysis. Within instrumental multi-element chemical analysis in general, many methods for the qualitative and quantitative determination of rare earth elements are delineated. These include different spectrometric techniques, such as atomic absorption and emission spectroscopy (AAS and AES/ OES) as well as mass spectrometry (MS), which have undergone remarkable changes by the use of inductively coupled plasma (ICP-AES and ICP-MS). Furthermore, there are chromatographic techniques (HPLC) and radio-analysis (NAA) (Houk, 1978), (Evans, 1990), (Alfassi, 1998), (Krafka, 1999), (Nopper, 2003). X-ray fluorescence analysis, which is a variation of luminescence analysis, has also been documented for rare earth determination in plant samples (Zhou, 1995). Other methods include polarography, which is based upon the reduction of lanthanide 3+ to lanthanide 0 or lanthanide 2+ if this is stable, however, it is rarely used today.

At present, NAA and ICP - MS are the preferred analytical methods regarding rare earth determination in animal and human tissue as well as in environmental samples (Tyler, 2004), (Liang et al., 2005) and will therefore be treated here. Their principles, instrumentation and basic analytical capabilities will be chosen for a general description. Additionally, the chapter will exemplify some uses that will be given closer attention in Chapters 10 and 12, yet, sample preparation will only be given marginal treatment in this description. In the end, NAA and ICP - MS are shortly compared with each other including their major advantages and disadvantages. A full treatment of the currently available studies would exceed the purpose of this thesis. Thus, for a more comprehensive study the following sources are recommended Topp (1965), Ryabchikov et al. (1959), de Soete et al. (1972), Bowen (1975), Houk (1978), Boynton (1979), Krafka (1999), Alfassi (1998).

8.1 Neutron Activating Analysis (NAA)

Neutron Activation Analysis was discovered in 1938 when Hevesy and Levi (Boynton, 1979) found out that samples containing rare earths become radioactive after exposure to a source of neutrons. Today, it still constitutes a highly sensitive and accurate technique for both qualitative and quantitative detection of rare earth elements especially at low concentrations, while other routine methods, such as AAS, ICP - OES and ICP - MS, find it difficult to determine rare earths at very low levels. Limits of detection for rare earth elements are presented in Table 8.1. The principle of NAA is quite easy to understand, even though, neutron activation analysis is constantly improving, as detailed information on the properties of decay, γ - energies and γ - emission probabilities become more and more available and new detector systems are developing (Krafka, 1999).

La	Ce	Dy	Eu	Er	Gd	Ho
0.05	0.2	0.00003	0.0001	0.002	0.007	0.003
Lu	Nd	Sm	Tb	Tm	Yb	Sc
0.0003	0.03	0.001	0.03	0.2	0.02	0.001

Table 8.1: Detection limits (μg) of rare earth elements for neutron activation analysis (Krafka, 1999).

Generally speaking, a nuclear reactor is used as the source of neutrons in which a sample is irradiated in a flux of thermal neutrons (median neutron energy of 0.025 eV). Alternatively, particle accelerators or radioactive nuclides may be used. After the absorption of neutrons into their atomic nucleus, stable isotopes of the elements present in the sample turn into instable radioactive products, which instantaneously de-excite into a more stable form emitting one or more characteristic prompt gamma rays. As this new configuration mostly yields a radioactive nucleus, further slow emission of gamma rays occurs in accordance with the unique half-life which usually follows radioactive decay (Boynton, 1979), (Reinhardt et al., 2001).

The gamma energy and the half-life time are mutually independent parameters and constitute characteristic features of an element. Their γ spectroscopic analysis therefore permits a definite identification of the radionuclides that are produced, that is of the elements present in the sample (Krafka, 1999). To measure these gamma rays, semiconductor detectors, primarily hyperpure germanium (HPGe) detector systems are employed. These are further associated with other electronics including a computer-based multi-channel analyzer (Glascock, 2005).

For exact information on the concentration, a comparator standard containing a known amount of the element of interest needs to be irradiated together with the sample. Measured on the same detector, the specific activity of the particular element in the sample is equal to the one in the standard. Nowadays, multi-comparator methods are used in which standards of the elements of interest are mixed together, thus creating a single composite standard that can be included in every irradiation (Boynton, 1979), (Glascock, 2005).

Depending on the need for chemical separation, the technique of neutron activation analysis may vary. If chemical separations are required after irradiation in order to remove interfering matrixes or to concentrate the radioisotope of interest, the technique applied is called radiochemical neutron activation analysis (RNAA). There is a further distinction between the chemical separation of the whole group of rare earths or of single elements. With instrumental neutron activation analysis (INAA), no chemical processing is necessary which is particularly important for very rare samples as this method is considered to be nondestructive (Krafka, 1999). In this case, more than thirty elements can be analyzed simultaneously by using automatic sample changer, hence little operator attention is required (Glascock, 2005). If chemical separations are performed before irradiation, the technique is called chemical neutron activation analysis (CNNA), a technique which is usually not needed for rare earth containing samples (Boynton, 1979), (Krafka, 1999).

The application of NAA for the determination of rare earths is quite multi-functional. It comprises environmental (archaeology, geological science, plant and soil science, environmental pollution, food and health related studies) (Wyttenbach et al., 1996), (Yusof et al., 2001), (Abdel Haleem et al., 2001), (Glascock, 2005), industrial (control of cleanness), medical (contents in tissues, nuclearmedical diagnostic and therapy) (Krafka, 1999) and even forensic studies (e.g. in finger printing to compare material found on the suspect with material from the scene) (Boynton, 1979). Some illustrative examples of NAA application, including sample preparation and procedure, will be introduced here. These examples have been selected on the basis of rare earth utilization described in Chapters 11 and 12.

RNAA, for example, has been used successfully to determine rare earth contents in wheat powder and human hair at concentrations of 0.11 - 26.8 ng/g (Cao et al., 2002a). Irradiation was thereby performed at a thermal neutron flux of $3 \cdot 10^{13}$ ncm^2/s. After four days decay, the irradiated samples were dissolved in HNO_3 and $HClO_4$ in the presence of La^{3+} and Ba^{2+} carriers. After complete dissolution, the media was changed to HCl and La^{3+} as well as HF were added to form rare earth fluorides, which were further centrifuged. For sample counting, a computerized HPGe γ-ray spectrometer (2.0 keV) was used.

Li et al. (2002), however, have proven that INAA is also a sensitive, convenient and reliable method for the research on the biological effects of rare earths in animals at low concentration. For sample preparation, a certain amount of organs or serum was taken on Teflon film and dried by an infrared lamp before it was wrapped with aluminium foil for irradiation, whereas bone samples only needed to be heated at 700 °C for three hours before they could be used directly. The samples were irradiated together with the artificially mixed rare earth chemical standards in a heavy water nuclear reactor at a neutron flux of approximately $6 \cdot 10^{13}$ ncm^2/s for 16 hours. After 7 days and after 20 days, the radioactivities were counted with a high purity Ge detector that had a resolution of 1.85 keV.

Rare earth contents in different soils and plants have been determined by using both INAA and RNAA (Krafka, 1999). They were in the range of ppm in soils and ppb in plants. The material was first dried and then dry ground before irradiation. Only plant samples were incinerated before long-term irradiation. Values of both plants and soil from identical sites permitted the calculation of transfer ratios which were in the range of 0.3 - 3 %, and thus provided information on the uptake of rare earths by plants. NAA was further used to determine information on the elemental composition of rare earth containing fertilizers used in China. In addition to soil and plants, samples of muscle, liver, spleen and bone of pigs and broiler have also been tested for their rare earth contents. Those samples were lyophilized before INAA and RNAA respectively were applied (Schuller et al., 2002). In some cases, application of a group separation after irradiation might be useful on account of better sensitivities (Wyttenbach et al., 1996). It ensures that all measured samples have exactly the same composition, and thus are independent of the nature of the irradiated materials.

8.2 Inductively Coupled Plasma – Mass Spectrometry (ICP - MS)

For a long time neutron activation analysis has been the method of choice for ultra trace element analysis providing detection limits of up to 10^{-15} g/g (Krivan, 1985). But with inductively coupled plasma mass spectroscopy (ICP - MS), a further method that is as sensitive as INAA and moreover recording some additional elements has been established (Krafka, 1999).

ICP - MS is based upon the atomization and ionization of a sample in high - temperature plasma (Schmidt and Gebel, 2000). The instrument comprises a sample introduction system, the argon plasma, the interface region with two apertures, a series of ion lenses, a quadrupole mass spectrometer and a detection system, which is attached to a computer (Alfassi, 1998). The sample, typically in liquid form, is pumped into the sample introduction system consisting of a spray chamber and a nebulizer. It emerges as an aerosol and, by using a sample injector, enters the base of the plasma (Thomas, 2001). The plasma is generally produced by the interaction of an intense magnetic field on a tangential gas flow (normally argon) streaming at about 15 l/min through a concentric quartz tube (torch). The gas is thereby ionized. When seeded with a source of electrons from a high-voltage spark, it forms a very high temperature plasma discharge (∼10,000 K) at the open end of the tube (Marabini et al., 1992), (Smarteam, 2005). Traveling through the different heating zones of the plasma torch at atmospheric pressure, the sample aerosol is dried, vaporized, atomized, and ionized. Thus, when it finally arrives at the analytical zone of the plasma, at approximately 6000 till 7000 K, only excited atoms and ions exist that represent the elemental composition of the sample (Thomas, 2001).

In ICP - MS, the plasma torch is positioned horizontally and is used to generate positively charged ions rather than photons (Smarteam, 2005). The extracted cations are further conducted through two orifices called sampler and skimmer into a vacuum chamber, which contains an ion lens system, a quadrupole mass spectrometer and a detector system. Passing the ion lenses, the ions are focused while non-ionized species and photons are excluded. The ions finally reach the mass spectrometer where they are separated according to their masses (Alfassi, 1998). Every element has at least one isotope whose atomic mass is unique, hence constitutes a characteristic elemental feature which enables the qualitative and quantitative analysis of a sample. As single ions are recorded after mass separation, even very small amounts may be detected. Besides qualitative and quantitative analysis, ICP - MS permits the determination of the isotope ratio (Schmidt and Gebel, 2000). Sample preparations might be quite complicated and extraction procedures include nitrohydrochloric acid, boric acid or perchloric acid breakdown as well as microwave breakdown.

For the purpose of rare earth determination the application of ICP - MS can be seen as greatly resembling the one of NAA described in Section 8.1. In animal feeding studies, the actual amount of rare earths present in the feed of pigs (Eisele, 2003) and fish (Tautenhahn, 2004) has been analyzed successfully by ICP - MS. Eisele (2003) has also used ICP - MS to determine the contents of rare earths in organs of pigs. While for feed samples 0.25 g was required, the amount of material needed for organ content analysis was ten times higher. The sample material was heated in a silicate crucible for four hours before it was extracted with HNO_3, H_2O_2 and H_2O at 220 °C. Prior to the determination by ICP - MS, the solution needed to be diluted with H_2O. ICP - MS has further been used for the determination of rare earths in bovine whole blood reference material with satisfying results. It has been found that rare earth elements are ranging from 0.90 pg/g for Tm to 1880 pg/g for Ce (Fujimori et al., 1999). Additionally, Fleckenstein et al. (2004) used ICP - MS for the determination of rare earth contents in different organs of broilers. For the extraction of sample material, a microwave-induced pressure extraction was recommended. With rare earth contents in kidney, liver and fat of 5 - 100 μg/kg, ICP - MS has been proven suitable for the detection of rare earths in animal tissue. For geological reference material, detection limits are listed in Table 8.2.

Element	Sample	Detection limit	Reference
La	geological reference material	26.7 (in μg/g)	Houk (1978)
La	soil/rock	0.01 (ng/g)	Linhardt (1997)
Ce	geological reference material	54.4 (in μg/g)	Houk (1978)
Ce	soil/rock	0.02 (ng/g)	Linhardt (1997)
Dy	geological reference material	6.59 (in μg/g)	Houk (1978)
Eu	geological reference material	1.99 (in μg/g)	Houk (1978)
Er	geological reference material	3.74 (in μg/g)	Houk (1978)
Gd	geological reference material	7.1 (in μg/g)	Houk (1978)
Ho	geological reference material	1.29 (in μg/g)	Houk (1978)
Lu	geological reference material	0.54 (in μg/g)	Houk (1978)
Nd	geological reference material	28.9 (in μg/g)	Houk (1978)
Sm	geological reference material	6.8 (in μg/g)	Houk (1978)
Tb	geological reference material	1.08 (in μg/g)	Houk (1978)
Tm	geological reference material	0.53 (in μg/g)	Houk (1978)
Yb	geological reference material	3.55 (in μg/g)	Houk (1978)

Table 8.2: Detection limits of rare earth elements in geological standard reference material using inductively coupled plasma mass spectroscopy.

8.3 Comparison of NAA and ICP - MS Techniques

Although both methods have shown high sensitivity and comparable detection limits for the determination of rare earths (Krafka, 1999), (Cao et al., 2002a), some advantages and disadvantages exist, as shown in Table 8.3, which will be explained thereafter.

One of the major advantages of neutron activation analysis, especially INAA, relies on their minimal sample preparation requirements. Accordingly it avoids errors due to incomplete extraction, analyte losses or contamination by polluted chemicals that occur in ICP - MS. Sample preparation is confined to weighing into polyethylene or high purity silica tubes and afterwards heat sealed. Required sample quantity are only a few milligrams to a couple of grams while individual chips may also be wrapped with aluminium foil (Boynton, 1979). But solid samples can be analyzed without special treatment.

In the case of ICP - MS analysis, a method originally developed for the analysis of liquid samples, it is necessary to extract the probed material. Nowadays, laser ablation and electrothermal evaporation techniques are available for the analysis of solid samples. For each analyzed material precise optimization is needed, as standardization has proven to be problematic (Moens and Dams, 1995). Nevertheless, with the introduction of laser ablation, inductively coupled plasma mass spectroscopy has been remarkably changed. Hence, LA - ICP - MS is now beginning to displace INAA in the field of archaeology and later may also be used in other fields (Durrant and

Ward, 2005). But the fact that NAA constitutes a nondestructive analysis, which in turn allows repetitive measurements, is probably hard to replace. Furthermore NAA exhibits negligible interferences with both matrix and elements. Moreover, it is independent of the type of chemical bonding. Matrix effects, however, often constitute a problem in ICP - MS. This disadvantage may be overcome by the use of multiple standards and by certain dilution procedures, but currently only at the expense of sensitivity.

As to the number of elements that are determinable, up to 80 samples per day may be analyzed by ICP - MS by providing additional information on the isotope composition of the present elements (Krafka, 1999). By contrast, INAA allows the simultaneous analysis of more than thirty elements with comparatively little time and effort (Glascock, 2005). Compared to spectrometric detection methods, NAA seems very advantageous, as *big samples* up to 1 kg will probably be analyzed in the near future, including very heterogeneous material such as trash (Henkelmann and Krafka, 1999). However, since NAA requires access to a nuclear reactor, it involves the danger of working with radioactive material, hence needs strict security measures. It is also expensive and requires several weeks for the determination of some long-lived elements. As a result, NAA does not pose an alternative for routine analysis despite its very low detection limits. Nevertheless, based on its high sensitivity and accuracy NAA is indispensable especially for the certification of standardized reference material (Krafka, 1999), (Durrant and Ward, 2005).

Neutron Activation Analysis (NAA)	
Advantages	Disadvantages
high sensitivity no matrix interference little sample preparation nondestructive analysis multi-element analysis identification with two mutually independent parameters a) energy of γ - radiation b) half-time of radionuclide	access to a nuclear reactor long analysis duration (especially for RNAA) high costs radioactivity high time and effort
Inductively Coupled Plasma Mass Spectroscopy (ICP - MS)	
Advantages	Disadvantages
high sensitivity high sample throughput information on isotope composition	sample preparation including - contamination hazard - incomplete extraction - loss of analyzed material matrix interferences

Table 8.3: Comparison of the advantages and disadvantages of NAA and ICP - MS.

CHAPTER 9

TECHNICAL APPLICATIONS OF RARE EARTH ELEMENTS

TECHNICAL applications constitute the major part of commercially used rare earth elements in Western countries. But this chapter can only give a brief description due to the multiplicity of applications.

Industrial processes and commercial utilizations of rare earth metals started in 1903, when Carl Auer von Welsbach discovered their pyrophoric properties and thus found alloys which were ideal for the development of flints as they could ignite themselves through scratching with hard and sharp surfaces. Before that, he had already invented what is known as the incandescent mantle or *Auer-Glühkörper* (1891), which, besides thorium, also contained traces of rare earths. Following these discoveries, *Treibacher Chemische Werke* was founded in 1907, and along with that the first industrial production of ferrocerium-lighter flints began. Nowadays, ferrocerium can still be found in every disposable lighter and purchased as *Auermetal* from *Treibacher Industry AG* (Welsbach, 2006), (Calvert, 2003). Yet this is just one example for the multiple technical uses of rare earths.

At the same time industrial production of rare earth materials also developed in other countries including the United States. In 1985 rare earth manufacturing increased tremendously especially in China (Richter, 2003), while at present the worldwide demand of rare earths is still increasing worldwide, as shown in Figure 9.1. The amount of rare earth oxides (REO) processed in 2006 has been estimated to be approximately 108 000 tons. In 1996, 65 % of manufactured rare earth ores originated from China, whereas in the Western world, main production took place in the United States (Haid and Wettig, 2000). Hence, the Peoples Republic of China constitutes the world's largest producer and supplier of rare earths in terms of mineral concentrates, alloys, metals, oxides and other compounds. This is attributed to the fact that large rare earth reserves are found in China (Richter and Schermanz, 2006). Regarding rare earth reserves, China is closely followed by the Commonwealth of Independent States, that is the former USSR, and the United States (Table 9.1).

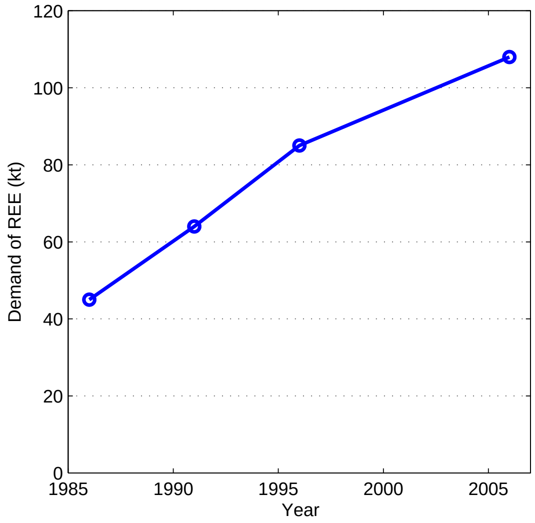


Figure 9.1: Worldwide demand of rare earth elements oxides (in kilo tons) from 1986 - 1996 and estimation for 2006 source; with 45 kt in 1986, 64 kt in 1991, 85 kt in 1996 and 108 kt in 2006 (Haid and Wettig, 2000).

Location	Reserves (kilo tons)		
	economical mined	reserve base	% of the world reserves
China	27000	89000	59.3
CIS	19000	21000	14.0
USA	13000	14000	9.3
Australia	5200	5800	3.9
India	1100	1300	0.9
Canada	940	1000	0.7
South Africa	390	400	0.3
Brazil	110	200	0.1
Malaysia	30	35	0.02
Sri Lanka	12	13	0.008
other countries	21000	21000	14.0
Total	88000	150000	100

Table 9.1: World rare earth reserves (Hedrick, 2004).

In line with the enormously increasing production of rare earths from ≈6000 t/a in 1963 to 85000 t REO in 2002, of which 75000 t were produced in China, research on technical applications of rare earths is progressing as well.

On account of the high disposability of rare earths, prices of rare earth oxides are low. In China, in 1995, they were 16.50 US$/kg for 99 - 99.9 % cerium oxide, 17 - 19 US$/kg for 99% neodymium oxide and 25 - 82 US$/kg for 99.9 - 99.999% yttrium oxide, 280 - 380 US$/kg for 99,95 - 99,99% for terbium oxide and 370 - 420 US$/kg for 99,99% europium oxide (Richter, 1996). Yet low prices as well as great availability of rare earths are not only of interest for industrial production but also their possible use as feed additives. In Switzerland, where rare earth containing feed additives may already be purchased commercially, less than one Swiss franc has to be paid for rare earth supplementation of 100 kg food (one Swiss franc = 0.65 € = 0.78 US$ (Oanda, 2006)) (Azer, 2003), while approximately 5 US$ = 4.15 € are charged for 1 kg of rare earths, in addition to transportation costs. These low costs may additionally be explained by the fact that rare earths used in agriculture are usually gained as by-products of technical processing, whereas high purity products are required for technological purposes.

There are classical applications of rare earths, such as lighter flints, carbon arc lamps, Auer-incandescent mantles, polisher, glass and ceramic additives (Richter, 2003), (Osoon, 2005). Current applications of economic importance, however, comprise their use as catalysts, as additives in glass and ceramic industry (coloring, decoloring, polishing, UV absorber) as well as in metallurgy, as permanent magnets, as fluorescent and pigments and miscellaneous such as laser materials, superconductors, data savers, glass fiber cables, cement-additives or in nuclear technique, magnetic cooling, jewelery, textile refinement, grease, coating, solar energy systems and medical techniques (Haid and Wettig, 2000), (Richter, 2003), (Calvert, 2003), (Chengdu Beyond Chemicals, 2005), (Seilnacht, 2006), (Richter and Schermanz, 2006). As a description of all world-wide usages would go beyond the scope of this thesis some technical applications have been selected as being representative.

The high potential of rare earths in technical applications is ascribed to their chemical and physical properties, which were specified above in Chapter 4. Early uses of rare earths were mainly based on their ease of oxidation, whereas subsequent electronic and magnetic applications rely on further properties arising from their characteristic 4f electrons. Furthermore, their high capture cross sections made them useful tools in nuclear technology.

Being oxidized easily, rare earths are both used as reducing agents for hardly reducible metals and applied as getters, especially in electron tubes at high temperatures. Furthermore, the addition of rare earths to metals or metal alloys leads to desulfurization and deoxidation thereby improving physical properties of these alloys. Inexpensive alloys, such as misch metal which is composed of cerium and lanthanum, are used for this purpose. Hence, deoxidation following cerium addition has been reported to improve softness, density and casting of cast iron, while cerium may also control grain growth in chilled casting. In addition, carbon and other impurities are removed easily in cast iron or steel through rare earth application. Also, grain refining may be promoted in high-grade steel, while rolling, tensile strength as well as impact, creep and corrosion resistance can be increased as well (Gmelin, 1976), (Osoon, 2005). Yet, properties of non-ferrous alloys may also be improved by rare earth addition. Accordingly, grain refining is promoted in Al or Mg containing alloys, while electrical and thermal conductivities may be improved in Al alloys. Furthermore, increased corrosion resistance in Cr alloys and scaling resistance in heater windings in other metals or alloys are found to be improved by rare earths. Their utilization in metallurgy comprises one of the most important fields of rare earth application.

Misch metal is additionally also included in nickel metal hydride rechargeable batteries, which are about to replace nickel cadmium batteries in powering portable electronic devices, such as laptop computers and mobile phones (Osoon, 2005), (Calvert, 2003). Their use in this respect is based upon the ability of alloys composed of (La, Ce)Ni_5 and finely divided Er to absorb large amounts of hydrogen, which in turn enables them to store H_2 in smaller space compared to, for example, compressed gas cylinders (Gmelin, 1976), (Chengdu Beyond Chemicals, 2005).

Furthermore, lanthanide metals were shown to present a certain catalytic potential (Sun and Schumann, 2005) allowing their use in cracking processes (La, Nd and Pr) and in hydrocarbon oxidation (Ce) (Gmelin, 1976), (Seilnacht, 2006). One to five percent of rare earth chloride may already increase the catalysts cracking efficiency of zeolite catalysts. In addition, cerium oxide is also used as a catalyst in self-cleaning ovens (Calvert, 2003). Moreover, rare earths are included in autocatalytic converters and CFC catalysts, in which they may stabilize the gamma-alumina support and enhance the oxidation of pollutants (Krebs, 1998), (Junxi Jan and Jianchun Zhao, 1999), (Osoon, 2005). Accordingly, lanthanum is found in fuel cells (Rhodia, 2005) and cerium in fluid catalysts. Thus, rare earths have been found useful for the control of automotive emission. In addition, their high neutron capture cross sections (especially Sm, Eu, Gd, Dy, Er and Tm) enable them to be used as components of reactor control rods (Gmelin, 1976), (Krebs, 1998), while europium, dysprosium and thulium may also be applied as neutron absorbers to nuclear reactors (Bergmann, 2002). Based upon its ability to absorb neutrons, gadolinium can also be included in neutron-shielding metals (Manych, 2003).

With respect to electronics, rare earths are found in band lamps, ceramics for electronics (lanthanum, cerium, praseodymium), in micro-wave filters (samarium), cathode ray tubes (CRT) and flat plasma tv screens (europium, thulium, yttrium) or as phosphors and luminescence materials (europium, terbium, dysprosium) (Krebs, 1998), (Rhodia, 2005). Praseodymium is also used in television tubes functioning as the activator of green luminescent substances while europium may activate red ones (Bergmann, 2002).

Furthermore, rare earths are applied within the glass industry for coloring and decoloring (Richter, 2003). Lanthanum, for example, is used as glass additive in high quality lenses of optical devices including scientific instruments and cameras (Krebs, 1998), (Seilnacht, 2006), whereas didymium, the mixture of neodymium and praseodymium, is involved in the production of welders' and glass workers' goggles, (Manych, 2003), (Calvert, 2003), (Bergmann, 2002). Moreover, blue colored glass in astronomical and laboratory observation instruments may also contain neodymium as this can absorb the yellow sodium line in the visible light spectrum (Krebs, 1998).

Rare earths also constitute major components of several solid-state lasers including Nd:YAG, Er:YAG, Gd:YAG and Ho-YAG lasers (neodymium, erbium or holmium-doped yttrium aluminium garnet) (Calvert, 2003), with Nd:YAG being among the most important high power lasers applied to both science and technology (Eichler, 2003). It has also been reported that europium may be applied in addition to the glue of postage stamps so that they can be read by electronic sorting machines in U.S. post offices. Promethium, which is not found in daily devices, may however serve as the heat source in spacecraft including unmanned satellites or space probes since it can be used in nuclear-powered batteries (Krebs, 1998), (Bergmann, 2002).

Another field of rare earth application comprises permanent magnets. High performance permanent magnets are usually based upon compounds with outstanding intrinsic magnetic properties, optimized microstructure and alloy composition (Goll and Kronmuller, 2000). It has been early shown that lanthanide alloys with cobalt (e.g. $LnCo_5$) dispose of desired properties in order to serve as permanent magnets (Gmelin, 1976). Thus, pure Ho and Dy, for example, have been useful as pole pieces for low-temperature high field strength magnets. Presently, the combination of rare earth metals (Nd, Pr, Sm) with transition metals (Fe and Co) constitutes the most powerful permanent magnet materials. Permanent magnets are involved in various fields including electrical, automotive and mechanical engineering, computer, telecommunication technology, navigation, aviation and space operations. Though Sm-cobalt ($SmCo_5$-Sm_2Co_{17}) is quite expensive due to the incorporated cobalt, its use as a high performance magnet has already been established in industrial, military and aerospace applications (Calvert, 2003), (Bergmann, 2002). However, cheaper magnets such as neodymium-iron-boron ($Nd_2Fe_{14}B$) also exist and are nowadays found, among other uses, in automobile starting motors, windscreen wiper motors, computer disc drives, compact disc players and camera motors (Osoon, 2005).

Moreover, permanent magnets have also entered medical technology. According to Noar and Evans (1999), rare earth magnets are useful tools in orthodontics in case of tooth intrusion, retainers, expansion and tooth impaction. Yet due to unfavorable corrosion of $Nd_2Fe_{14}B$ magnets, robust coating is required. Furthermore, regarding medical technical applications, rare earths are also found in intensifying screens in radiology (van den Hurk, 2003), (Vetline, 2005), (Klose, 2006) and in X-ray filters (Gmelin, 1976), while ytterbium may also be used in portable X-ray machines, as it can produce X-rays without the need of electricity (Krebs, 1998), (Bergmann, 2002).

Constituting important laser materials, rare earths have also become indispensable in laser medicine (Mordon et al., 1987). Nd, Er or Ho:YAG lasers have been described to be used for therapeutic purposes including various surgical procedures (White et al., 1991), (Marker et al., 1995), (Rofeim et al., 2001). Thus, in terms of lasers, rare earths constitute an important part in dentistry, ophthalmology (e.g. cornea surgery), dermatology, angioplasty (e.g. removal of atherosclerosis), urology, gastroenterology and neurosurgery (Eichler, 2003). Neodymium YAG lasers, for example, can be used for the treatment of papillomavirus lesions (Zaak et al., 2003), at the same time holmium YAG laser lithotripsy is also performed (Shamamian and Grasso, 2004). Yet holmium may also be found in radioactive metallic stents covered with $holmium^{166}$, which have been developed for radiotherapy including malignant biliary strictures (Won et al., 2005).

In conclusion, technical applications of rare earths are highly manifold, as shown in Table 9.2. On the one hand they are part of several daily devices, while on the other, they become more and more important in fields, like spacecraft, military and medicine. Through continuous research their fields of application are both improving and expanding (Schuchardt, 2000), (Manych, 2003), (Sun and Schumann, 2005). As to environmental considerations, new applications may include the substitution of heavy metal as pigments for paint and plastics as well as substitutes of CFC in refrigerators (Osoon, 2005). In addition, they may be applied with superconductors and in cement manufacturing for energy savings.

Element	Application
Lanthanum	superconductors, catalysts, lasers, fluorescent materials, optical devices
Cerium	lighters, catalysts, glass additives, ceramics, magnets filtering rays,
Praseodymium	permanent magnets, lighters, glass additives, ceramics, cryogenic refrigerants
Neodymium	high strength permanent magnets, lighters, lasers, glass additives, infrared filters
Promethium	in terms of nuclear-powered batteries in spacecraft
Samarium	lighters, permanent magnets, condensers, nuclear reactor control and neutron shielding, micro-wave filters
Europium	fluorescent materials, cathode ray tubes, flat plasma tv screen, imaging plates, nuclear reactor control rods
Gadolinium	magnets, glass additives, laser, single crystal scintillator, computer memory chips
Terbium	fluorescent materials, magneto-optical materials
Dysprosium	fluorescent materials, magneto-optical materials, ceramics
Holmium	electrical materials, lasers
Erbium	glass additives (infrared absorber), ceramics, lasers, optic fiber
Thulium	fluorescent materials, cathode ray tubes, portable x-ray machines
Ytterbium	condensers, research
Lutetium	superconductors, single crystal scintillator, fluorescent materials, rechargeable batteries
Yttrium	superconductors, cathode ray tubes, lasers, radars, fluorescent materials, catalysts, ceramics, portable x-ray machines
Scandium	cathode-ray tubes, lasers, fluorescent materials

Table 9.2: Technical applications of rare earth elements.

CHAPTER 10

THE APPLICATION OF RARE EARTH ELEMENTS TO MEDICINE

SOON after their discovery, first medical applications were described for rare earths. These days, the uses of rare earth elements have exceeded technical and agricultural areas and are becoming part of medicine. Comprising many biochemical and pharmacological properties of clinical relevance, lanthanides have been of great interest for medical purposes. They have been shown to act as antimicrobial, anticoagulant, cytotoxic and phosphate-binding substances, while most of their effects are ascribed to their influence on Ca^{2+} - depending processes, which may also be involved in certain diseases. In the past, inhibitory effects of rare earths on calcium-dependent physiological processes constituted the main basis for their pharmacological applications. Yet not all biochemical and pharmacological properties may be attributed to their resemblance to Ca^{2+}. In addition, lanthanides have the ability to accumulate in tumor tissue. As they provide various radioisotopes emitting α β or γ - radiation – some of them even possess paramagnetic properties – they have become useful for anticancer diagnosis and therapy. Nevertheless, first attempts to introduce lanthanides as useful drugs have not been very successful either because of their narrow therapeutic index or because of the development of superior reagents of less toxicity. The situation has changed since the end of the 20^{th} century as research progressed and new ideas for the use of lanthanides were developed (Evans, 1990), (Wang et al., 2003b), (Damment and Totten, 2003). The following sections will present an overview of former, present and future applications of rare earth elements to medicine.

10.1 Former Use of Rare Earth Elements

10.1.1 Antiemetics

The use of lanthanides for medical purposes first began with their prescription as antiemetics. Cerium oxalate introduced as an antiemetic in the middle of the nineteenth century was beneficial in relieving vomiting. Orally applied, cerium oxalate was especially used for the treatment of vomiting during early pregnancy (Simpson, 1854), (Browning, 1969), (Evans, 1990). Subsequently, it was prescribed with various success for all sorts of gastrointestinal disturbances associated with vomiting, even for coughs and neurological disorders (Wilcox, 1916). Investigating the mechanism of its antiemetic property, Baehr and Wessler (1909) found out that cerium oxalate prevented local irritation of the gastric mucosa by forming a protective coating. Though cerium oxalate administered orally was unable to inhibit the vomiting of central origin in dogs, soluble cerium salts, given intravenously, were shown to prevent apomorphine-induced vomiting. A fact that was attributed to poor gastrointestinal absorption and therefore low bioavailability. In order to overcome those limitations including its unreliable therapeutic properties, a new formulation, colloidal cerium oxalate, was introduced. It was predominately prescribed for vomiting in pregnancy and all sorts of motion sickness. Though cerium oxalate stopped being applied for digestive disorders in the early twentieth century, it was still distributed as *Peremesin®* *Heyden* for the treatment of several kinetoses including seasickness. However, around 1950 it was withdrawn from the market because of radioactive residues (Werner, 1955), (Richter, 2006). The replacement of cerium oxalate as to the relief of vomiting in pregnancy and motion sickness was soon found in other drugs (e.g. antihistaminic meclizine) (Jakupec et al., 2005). But even though *Peremesin®* *Heyden* was commercially available until 2005, it did not contain any cerium oxalate but meclozine, as active agent (Apo-line, 2005).

10.1.2 Antimicrobial Agents

Early attention was drawn to the fact that rare earths provide antimicrobial properties and then research strongly aimed at harnessing these properties for clinical use. Yet attempts to use lanthanides as antibacterial drugs in the treatment of tuberculosis, leprosy or cholera failed (Evans, 1990).

10.1.3 Anticoagulation Agents

Nevertheless, preparations containing neodymium, which is the least toxic of the rare earth elements, were introduced in 1936 as anticoagulants and thrombolytic agents. Prolonged clotting time of mammalian blood linked to intravenous administration of lanthanides had been reported for quite some time before lanthanides started being used for clinical purposes (Goosens, 1964). Experiments on rabbits demonstrated that one to two hours after intravenous injection of 60 mg/kg $Nd(NO_3)_3$ the blood did not clot anymore (Beaser et al., 1942). The underlying mechanism is only partly understood. Hunter and Walker (1956) were the first to ascribe the effects of lanthanides to specific antagonism of Ca^{2+} in blood. Today, it is generally assumed that the ability of lanthanides to inhibit certain Ca^{2+} - requiring enzymatic reactions involved in blood clotting accounts for their anticoagulant effect since Ca^{2+} is required for at least four reactions (activation of factor IX and X, conversion of prothrombin to thrombin and cross-linking of the fibrin clot) (Evans, 1990), (Funakoshi et al., 1992). Nevertheless, it is also possible that lanthanides interfere with blood clotting through the inhibition of platelet aggregation. Holmsen et al. (1971) reported that lanthanides are capable of inhibiting ADP-induced platelet aggregation. Nagy et al. (1976), however, found out that a single large dose of La^{3+} interfered with prothrombin activity, while smaller doses of La^{3+} inhibited coagulation through a different mechanism possibly involving a disturbance in liver function. It was hoped that lanthanides could be used in transfusion equipment or in artificial organs taking advantage of both their anticoagulating and anti-inflammatory properties, but later reports of acute and chronic side effects including chills, fever, muscle pain, abdominal cramps, hemoglobinemia and hemoglobinuria indicated their undesirability (Evans, 1990). Despite great efforts which finally lead to the development of less toxic derivatives, rare earths were excluded from the market as safer, more effective and cheaper drugs, such as heparin, became available.

10.2 Present Use of Rare Earth Elements

10.2.1 Lanthanum Carbonate Used as Phosphate Binder

Though in the past, rare earths failed to be introduced in medicine mostly due to the development of more effective and less toxic drugs, the inverse has been shown recently. As it is known that patients suffering from chronic renal insufficiency develop hyperphosphatemia, drugs are required to lower phosphate levels. However, the use of former phosphate-binding agents based on aluminium or calcium has been overshadowed by severe side-effects including aluminium-related bone and central nervous system toxicity as well as increased risks of hypercalcaemia and cardiovascular calcification. Although the more recently introduced drug, sevelamer hydrochloride (*Renagel*®), presented less coronary and aortic calcification and lower cholesterol levels than calcium-based phosphate binders, its application has been limited due to gastrointestinal adverse effects, large pill burdens and high costs.

In search of alternatives, scientists came across lanthanum carbonate, a rare earth salt that provides highly effective phosphate binding properties that make it beneficial for the treatment of hyperphosphatemia. Hyperphosphatemia results from renal failure as the kidney becomes unable to excrete phosphate properly. Left untreated, it will lead to the stimulation of parathyroid hormone and the suppression of vitamin D_3 production. This further causes renal osteodystrophy, metastatic calcification and increased morbidity probably due to increased myocardial, vascular calcification and cardiac microcirculatory abnormalities. In the process of vascular calcification, phosphate seems to play a major role. Additionally, it has been stated that hyperphosphatemia is directly associated with reduced life expectancy. Hence, safe and effective phosphate binders were urgently needed to control phosphate serum levels (Harrison and Scott, 2004), (Behets et al., 2004b), (Hutchison and Albaaj, 2005). Preclinical and clinical studies reported lanthanum carbonate to be an effective phosphate binder with very low toxicity and minimum gastrointestinal absorption thus offering a good safety profile. Oral administration of 1 g of lanthanum carbonate three times daily was proved to be efficient, while additionally showing good tolerability, whether taken during or shortly after eating.

Its efficiency is based upon the formation of a water-insoluble compound after binding to phosphate which enables lanthanum carbonate to decrease serum phosphorus levels, calcium x phosphorus product and serum parathyroid hormone (PTH) levels in patients with end-stage renal disease (ESRD) significantly, while the phosphorus balance is maintained (Fiddler et al., 2003b), (Fiddler et al., 2003a), (Sack et al., 2002), (Hutchison and Webster, 2003), (Hutchison et al., 1998), (Finn et al., 2003), (Finn, 2003), (Stewart et al., 2003), (Hutchison and Albaaj, 2005). Less than 0,001 % of the lanthanum dose was absorbed into the systemic circulation when given with food and even oral administration of a cumulative 15 g dose only resulted in very low lanthanum plasma levels < 1 ng/ml (Stewart et al., 2003), (Fiddler et al., 2003a), (Steward and Frazer, 2002). In addition, it is reported to be well tolerated, whereas most adverse events were mild to moderate in severity with gastrointestinal events, such as vomiting, nausea and diarrhoea, being the most common. Long-term studies have been consistent with previous findings in efficacy and safety. Furthermore, the lack of any acute or long-term central nervous system toxicity confirms the low potential of lanthanum carbonate to enter brain tissue (Harrison and Scott, 2004), (Hutchison et al., 1998), (Pennick et al., 2004), (Jones et al., 2004). Even though it is known that lanthanides are able to bind to DNA, RNA and nucleotides in vitro, lanthanum carbonate has neither in vitro nor in vivo demonstrated genotoxicity, which might be ascribed to the fact that this chemical class is unable to penetrate the cell membrane of healthy, intact cells (Evans, 1990), (Damment et al., 2004). However, Lacour et al. (2005) hypothesized that the accumulation of lanthanum after oral administration in chronic renal failure might be far above the lanthanum concentration observed under normal conditions. They demonstrated that feeding a lanthanum carbonate containing diet to healthy rats led to a tenfold increase of tissue lanthanum contents in some organs including liver, lung and kidney. However, a close focus on the experimental design and the calculation of tissue contents showed that these results have to be considered as artifacts. High contents found in lung tissue turned out to be the result of inhalation of particles from the diet rather than from oral intake since lanthanum carbonate was applied in terms of powder instead of pellets. Lung deposition of rare earth elements following inhalation has been reported before, while, at present, there is no study describing this after oral application. In accordance with this case, Rambeck (2005) has pointed out that caution must be paid when interpreting animal data.

Previous experiences with aluminium-based phosphate binders, which revealed bone toxicity, aroused suspicion towards the use of lanthanum carbonate after effects on bone were observed. Further studies, however, proved that high-dose induced effects of lanthanum carbonate on bone mineralization in chronic renal failure rats are attributable to phosphate depletion and not to direct bone toxicity (Damment and Shen, 2005), (Damment et al., 2003), (D'Haese et al., 2003). On the contrary, lanthanum has even been shown to improve bone-cell activity, it thus demonstrated positive effects on bone metabolism. After one year of treatment, the mean lanthanum content was low and the development of renal osteodystrophy was reduced (D'Haese et al., 2003), (Freemont and Denton, 2004). Based on this information, it can be concluded that patients receiving lanthanum carbonate may be less likely to develop osteopenia. Additional information concerning the possible use of rare earths in the treatment of osteoporosis will be provided in Section 10.3.4.

As to their use in the treatment of hyperphosphatemia, lanthanum carbonate has been granted first global approval as a new effective non-calcium, non-aluminium phosphate binder in Sweden in 2004 (Hutchison et al., 2004). Further marketing approvals were granted in the European Union and the United States in 2005. Presently, lanthanum carbonate is commercially available as *Fosrenol*®, while it will soon be marketed throughout Europe as well (Newswire Europe Ltd, 2005).

Based on these encouraging results, applications might also capitalize on phosphate binding properties of lanthanum carbonate in veterinary medicine. However, first studies designed to investigate phosphate lowering effects of lanthanum carbonate in cats failed to reproduce previously described results. As to phosphate levels in urine no significant differences were observed between animals receiving a lanthanum carbonate containing diet and control animals (Brugge, 2006). Nevertheless, it was reported earlier that phosphate lowering agents successfully used in cats did not affect phosphate levels in humans (Rambeck, 2006b). This indicates that there must be some differences between humans and animals with respect to phosphate metabolism.

10.2.2 Treatment of Burns

So far rare earth applications have not been able to profit from the specific antimicrobial properties of rare earths which are thought to be useful in combatting bacterial diseases, however, these properties are potentially valuable in new areas. In 1976, an ointment containing cerium nitrate-silver sulphadiazine for the topical treatment of burn wounds was introduced publicly (Monafo et al., 1976). Among its several advantages are easy and painless application and removal as well as the production of a yellow and leathery crust with good resistance to infection.

Burn injuries are still of great importance because they produce significant morbidity and mortality in developed countries. In Catalonia, 31 per 100 000 persons each year need special treatment, while the incidence and mortality due to burns is similar to other developed countries (Barret et al., 1999). The so-called burn disease, which causes infection with severe complications after a shock phase, constitutes a major problem in burn patients. High susceptibility to infection is based upon an acute and severe systemic and local inflammatory reaction which results from thermal injury that can be lethal. It has been proven that prompt excision of burn eschar and wound coverage improve chances for survival and prevent postburn immunosuppression (Deveci et al., 2000). Similarly, cerium silver sulphadiazine has also been shown to be safe and effective in the treatment of deep and extensive burns. By improving survival rates comparable to prompt excision, it seems to be a good alternative in patients not undergoing early wound excision and closure because of co-morbidity (Kistler et al., 1990), (Luo, 1990), (Boeckx et al., 1992), (Koller and Orsag, 1998), (Deveci et al., 2000), (de Gracia, 2001), (Lorenz et al., 1988). Scheidegger et al. (1992) reported that one single bathing with 0.04 mol/l cerium nitrate of not less than 30 min, on the first day of burn, neutralizes eschar toxic material and improves the chances for survival enormously.

Cerium nitrate has a potent antiseptic effect in human burn wounds, especially against gram negative bacteria and fungi (Monafo et al., 1976), (Fox et al., 1977), (Wassermann et al., 1989). Thus, it significantly reduces the degree of Pseudomonas aeruginosa contamination and improves cell-mediated immunity (Zapata Sirvent et al., 1986), (Boeckx et al., 1985). The characteristic yellow-green color of cerium nitrate treated eschars may result from oxidation of trivalent cerium to yellow ceric ions thus providing a continuous source of ionic cerium for microbial inhibition (Fox et al., 1977). Suppression of cell-mediated immunity is associated with the absorption of burn toxin known as lipid protein complex (LPC), which stimulates phagocytic cells and thereby causes the release of a variety of inflammatory mediators (Fang et al., 1996), (Eski et al., 2001), (Boeckx et al., 1992), (Monafo et al., 1976), (Sparkes et al., 1990), (Jakupec et al., 2005). It has been observed that cerium nitrate trivalently binds the lipid protein complexes and thus prevents its entry into the circulation (Sparkes, 1993), (Deveci et al., 2000). As an alternative to direct interaction of cerium nitrate with the burn toxin or immunosuppressive factors, Ce^{3+} ions might exert direct impact on the cells producing those molecules (Evans, 1990). IL-6 and TNF-α are important mediators of the acute and severe inflammatory reaction in thermal injury. It was reported that cerium nitrate is capable of suppressing the elevation of TNF-α levels by increasing IL-6 levels (Sparkes, 1997), (Deveci et al., 2000). Both its antiseptic and immunomodulatory properties as well as the formation of a physical barrier made of yellow-green eschar contribute to the effects of cerium nitrate. While Hirakawa (1983) stated that prolonged topical treatment of cerium nitrate/silver sulfadiazine cream or cerium nitrate solution for burn injuries results in considerable absorption of silver and cerium into the liver and the kidney, no increasing toxicity was reported by Boeckx et al. (1992), Fox et al. (1977) and Evans (1990). Nowadays, cerium nitrate-silver sulphadiazine is marketed throughout Europe, but is only available as *Flammacerium*® in the UK (Garner and Heppell, 2005).

10.2.3 Diagnosis and Treatment of Cancer

Cancer research in the early twentieth century aroused interest in rare earth treatments as potential anticancer drugs. In a first instance, a solution of cerium III iodide was applied to patients suffering from lymphogranulomatosis (M. Hodgkin) or inoperable tumors. The results obtained had been highly promising, reducing tumor sice and improving life quality (Lewin, 1924), (Cohn, 1925). It was suggested that cerium might act either on its own or as an activator of iodine. Better effects of cerium iodide, compared to other iodide compounds, had been reinforced in an rabbit sarcoma study (Ito, 1937). In contrast to those findings, Maxwell and Bischoff (1931) could not note any effects of cerium chlorides on tumor tissue using an experimental tumor model in rats.

The development of cancer is thought to be associated with iron overload resulting in activation of the ROS which, along with other factors, leads to intranuclear changes and finally to alterations in cell proliferation and differentiation processes. Within this action, the signal transduction system, cell cycle and immunological functions are also out of order. Comprising iron uptake blocking, ROS inhibiting, signal transduction influencing as well as cell proliferation modulating properties, which were described in Chapter 5, lanthanides provide several abilities that might interfere with the development of cancer. However, the duality of their actions definitely evokes certain problems and studies on anticancer properties of rare earths are therefore still controversial.

Several Chinese studies reported inhibitory effects on growth of sarcoma cells and Lewis lung cancer cells in mice as well as on leukemic cells (Yang et al., 1992b), stomach and lung cancer cells in humans (Wang et al., 2003b). Additionally, Jiang et al. (2004) stated that low dose of lanthanum nitrate could inhibit the progression of preneoplastic lesions in rat hepatocellular carcinoma studies. Antineoplastic action of rare earth elements were also reported in further studies (Liu et al., 1999a), (Yang et al., 1997). It was assumed that anticancer effects are based upon inhibition of tumor cell proliferation, increase in macrophages and polymorphonuclear leukocytes activity as well as T-cell proliferation or selective cytotoxicity (Wang et al., 2003b).

Yet, antineoplastic effects were not only reported in China. Hence, suppression of tumor activity in lymphatic leukemia and lymphosarcoma bearing mice was shown by Anghileri (1975), who related the mechanisms involved to effects on tumor metabolism of calcium and magnesium. Sato et al. (1998) described reduced growth of melanoma cells after lanthanide administration which they attributed to morphological changes and cell cycle arrest in the G_0/G_1 phase. Strong cytotoxic effects of cerium compounds on cancer cells were also shown by Jakupec et al. (2002). They suspected interactions with calcium behind the effect since calcium plays an important role in controlling cell cycle and proliferation processes. Accordingly, Weiss et al. (2001) proved antiproliferative actions of lanthanides on human colon cancer cells to be caused by an interruption of required calcium supply. Further speculations on the mechanism of anticancer action include enhanced expression of tumor suppressor gene, decreased calmodulin levels (Ji et al., 2000) or apoptosis, as is already seen in leukemic cells (Dai et al., 2002). Furthermore, it has been shown that lanthanides may facilitate the cellular uptake of certain drugs, e.g. cisplatin, by increasing cell permeability (Canada et al., 1995) as suspected earlier by Lewin (1924) and Cohn (1925). Although rare earths seem to provide a certain potential for the use in cancer chemotherapy, more detailed research is necessary before rare earths can be applied clinically.

However, as various radioisotopes exist among lanthanides, their ability to emit α, β or γ - radiation may enable them to approach tumor therapy from another direction. Thus, in nuclear medicine and isotopic diagnostics, radionuclides of heavy rare earths (^{177}Lu, ^{153}Sm, ^{171}Eu, ^{157}Dy) have been investigated for their use in bone imaging and internal radiotherapy of bone neoplastic metastases from breast or prostate (Marciniak et al., 1996). In addition, ^{90}Y was shown to be a suitable radionuclide for therapeutic purposes. ^{90}Y is a pure β - emitter with a penetration depth of 1 cm and a half-life time of 60 hours.

Nevertheless, despite their high metabolic affinity for malign tissue which is useful in tumor scanning, lanthanide radionuclides are rather directly placed at the site of the tumor. This can be done by either intra- or peri-tumor injections or by surgical implantation, thereby minimizing any toxic effect on healthy neighboring tissue. Using colloidal lanthanides, one can take advantage of the fact that insoluble complexes are well retained at the injection site (Evans, 1990). But, intraperitoneal administration of lanthanides may be applied in case of ascites tumor. In the past, lanthanum was shown to be a potent inhibitor of Ehrlich ascites tumors in mice, which could successfully reduce the number of tumor cells and prolong the survival (Lewin et al., 1953). Yet, in human tumors, mainly surgical implantation was used, thereby allowing the successful treatment of Nelson’s syndrom, Cushing syndrom as well as treatment of mammary and prostatic carcinoma (Haley, 1979). Treatment of cancers may also take advantage of the fact that tissue concentrations of lanthanides alter during cancer (Evans, 1990). Thus, measuring lanthanide concentrations may provide valuable diagnostic and prognostic information. As to bone seeking radionuclides, such as ^{153}Sm, it has been reported that they may also be used efficiently to relieve the pain originating from bone metastases (Bayouth et al., 1994), (Serafini, 2000).

At present, lanthanide-loaded micro-particulate systems are under investigation for cancer imaging or as radionuclides for therapy. Advanced biodegradable drug delivery systems based on liposomes and polymeric nanoparticle have already significantly improved anticancer therapies. They are effective tools that carry anticancer drugs to their site of action. Co-loading with non-radioactive or radioactive lanthanides may further expand their use (Zielhuis et al., 2005). Additionally, based on their inhibitory action on the reticuloendothelial system (RES), lanthanides might also be able to enhance the effectiveness of monoclonal antibodies and liposome-encoated drugs, thereby preventing their sequestration by the RES.

10.2.4 Contrast Agents

Lanthanides have not only become a useful tool in scintigraphic imaging as described above in tumor diagnostic and therapy, but also as contrast agents in several other imaging techniques. Based upon their paramagnetic properties (Chapter 4), lanthanides have been introduced as contrast agents in magnetic resonance imaging, which is one of the most powerful techniques in medical diagnosis and biomedical research. Administration of contrast media is designed to enhance the contrast between normal and diseased tissue or to indicate organ function or blood flow. Gadolinium was found to be superior to other lanthanides in terms of proton spin-lattice relaxation times (Evans, 1990). Possessing seven unpaired electrons, each gadolinium particle itself is a micro-magnet, thus capable of accelerating the relaxation of water protons in surrounding tissues. In 1988, $[Gd(DTPA)(H_2O)]^{2-}$ was approved as first commercial contrast material (Helm et al., 2003). Presently, gadolinium(III)chelates are widely used as intravenous contrast agents in clinical practice including mammography, diagnosis of liver metastasis or malign liver tumors, or verification of postoperative results, e.g. after liver transplantation or heart surgery by visualizing the blood flow (Bilow, 2002), (Reimer and Vosshenrich, 2004). Furthermore, improved diagnostic illustrations of brain tumors have been reported after using gadobenate dimeglumine, a gadolinium containing contrast agent (Knopp, 2004). In addition, lanthanide containing contrast agents are also applied in computer tomography to sharply brighten the image. Even small tumors of less than 5 mm, which stand out clearly as they do not take up injected lanthanide particles, have thereby been identified in liver tissue (Evans, 1990). Using gadolinium as computer-tomographic contrast agents, good vascular, sufficient renal and suboptimal hepatic enhancements were reported (Gierada and Bae, 1999).

In addition, lanthanides have also been used in cisternography to delineate cavities of extracellular compartments and provide information about fluid flows. Andrews and David (1974) were first to investigate the use of lanthanide DTPA complexes (^{169}Y-DTPA), that are known to be highly stable, for the measurement of spinal fluid kinetics. Thus, images of excellent quality were obtained. Furthermore, intra-articular injections permitted scintographic detection of synovial cysts. As Ln-DTPA complexes are rapidly excreted by the kidneys, they have also become useful markers to monitor glomerular filtration rates (Evans, 1990). Moreover, due to low gastrointestinal absorption, lanthanides are efficient digesta markers in nutritional studies on both experimental animals and humans (Krysl et al., 1985), (Schuette et al., 1993), (FairweatherTait et al., 1997), (Bernard and Doreau, 2000), (Xue and Cui, 2001).

10.3 Potential Future Uses of Rare Earth Elements in Human Medicine

10.3.1 The Treatment of Joint Diseases

Direct intra-articular injection of lanthanide radionuclides may also become established in radiosynectomy, that is nonsurgical destruction of inflamed synovia found under arthritic conditions. Inflammation of synovia, which is the tissue between diarthrodial joints, causes articular destruction, pain, swelling and loss of motion (Evans, 1990). According to Kahan et al. (2004), intra-articular injected ^{169}Erbium citrate was effective in arthritis diseased finger joints, whereas Yarbrough et al. (2000) suggested that ^{153}Sm may be useful for synovectomy of inflamed synovial membranes, as shown in osteochondral chip-induced synovitis. In addition, injection of ^{166}Ho ferric hydroxyide into the joint was safe and effective in patients suffering from chronic synovitis of different origin (Ofluoglu et al., 2002).

Based on anti-inflammatory properties of lanthanides, their use in arthritic joints had been suggested before. The high degree of intra-articular retention after injection as well as limited accumulation in other parts of the body might additionally favor their use in the treatment of arthritis (Evans, 1990). Anti-inflammatory effects of lanthanides were reported in several studies. According to Jancso (1961), angiotaxis and edema following increased vascular permeability, caused by inflammatory agents, was inhibited by several inorganic salts of La^{3+}, Ce^{3+}, Nd^{3+}, Pr^{3+}, Sm^{3+}. This was confirmed by Basile et al. (1984), who described that lanthanide chlorides (Pr^{3+}, Gd^{3+}, Yb^{3+}) decreased histamine and serotonin induced vascular permeability. Furthermore, it was reported that lanthanides may affect several cellular responses to inflammation including the activation of lymphocytes (Yamage and Evans, 1989), macrophages, and polymorphonuclear (O'Flaherty et al., 1978) as well as leukocyte chemotaxis (Boucek and Snyderman, 1976). A high affinity of lanthanides for inflammatory sites has already been revealed in several imaging studies.

At present, rare earth containing feed additives (*Ultra-spur*®) for dogs are commercially available. According to Rowedo (2006), they are expected to support both the formation of bone and joints in dogs. Small amounts of *Ultra-spur*® applied at 1 g per 5 kg to the feed of dogs over an experimental period of four years were reported to decrease the incidence of hip dysplasia. Furthermore, *Ultra-spur*® is recommended to enhance the immune system and prevent gout. Yet this information has to be considered very carefully regarding the questionable reliability of the source as no further scientific data on this product is available.

10.3.2 Prevention of Caries

Though early studies on the use of rare earth salts as caries preventing drugs were controversial, their application as to caries prevention has been proposed by Chinese scientists (Zhang et al., 1999d). While neither topical use of cerium salts nor mouth-rinsing with lanthanum chloride showed any effect (Regolati et al., 1975), (Beazley et al., 1980), yttrium nitrate, in contrast, injected intra-peritoneally or administered via drinking water was capable of reducing caries development in rats (Mercado and Ludwig, 1975). Since rare earths exhibit a high affinity for teeth and bones, this effect was thought to be ascribable to the incorporation of rare earths into the teeth rather than to antimicrobial properties of rare earths (Zhang et al., 1988). Incorporation of lanthanides is supposed to harden tooth enamel by reducing its solubility. These findings were confirmed by Banoczy et al. (1990), who demonstrated cerium uptake in both healthy enamel and into incipient carious lesion. The developed cerium-apatite has proven to be harder and more resistant. It was shown earlier that incipient dental caries at the stage of demineralization can be reversed by local application of fluorides through remineralization. Rehardening of surface enamel after lanthanum treatment was also reported by Collys et al. (1990). They also stated that a solution containing both lanthanum and fluoride could form a protective acid-resistant surface coating. According to Chinese scientists, lanthanum can also successfully prevent degradation processes of cemental root collagen by inhibiting clostridium histolyticum collagenase (Li et al., 1997). The combination of lanthanum and fluoride seems to be more efficient than each by itself (Collys et al., 1990), (Zhang et al., 1999d). Rare earths might therefore become a useful tool for caries prevention.

10.3.3 Prevention of Atherosclerosis

Following reports on the inhibition of atherosclerotic processes due to oral administration of $LaCl_3$ to rabbits (Kramsch and Chan, 1978), it was suggested that rare earths might be capable of generally preventing atherosclerosis. Atherosclerosis is caused by the formation of plaques on the internal surface of certain arteries. By being composed of collagen, elastin, cholesterol and calcium, those plaques can partially or totally obstruct blood vessels and thus provoke myocardial infarction.

Rabbits given a $LaCl_3$ containing diet presented decreased values for total cholesterol, collagen elastin, total calcium and non-lipid phosphorus. $LaCl_3$ showed a dose-dependent protection from increased cellularity of the intima, accumulation of collagen, damaged elastic fibers and from calcium, lipid and glycosaminoglycan deposits in the aorta, pulmonary arteries as well as in the major coronary arteries. No side effects on other tissues or physiological parameters have been reported. Later work has also shown that $LaCl_3$ is not only capable of inhibiting the development of arteriosclerosis but also of regressing already formed plaques (Kramsch et al., 1980), (Kramsch et al., 1981). Another study performed by (Ginsburg et al., 1983) confirmed the suppressive effect of orally administered $LaCl_3$ on atherogenesis in the aorta of rabbits. However, in this study lanthanum chloride was ineffective against the development of atherosclerosis in the coronary arteries. The exact mechanism is still not well understood. But a relation to antagonization of Ca^{2+} - dependent biological processes by inhibiting or replacing calcium is generally agreed, since other calcium channel blockers such as verapamil and nifedipine present similar results (Evans, 1990). Wang et al. (2003b) suggested that lanthanides exert their anti-sclerotic effects by preventing processes involved in plaque formation such as phagocytosis of lipids by macrophages, ROS - related pathological events (oxidation of low-density-lipoproteins, endothelial injury), platelet aggregation and calcification. Notwithstanding previous findings, Zhu et al. (1997) reported a significantly higher incidence of arteriosclerosis of the fundus oculi and a significantly increased serum cholesterol and IgM level among people living in a rare earth area. Thus, a direct or indirect effect of rare earths was assumed. It was suggested that the formation of arteriosclerosis could be facilitated by immunogenic damage of the vascular wall. Yet, Liu et al. (2004) was able to confirm the results obtained by Kramsch et al. (1980). After the administration of lanthanum chloride to rabbits fed a high lipid diet, less pathological changes of atherosclerosis occurred and even already present bone alterations could be reversed to some extent.

Since atherosclerosis is a major cause for cardiovascular diseases, further research on anti-atherosclerotic properties of lanthanides is highly recommended, especially with regard to their low oral toxicity and, according to Kramsch and Chan (1978) and Liu et al. (2004), high effectiveness.

10.3.4 Treatment of Osteoporosis

In line with their high affinity for bone (Arvela and Karki, 1971), (Evans, 1990), it was hypothesized that rare earths might also be used in the treatment of bone diseases. Indeed, within the scope of studying lanthanum carbonate as phosphate binding agents effects on bone mineralization had been evident in chronic renal failure rats. In addition, neither parathyroid hormone levels nor bone histology were affected by lanthanum application (Torres et al., 2003), (Behets et al., 2004a), (Hutchison and Albaaj, 2005), and no toxic effects could be observed on bone due to lanthanum deposition (Malluche et al., 2004a), (Malluche et al., 2004b). Quite the contrary, further studies revealed that lanthanum exerted positive effects on bone metabolism in terms of improving bone-cell activity (Torres et al., 2003), (D'Haese et al., 2003), (Freemont and Denton, 2004). Enhancing effects of lanthanum on bone formation and density, as well as on the activity and differentiation of bone cells have been summarized by Atherton et al. (2002).

Analyzing the location of lanthanum within the bone of chronic renal failure rats, it was shown that lanthanum was mainly located at the bone surface (Beherts et al., 2005), indicating that lanthanum deposition may involve binding to organic matrix, hetero-ionic exchange with calcium and precipitation of insoluble amorphous lanthanum phosphate. Decreases in calcium phosphorous ratios were noticed in pig bones after lanthanides were supplemented at low concentrations to the feed (Knebel, 2004), (Prause et al., 2005c). Yet, they were solely attributed to significant reduced calcium contents. Additionally it was shown that effects on bone calcium contents were dose dependent (Table A.1). At low dose application, calcium contents were reduced, whereas the inverse occurred at high concentrations. Increase in bone calcium levels due to lanthanum treatment was also observed by Torres et al. (2003), while Prause et al. (2005c) described reduced bone magnesium contents. It has been suggested that isomorphically substitution of calcium and magnesium may account for these changes (Evans, 1990). Dose-dependent effects were also demonstrated in another study designed to investigate the effects of lanthanide ions on bone resorbing function of osteoclasts by culturing rabbit osteoclasts on bone slices. While osteoclastic activities were inhibited at low concentrations of La^{3+}, Sm^{3+}, Er^{3+}, Nd^{3+}, Gd^{3+}, the inverse was observed when high concentrations of La^{3+}, Sm^{3+}, Er^{3+} were applied (Zhang et al., 2003). Thus, lanthanides are capable of affecting bone loss dose-dependently.

On this basis, it has been concluded that lanthanum might be useful in the treatment of osteoporosis. This is a hypothesis that could be further fleshed out in recently performed feeding experiments on ovariectomized (OVX) rats that were used as small animal model of postmenopausal osteoporosis. Results from this study revealed that rare earths may restore accelerated bone loss in rats (Wehr et al., 2006). Accordingly, lanthanum was shown to decrease both the urinary excretion of collagen crosslinks (pyridinoline), a specific marker of bone and cartilage collagen degradation correlating with bone turnover (Delmas et al., 1991), and the serum concentration of osteocalcin in OVX rats, while increasing calcium concentrations in tibia bone (Table A.2). Thus, lanthanum was not only capable of normalizing high bone resorption following OVX but also of adding bone to the osteoporotic OVX rats. Similarly, higher osteocalcin levels were observed in humans after lanthanum carbonate application, indicating enhanced osteoblastic activity and bone formation (Malluche et al., 2004a).

Based upon these results, it is suggested that lanthanum may be seen as being beneficial in further studies and possibly also be useful in the treatment of osteopenia following ovarioectomy. The use of lanthanum for the treatment of several bone diseases including osteoporosis has already been patented in the United States (Atherton et al., 2002).

10.3.5 Miscellaneous

Further possible medical applications have been suggested including antidiabetic actions, therapy of skin diseases, prevention of immune-related rejection following organ transplantation as well as inhibition of scar formation.

Antidiabetic actions exhibited by lanthanides comprise hypoglycemic effects (Evans, 1990), inhibition of hepatic gluconeogenesis (Wang and Xu, 2003) and ROS (reactive oxygen species) induced cell injury (Shimada et al., 1996) as well as effects on insulin secretion and insulin receptor binding (Williams and Turtle, 1984), (Enyeart et al., 2002). On this basis, lanthanides may be useful in the treatment of diabetes.

Effective application of lanthanides has also been suggested regarding the suppression of immune response in patients following organ transplantation, as $GdCl_3$ was shown to prevent the induction of portal venous tolerance in rats which had received cardiac allograft transplantation (Kamei et al., 1990). The effectiveness was ascribed to the inhibition of alloantigen uptake by Kupffer cells. Since the formation of reactive oxygen species (ROS) is responsible for microcirculatory failure in rats after liver transplantation, $GdCl_3$ was able to improve microcirculation by reducing ROS-related oxidation processes (Schauer et al., 2001). In a similar manner, the survival rate of rats was increased by $GdCl_3$ after liver transplantation from ethanol-treated donor rats (Zhong et al., 1996). However, prolonged survival was also achieved in rats after human insulinoma cells were implanted to liver tissue (Lazar et al., 1997). These results indicate that gadolinium chloride might be beneficial for the prevention of immune-related rejection and loss of function of transplanted organs.

Furthermore, drugs containing lanthanides have been developed in China for the treatment of serious skin diseases including psoriasis, which is the third most common reason to visit dermatologists, and a patent has already been applied for (China Rare Earth Information Net, 2005).

The cause of psoriasis is still not clarified, however, clinical lesions are the results of hyperproliferation and abnormal cell differentiation in the epidermis. Genetic, immunological as well as environmental factors are considered to be involved in the development of psoriasis (Camisa, 2004). The mechanism underlying the treatment of psoriasis by lanthanides is supposed to comprise interference with cell metabolism and DNA synthesis. Based upon their ability to act as phosphatases, it is assumed that lanthanides may remove pathological changes in the nucleic acid chain, additionally, the structure of diseased skin cells is considered to be affected selectively. Lanthanides may also restrain the expression of psoriasis genes. Furthermore, they can enhance the activity of T lymphatic cells. Clinical trials performed on humans in China demonstrated good results following the application of lanthanide containing products to diseased skin.

In addition, recent experimental results have suggested that lanthanum chloride can prevent and treat scar formation by inhibiting the expression of collagen proteins in wound tissue (Zhong et al., 2003). However, these results need to be confirmed in further studies.

In conclusion, lanthanides have already been established in medicine as drugs (*Fosrenol*®, *Flammacerium*®) and as contrast agents. Nevertheless, based on further useful biochemical and pharmacological properties, such as anti-inflammatory, anti-neoplastic or anti-sclerotic characteristics, lanthanides may find their way into additional medical areas.

CHAPTER 11

APPLICATIONS OF RARE EARTH ELEMENTS TO AGRICULTURAL PLANTS

SOME reports on the action of rare earths on plant growth were published by Russian, Romanian and Bulgarian scientists in the early nineteenth century which reported mostly positive effects. In 1972, systematic research started in China and was beginning to have a practical impact on China's agriculture (Guo et al., 1988). Even shortly afterwards, outstanding growth enhancing results of rare earth applications at low concentrations to various plant species were reported in China and the commercial use of rare earths in agriculture was started. Since the People's Republic of China disposes of large resources, it had been searching for applications which did not require one specific rare earth element, but would allow the commercialization of the whole spectrum of elements in the mix that nature itself provides. A first attempt was seen in the application of rare earth elements as growth stimulants to agricultural plants. In turn this experiment aroused the interest of other countries, especially of those that also possessed large amounts of rare earth resources, such as Australia. However, there was the difficulty that the Chinese research, which provided the only source of information on agricultural use of rare earths, did not become available internationally until the 1990s. Even today most of that information is almost unavailable to Western scientists, since the access to the source is difficult, but also since most reports are only written in native language and were not available in English, which hampers a clear understanding. Additionally, the Chinese papers are often lacking details of experimental methods and statistical treatment of the data, which made a critical evaluation of most of the published information difficult. Thus, knowledge on the efficacy and effectiveness of rare earth application to plant production was still patchy and often hypothetical. Therefore it became evident that basic research on the potential biological activity of rare earths in plants needed to be conducted outside China in order to verify Chinese claims and to provide more detailed information. Yet, studies on the influence of rare earths on plant growth carried out in Australia, Germany and Austria showed conflicting results and there was evidence of both beneficial and detrimental results. In contrast to earlier Western studies performed within the period from the thirties to the seventies, the majority of recent investigations could not confirm the outstanding yield enhancing effects reported in China.

Nevertheless, up to now several hypothesis have been proposed as to how rare earths may effect plant growths. These hypotheses range from predicting effects on transportation mechanisms, accumulation of ions, nitrogen fixation over influences on calcium metabolism and photosynthesis to the protection against certain plant diseases or draught. The high diversity of possible effects of rare earths on plants indicates the complexity of this subject. However, in China, rare earths are not only used as fertilizers in agricultural plants but also as feed additives in farming animals (Section 12.1). Information on the influence of rare earths on plants, therefore, is also valuable for a feasible improvement of husbandry. Since plant and animal production are closely related to each other, they also constitute important background data that pave the way for the potential application of rare earths to farming animals (Chapter 12) in Western countries. It is generally agreed that more than 90 % of orally applied rare earths are excreted in faeces (Chapter 6). Hence, feeding rare earths to animal husbandry will also affect plants indirectly as this automatically leads to increased contents of rare earths in organic fertilizers which in turn are applied to plants. As a result, their effects on plants, including both risks and benefits, need to be evaluated before rare earths can be introduced as performance enhancers to animal production. That information will also be necessary in order to assess the environmental impact of rare earths, which may result from increased agricultural application (Chapter 7).

Therefore, it is the aim of this Chapter to present the results obtained so far in China (Section 11.1) and in other countries (Section 11.2) and compare the yield enhancing effects of rare earths on plants. In addition, their physiological and biochemical effects on plants (Section 11.4) will be included in reference to Chapter 5, in order to provide possible explanations for their influence on agricultural crops. On this basis, further research steps will be presented. Some reviews on this topic have already been published before by Brown et al. (1990), Hu et al. (2004) and Tyler (2004).

11.1 China

11.1.1 Effects of Rare Earths on Plant Growth, Yield and Quality

Today the use of rare earth elements as trace nutrients in agriculture including plants and animals is widely practised in China. Their application to farming animals will hence be described in Section 12.1. In China, extensive research started in 1972, involving both pot trials and field demonstrations, and since then a great variety of plant species has been tested. Different methods of rare earth applications and various concentrations, mostly low ones, have thereby been investigated. To date, yield increases for 50 plant species including cereal, sugar and industrial crops, fruits and vegetables, and for 20 species of trees and pasture grasses have been reported. Some of them are listed in Tables 11.1 and 11.2.

Plant species	Increase in yield (%)	Effect on quality of the product	Reference
Cereal crops			
Maize	6 - 12	–	Guo (1993)
Wheat	6 - 15	tendency of incr. Lysine content	Xiong (1995)
Rice	5 - 15	–	Xiong (1995)
	5 - 10.3	–	Wan et al. (1998)
Oat	6.43 - 26.4	–	Xia and He (1997)
Barley	18.6	–	Xia and He (1997)
Sugar crops			
Sugar Cane	8 - 20	incr. sugar content of 0.5 %	Xiong (1995)
Beet	8 - 15	incr. sugar content of 0.4 %	Xiong (1995)
Industrial crops			
Rubber Tree	6 - 20	–	Xiong (1995)
Tobacco	7 - 16	elevated grade rate of 10 %	Xiong (1995)
Soybean	6 - 12	tendency of incr. protein and oil content	Xiong (1995)
Peanut	8 - 15	–	Xiong (1995)
Cotton	5 - 12	incr. weight of single boll of 0.1 g	Xiong (1995)
		incr. span length of fibre of 0.1 - 0.4 %	
	5 - 10	–	Xia and He (1997)
Ramine	7 - 15	incr. fibre count of 10 - 15 %	Xiong (1995)
Flax	stem 8 - 12	incr. fibre of 10 - 15 %	Xiong (1995)
	seed 10 - 14	–	
Rape	14 - 24	incr. oil content of 2 %	Xiong (1995)
Fruits			
Apple Tree	10 - 22	incr. sugar content 0.5 - 10 %	Xiong (1995)
		incr. Vit. C content of 20 %	
		doubled cyanin content	
Watermelon	8 - 12	incr. sugar content of 0.8 %	Xiong (1995)
	22.9	incr. sugar content	Wan et al. (1998)
Honey melon	75 - 111.4	–	Wan et al. (1998)
Grape	10 - 15	incr. sugar content of 20 %	
		incr. Vit. C content of 20 %	
Chinese Gooseberry	10 - 25	incr. sugar content of 1.3 - 2. %	Xiong (1995)
		incr. Vit. C content of 40 - 42 $mg/100g$	
Banana	8 - 14	incr. sugar content of 3 - 4 %	Guo (1993)
		incr. Vit. C content of 4 - 6 %	Xiong (1995)
Orange	8 - 38	incr. sugar content of 0.6 %	Wan et al. (1998)
Vegetables			
Potato	10 - 14	incr. starch content of 1 %	Guo (1993)
Tomato	16	–	Wan et al. (1998)
Chinese Cabbage	10 - 20	incr. head-forming rate, 3.5 leaves/head	Xiong (1995)
Cucumber	13 - 15	–	Xiong (1995)
Edible Fungus	10 - 30	incr. amino acid content of 40 %	Xiong (1995)

continued on next page

Plant species	Increase in yield (%)	Effect on quality of the product	Reference
Pasture Grasses			
Sibirian Wild Rye	Hay 15 - 25	incr. CP of 3 - 9 %	Xiong (1995)
	Seed 10 - 15	–	
Alfalfa	Hay 5.2 - 33	incr. CP of 3 - 10 %	Xiong (1995)
	Seed 10 - 15	–	
	17	incr. grain weight of 5 %	Guo (1993)
Shadawang	Fresh grass 10 - 20	–	Xiong (1995)

Table 11.1: Effects of rare earth elements on crops and pasture grasses in China; incr.: increased, Vit.: Vitamin, CP: crude protein.

Tree species	Results	Effects on product quality
Changbai Larch	incr. stocking by 6 - 12 % incr. sapling yield by 6000 plants per mu (1 mu = 1/15 ha)	raised grade of stock enhanced resistance
Scotch Pine	incr. stocking by 6 - 10 % incr. sapling yield by 2000 plants per mu	raised grade of stock enhanced resistance
Red Pine	incr. sapling yield by 12.8 %	raised grade of stock enhanced resistance
Chinese Pine	incr. sapling yield by > 10 %	raised grade of stock enhanced resistance
Small Black Poplar	incr. stocking by 10 % incr. sapling yield by 2500 plants per mu	raised grade of stock enhanced resistance
Mulberry	incr. stocking by 15 % incr. leaf yield	incr. soluble sugar by 35 %

Table 11.2: Effects of rare earth elements on trees in China; incr.: increased (Xiong, 1995).

Common responses of plants to rare earth application are to be in the order of 5 to 15 % and sometimes even higher (Xiong, 1995). In addition to plant yield increases, improvements in product quality, comprising increased sugar content in sugar cane, increased vitamin C content in grapes and apples and increased fat and protein content in soybean (Brown et al., 1990), (Wan et al., 1998) have also been reported for a wide range of crops. Furthermore, rare earth supplementation was reported to decrease the content of chemical residues in several crops such as rice, orange, water melon, grape and pepper.

As far as accessible, past and present Chinese literature on the effects of rare earths on growth and yield enhancement as well as on quality improvement in plants will be summarized and presented on the basis of some selected plant species. Some additional information on their possible mode of action is also provided. However, since general physiological and biochemical effects of rare earths in plants may account for their beneficial effects in plants, this whole complex will be discussed in detail in Section 11.4. Although nowadays mostly mixtures of rare earth elements are used in Chinese rare earth-containing fertilizers, in experimental designs both single and mixed rare earth elements were applied in order to evaluate their potential.

Several solution culture experiments with sugar beet seedlings have been performed by Feng (1987). The results showed that in 48 % and in 32 % of all cases, root length and plant height respectively could be increased by the application of rare earths at concentrations of 0.01 % up to 0.1 %, whereas in 10 - 55 % of all cases dry weight was also increased. Furthermore, advanced germination and rhizogenesis were found in sugar beet seedlings after a two year storage period. At high concentrations, however, inverse effects were noticed. Further studies showed that sugar beet seeds without lignified septals presented higher germination rates compared to those with lignified sepals. It was therefore suggested that the lignified sepal might disturb the uptake or translocation of rare earths in plants.

In the last twenty years, extensive research on the application of rare earths to sugar beet has been carried out in China. Out of 124 field experiments. 84 % demonstrated significant improvements in both yield and quality of sugar beets as a result of rare earth application. Average increases of 7 % for tuber yield and 5 % for tuber sugar content were reported in these trials (Guo et al., 1988), (Jie, 1986), (Jie and Zheng, 1988), (Chen, 1986). Similar results were reported in other studies (Xiong et al., 2000). Increased yield and improved quality in terms of higher sugar content were also demonstrated in sugar cane (Saccharum officinarum L.) treated with 300 ppm REE/l (Kuang and Ma, 1998a). Measuring the activity of certain enzymes, an increase in acid invertase and amylase as well a decrease in indoleacetic acid oxidase were noticed. As these changes correlated positively with the observed growth enhancing effects, it has been concluded that rare earths increase yield and sugar content by influencing the enzyme activity in sugar cane.

Moreover, Kuang and Ma (1998b) were engaged in the effect of rare earth elements application on the nutritional metabolism of phosphate in plants. During these studies, rare earths have been shown to enhance the transformation of inorganic phosphate into organic phosphate compounds. Furthermore, higher amounts of nucleic acid, phosphatide and energy rich phosphate could be detected in plants, whereas the contents of phosphohexose decreased significantly. On this basis, it was assumed that these changes favor both the growth of sugar cane as well as the accumulation of sucrose. In addition, experiments with rice using a lanthanum supplemented mixture of rare earth elements showed yield increases of 6.5 % (Wan, 1995). It was observed that rare earths increased the number of tillers and tassels as well as grain weight. Numerous field trials had been performed previously with average increases being 7 % (Guo et al., 1988). It was also stated that spraying a solution of 0.01 - 0.03 % rare earths on rice plants increased the amount of white roots, that is the dry weight of roots by 36.7 % and 8.5 %, respectively, while root volume (0.94 - 5.4 %) and root activity (20 %) were also improved (Wang and Huang, 1985). Inverse effects on new root growth of rice were seen when contents of rare earths in the growth medium exceeded 5 mg/l, whereas below that root growth enhancement was observed (Ning and Xiao, 1989). A more recent study showed that the germination rate of natural aged rice seeds was significantly increased after treating them with lanthanum nitrate (Hong et al., 2000a).

Similar effects have been described in rapeseed. Hence, yield increases of 11.4 % were reported after spraying a rare earth nitrate containing solution of 300 μg/l. After seed dressing, increases of 7.6 % could be observed (Cai and Jing, 1989), (Cai and Zheng, 1990). Similar results were obtained by Ren and Xiao (1987). Accordingly, rapeseed yield increased by 3.7 to 48.4 % after spraying a rare earths containing solution at 100 - 1000 μg/l, whereas 500 μg/l provided the best results. Rare earth application has furthermore been able to increase the amounts of divarication in rapeseed by 32.4 %, the pod numbers by 26.7 %, the number of seeds per pod by 13.9 % and thousand grains weight by 6.2 % (Xiong et al., 2000).

Growth promotion after rare earth application was also observed in potatoes in pot experiments (Jie, 1987). Both seed dressing and foliar application increased yield of potatoes by 5.7 % and 4.8 % respectively. Results obtained from 43 field trials using 2880 kg/ha showed an increase in tuber yield of potato by 13.8 %. Spraying of 750 g rare earths per ha increased starch yield by 1.5 % and the ascorbic acid concentration in the tubers by 38.9 mg/kg. Thus, rare earths have been shown to promote potato upgrowth, improve tuber formation and growth as well as starch accumulation (Chen and Zheng, 1990).

In accordance with potatoes, Yang (1988) described quality improvements in cotton. Especially fiber intensity and the rate of fiber protraction was improved (Yang and Jiang, 1988). Increased cotton lint fiber yields of 5 - 12 % have been shown in other experiments. Rare Earths could increase the yield of cotton in 15 out of 19 field trials (Guo et al., 1988). Further studies demonstrated that these positive effects were proven to be exerted by both single and mixed rare earth elements. However, better results were obtained using La, Pr or a mixture of rare earths instead of Ce. Among further positive effects, increased biomass and root hair growth were reported (Zhu and Zhang, 1986). Moreover, enhanced nutrient absorption has also been observed.

In corn, yield responses in the range of 8.5 to 18.5 % were described after rare earth application (Xiong et al., 2000). Both growth and length of main roots were shown to increase in corn seedlings after rare earths were supplied, thus improving dry weight and yield (Zhang and Zhang, 1989). Cui and Zhao (1994) applied a rare earth nitrate containing solution to corn seeds. Under these conditions an increase of 15.4 % in leave area index, 25.5 % in free sugar content and 16.2 % in total amino acids was observed.

Increased content of total amino acids by 12 % with an increase of 11.9 % for lysine and of 21 % for histidine has also been described in wheat while at the same time yield increased (Guo et al., 1988). Out of 39 field trials, almost 90 percent showed positive yield response for spring wheat with an average increase of 7.5 % (Jie and Zheng, 1988). Quite recently, improved crop yields have been reported in winter wheat (Triticum aestivum L.) treated with rare earth based fertilizer (Zhang and Shan, 2001). In this study, increased dry shoot weight was observed after a rare earth fertilizer was applied at a rate of up to 2 mg rare earths per kg soil. However, over the range of 2 - 40 mg rare earths per kg soil almost constant values were obtained for dry shoot weight. With higher rare earth application rates, a gradual reduction occurred, which was ascribed to excessive concentrations of rare earths fertilizers. Long-term studies with rare earth fertilizers applied at 600 g/ha/year over a continuous ten-year period demonstrated that rare earths enhanced the output of wheat by 4 - 10 % per hectare (Hong et al., 1996). Another study reported increased root volume (12.2 %) and root dry weight (20 %) of wheat plants after the application of a rare earth elements solution (Jie and Yu, 1985).

To compare the effects of individual rare earth elements (La, Ce, Pr and Nd) with mixed rare earths, pot incubation experiments in wheat were performed. The greatest yield enhancement was thereby obtained with Pr, followed by a mixture of rare earths while lowest promotion was seen with Ce (Zhu and Zhang, 1986). Studies using seed dressing showed that after the treatment with 30 - 50 mg rare earths/l, the seed germination rate could be enhanced by 8 - 9 %, whereas further enhancement was seen with 60 - 120 mg rare earth nitrates per kilogram seeds (8.7 - 16.5 %) (Wu et al., 1984). Best results were obtained at a rate of 100 mg mixed rare earths per kilogram seeds, while higher amounts in the range of 160 - 200 mg/kg exerted inhibitory effects on the germination of wheat seeds (Yang, 1989a), (Yang, 1989b). A dose-dependent growth enhancing effect of rare earths has also been demonstrated by Chang et al. (1998). They showed that while, on the one hand, concentrations of less than 1 g/kg soil were beneficial to plant growth, higher doses of 1 - 2 g/kg soil, on the other hand, impaired the harvest. Based on these facts but also on the knowledge of the hormesis effect (Chapter 5) occurring in rare earths, it has been strongly assumed that an optimum concentration of rare earths exists, which, if exceeded, results in controversial effects. In addition, Chang et al. (1998) postulated that rare earths may exhibit positive effects on the nutrient uptake in plants by influencing its velocity and physics.

In soybean, another crop species which responded to rare earth application, yield could be enhanced by 8.9 and 8.1 %, respectively, (Xiong et al., 2000), (Qiao and Zhang, 1989). Even though yield increases of 18.3 % are reported in low fertility fields, they have been limited to 6.4 % in high fertility sites (Wen, 1988), hence indicating that crop response may be directly related to soil fertility. As previously reported in wheat, seed dressing using rare earths also increased germination of soybean seeds by 4.4 - 9.6 % (Xiong et al., 2000), (Chief Office of Helongjiang Farm, 1985). Even better results (74 - 94 %) have been obtained with seed soaking using 0.01 % - 0.1 % of rare earth-containing solutions (Zhu and Wu, 1982). It has further been reported that the application of a rare earth-containing solution at 0.5 mg/l accelerated soybean rhizogenesis, thus increasing root weight and length by 35 % and 10 % respectively (Wu et al., 1984). In accordance with previously described findings in wheat, higher concentrations have been inhibitive to root growth in soybean. However, mixing 15 - 35 g of rare earths with 15 kg soybean seeds that is 1 - 2 g REE per kg seeds led to increased root weight of 10.9 - 34.6 % (Xiong et al., 2000), (Chief Office of Helongjiang Farm, 1985). At the same time, accelerated root nodule formation and nitrogen fixation were observed (Chen, 1991). During this study it could be further noticed that the effects of rare earths present a strong dependency on the crop growing stages. Besides yield enhancement, the fat content was also increased in soybean by 0.4 % after seed dressing with rare earths, while after spraying at late flowering stage an increase of both fat and protein content of 0.49 % and 0.26 %, respectively, was observed. Nowadays, seed dressing and spraying of rare earths during seedling or flowering stage is part and parcel in Chinese soybean production (Xiong et al., 2000).

However, growth enhancement has also been demonstrated for further plant species treated with appropriate concentrations of rare earth elements. Wu et al. (1998), who investigated the effects of rare earth elements on tissue culture of Chaenomeles spiciosa, a genus of deciduous spiny shrubs, also confirmed growth enhancing effects of rare earths on this plant species. The application of rare earths contributed to an increase of stem-tips differentiation. Both the growth of over- and underground parts of the plant could be increased. They further demonstrated that a higher percentage of transplanted plants survived when previously sprayed with rare earths. Another study reported improved germination rates of scallion and onion of 13 - 14 % and of 23 - 45 % for eggplants after the application of 50 - 500 mg/l rare earths (Zheng et al., 1993).

Tea production could also be enhanced evidently after spraying rare earth nitrates at a rate of 300 mg/kg and a dosage of 0.225 kg/ha/year on tea plants (Wang and Wang, 1996), (Wang et al., 2000a). It was early noticed that the effects of rare earth elements on plant growth vary with both the individual element and the doses applied. Tang and Tong (1988) demonstrated that at low concentrations of 0.05 - 1 mg/l La, Pr, Nd and especially Ce increased the radical growth of Chinese cabbage while high concentrations of rare earths ($>$ 10 mg/l) prevented root growth. Cerium chloride has also shown marked effects on the cell metabolism of Chinese pine seeds with increased germination rates as well as seedling's heights and weights. Best results were obtained at a concentration of 0.5 mmol/l. The growth enhancing effects were ascribed to the higher enzyme activity of dehydrogenase and superoxide dismutase as well as to an increased content of photosynthetic pigments (Guo and Denkui, 1998).

In pot culture experiments, the effect of cerium on spinach growth was investigated by Fashui et al. (2002). Besides stimulating the growth of spinach, cerium could obviously also increase the chlorophyll content and the photosynthetic rate. It has been assumed that through this, cerium may exert its growth promoting effects on plants. Accelerated photosynthetic light reaction as well as growth promotion was also observed in tobacco (Nicotiana tobacum) seedlings after the treatment with 5 - 20 mg/l of lanthanum chloride (Chen et al., 2001). The optimum concentration for growth enhancement was reported to be 20 mg/l of lanthanum chloride in nutrient solutions. A gradual increase of the content of chlorophyll was seen with concentrations up to 20 mg/l, whereas a decrease occurred with concentrations exceeding 50 mg/l.

In tobacco as well as in peach trees (Prunus persica), investigations on the short term effects of rare earths on pollen showed increased pollen germination and pollen tube growth at low concentrations of 20 μmol/l lanthanum or cerium (Sun et al., 2003). For lanthanum, most effective concentrations for promotion ranged from 10 to 4 μmol/l, whereas inhibition occurred at doses $>$ 40 μmol/l. Inhibitory effects were also reported after rape plants were treated with lanthanum at high levels ($>$ 300 mg/kg). Higher doses ($>$ 600 mg/kg) even presented toxic effects (Zeng et al., 2001). A decrease in chlorophyll content was noticed at concentrations of more than 15 mg/kg, and with increasing concentrations, a gradual increase of peroxidase appeared. However, although not significant, growth and yield enhancement was observed after the application of low concentrations of lanthanum. The feasible application level of lanthanum was suggested to be below 15 mg/kg.

From previous information, it can be concluded that rare earth elements are not exerting beneficial effects on plant growth under any circumstances. Their effects may be divided into three groups: beneficial, inhibitory and toxic. In addition, it has been shown that the maximum threshold of rare earth concentration varies with the crop species. Generally, except for rape, growth promotion was expected by the application of less than 1 g/kg rare earth oxides to the soil, while the use of more than 1 - 2 g/kg rare earth oxides caused inhibitory effects (Chang et al., 1998).

Zhang and Taylor (1988) attributed the response to rare earth application to a combination of factors. Those factors include soil properties such as pH, organic matter and mineral content, methods, rates and timing of rare earth applications, crop conditions, such as variety and stage growth, as well as weather conditions. Based on field responses of crops to rare earths, critical concentrations of soluble (acetate extracted) rare earth elements in soils were obtained (Brown et al., 1990), (Asher, 1995). According to those, Chinese soils have been classified into five categories (Zhu and Liu, 1992): very low $<$ 5 mg/kg, low 5 - 10 mg/kg, medium 10 - 15 mg/kg, high 15 - 20 mg/kg and very high $>$ 20 mg/kg. Crop responses were reported to be most probable in soils containing less than 10 mg/kg available rare earths, while plants in soils containing more than 20 mg/kg soluble rare earths were considered unlikely to respond (Kuang et al., 1991).

11.1.2 Rare Earth Elements Used as Fertilizer

In accordance with results obtained from several field experiments, different types of rare earth-containing fertilizers were developed soon after research started. Over the last 30 years, these fertilizers have been used extensively while the commercially treated area constantly increased from 1330 ha in 1980 over 3300 ha (1981), 20 667 ha (1982) and 113 000 ha (1983) to 367 000 ha (1984) (Guo, 1985). In 1986, approximately 0.5 million ha of land in China was treated with rare earth fertilizer (Guo, 1987), while in 1989, the area increased almost threefold to 1.4 million ha (Asher et al., 1990) and almost another threefold to 3.73 million ha in 1993 (Bremmer, 1994). In 1995, the application rates of rare earth products for agricultural use reached a maximum of 1000 metric tons per year covering estimated 16 - 20 million ha (Diatloff et al., 1996). The increases of the cropland area treated with rare earth-containing fertilizer in China over the time are shown in Table 11.3.

Year	Area treated with Rare Earths (ha)	Reference
1980	1330	Guo (1985)
1981	3300	Guo (1985)
1982	20667	Guo (1985)
1983	113000	Guo (1985)
1984	367000	Guo (1985)
1986	0.5 million	Guo (1987)
1989	1.4 million	Asher et al. (1990)
1993	3.73 million	Bremmer (1994)
1995	16 - 29 million	Diatloff et al. (1996)

Table 11.3: Increase (ha) of cropland area treated with rare earth-containing fertilizer in China from 1980 to 1998.

In China, the primary sources of rare earths for agricultural use are soluble extracts from mineral ores including bastnaesite, monazite and ionic rare earth ore (Xiong, 1995). They usually are extracted by using nitric acid. More details on this are given in Chapter 3. *Nongle* (translated into English meaning happy farmer), which consists of a complex of soluble chloride forms of rare earth compound, was the first fertilizer produced for testing the efficacy of rare earths in field experiments (Guo, 1985). In 1986, another rare earth product, named *Changle* (meaning happiness forever), was registered as commercial fertilizer. Besides containing about 38 % rare earth oxides, it also included a number of elements essential to plant growth (Guo, 1986), (Brown et al., 1990). Rare earth-products used today basically comprise rare earth nitrates, rare earth chlorides, compound rare earth fertilizers with multiple trace elements, compound fertilizers of rare earth and ammonium bicarbonate (Xiong, 1995) and rare earth compounds mixed with amino-acids (MAR) (Pang et al., 2002). However, rare earth nitrates found in *Changle* still constitute the main preparation used in plant production. These fertilizers are reported to contain 25 - 28 % lanthanum oxide (La_2O_3), 49 - 51 % cerium dioxide (CeO_2), 5 - 6 % praesodymium oxide (Pr_6O_{11}), 15 -

17 % neodymium oxide (Nd_2O_3) and less than 1 % other rare earths (Xiong, 1995). This composition reflects that of by-products of industrially produced rare earths, which constitute the basis for the manufacture of rare earth fertilizers. In addition, another preparation containing 80 - 90 % lanthanum oxide has come into use.

Crop species	Application method	Amount of rare earths	Timing
Wheat	spraying	600 mg/l	end of March to mid April
Maize	blending seeds	3 g/kg	–
	immersing seeds	8 g/kg	–
Potato	blending seeds	6 g/kg	–
Rape	blending seeds	5 g/kg	–
Ramie	spraying	100 - 300 mg/l	seedling period
Flax	blending seeds	600 g/ha	–
	spraying		appear bud period
Reed	spraying	600 - 900 mg/l	seedling or flowering period
Chinese gooseberry	spraying	700 mg/l	flower and young fruit period
Haw	spraying	400 mg/l	flower period
Banana	spraying	300 - 500 mg/l	seedling and young fruit period
Astragali	spraying	300 mg/l	seedling period
Alfalfa	blending seeds	100 - 300 mg/kg	–
Mushroom	spraying	50 mg/l	–

Table 11.4: Application methods and concentration of rare earths according to various crops (Guo, 1993).

About 100 factories manufacture rare earth fertilizers for agricultural application in China while different methods of application exist. Rare earth ammonium bicarbonates, for example, are used as root fertilizers and are therefore applied directly to the soil. Besides soil application, other common methods such as foliar spraying, seed dressing or seed and root soaking are practised (Brown et al., 1990), (Diatloff et al., 1995a), (Li et al., 2001), (Tyler, 2004). It is generally recommended to apply rare earths at the primary growth stage although the proper timing of application depends on the crop and the growth stage, for example, wheat in the jointing stage, rice in the jointing and blooming stage, cotton in the blooming stage and rape in the full blooming stage (Chang, 2006). Recommended rates for *Changle* are reported to be 600 - 675 g/ha, which represents a rate of rare earth application of 150 - 170 g/ha (Asher et al., 1990). Up to now different amounts of rare earths and different methods of treatment have been established according to the crop species. Some of them are listed in Table 11.4. For all species, application needs to be performed every year, otherwise it will be inefficient (Pang et al., 2002).

11.1.3 Summary

In China, the application of rare earth-containing micro-fertilizers to agricultural plants has already been practiced for over 30 years and the commercially treated area is constantly increasing. Based on accomplished research and experiences gathered so far from commercial application, Chinese research has reported both physiological and yield responses of various plants and trees treated with low concentrated rare earth-solutions. Reported yield responses include increased dry and fresh matter in crop plants such as wheat, corn and rice, increased sugar content in sugar cane, increased starch content in potatoes, increased vitamin C content in grapes and apples and increased fat and protein content in soybean. The physiological responses comprise darker green foliage due to higher chlorophyll concentrations, enhanced rate of development, higher root production and stronger tillering. Furthermore, increased enzyme activity and amino acid contents and effects on nutrient uptake were described. However, rare earths are not exerting positive effects on plants under any circumstances. A strong dose-dependency has been noticed with high doses presenting adverse, even up to toxic, effects. Recommended doses vary with the plant species, yet for soil-dressing concentrations of less than 1 g rare earth oxides per kg soil have been advised. Besides the concentration, effects of rare earths are also influenced by soil properties, such as soil fertility, whereas high fertility soils showed less responsiveness. Application techniques include soil-, foliar- and seed- dressing with commercially available rare earth micro-fertilizers, however, they may differ among plant species. Yet, annual application is highly recommended and though timing is also crop dependent, the primary growth stage is generally favored. The fertilizers used contain a mixture of rare earths with lanthanum, cerium, neodymium and praseodymium accounting for their main components. Application of the mixture is probably because of easier, and therefore cheaper production rather than due to better effectiveness as some studies reported positive results no matter if a single rare earth element, such as lanthanum or praseodymium, or the mixture of rare earths was applied. However, controversial results were reported for cerium. On the one hand, some studies observed lowest promoting effects in cerium plants, in other studies, on the other hand, cerium exerted marked growth enhancing effects.

11.2 Western Countries

11.2.1 Studies on the Effects of Rare Earths on Plants under Western Conditions

Before extensive research started in China, in 1972, a few studies on the effect of rare earths on plants were published in Western countries. Among these, the study conducted by Chien and Ostenhout (1917) is considered to be the pioneer work on this field as it firstly described physiological effects of cerium on water-floss (Spirogyra). From 1935 to 1973, a couple of Russian articles were published on this topic reporting both nil and stimulating effects of rare earths on wheat growth (Savostin, 1934), (Savostin and Gobelev, 1935), (Savostin and Terner, 1937). Further studies used soil culture experiments to investigate the effects of lanthanum carbonate at a concentration of 20 - 60 mg/kg and cerium oxalate at a concentration of 60 - 120 mg/kg on the growth of two wheat cultivars. Results obtained were only positive in one of the varieties, while after cerium oxalate treatment negative effects on the yield were observed for both species (Savostin and Terner, 1937), (Kogan and Skripka, 1973). Yet positive effects on plant growth in peas, rubber plant and other crops due to the treatment with rare earth nitrates were reported in other studies (Drobkov, 1937), (Drobkov, 1941b), (Drobkov, 1941a). Similarly, Romanian scientists documented increased yield in wheat, soybean and sugar beet in response to the application of cerium chloride (Horovitz, 1974). At the same time, yield enhancing effects of 24 - 17 % in sugar beet treated with 50 mg/l and 100 mg/l cerium chloride were described in Bulgaria (Evanova, 1964), (Evanova, 1970). Additionally, Sharoubeem and Milad (1968) reported growth enhancing effects on mungbean (Phaseolus vulgaris) shoots and roots after a mixture of rare earths (Th, Ce, La, Pr, Nd) was applied as nutrient solution at 2.5 - 10 ppm, while best results were obtained at 5 ppm.

Today, it is not reproducible whether or not previous reports from Western countries drew the attention of China to the possible agricultural use of rare earths or whether, as considered more likely, research on the agricultural application of rare earths developed independently in China. Nevertheless, China has been the first country which started a systematical research, and thus commercialized the use of rare earth elements in agriculture. As described in detail in Section 11.1, results of Chinese research largely suggest that the supplementation of low dose rare earths to agricultural crops has beneficial effects on plant growth.

However, on the basis of poor documentation of these results in international scientific literature, knowledge on potential growth promoting effects of rare earths in plants has for a long time been deprived. Thus, before 1990, only a few additional investigations on rare earth application to plants were performed outside China. Among these both inhibitory (Pickard, 1970), (Balamani et al., 1986), (van Steveninck et al., 1990) and beneficial (Velasco et al., 1979), (Hanzely and Harmet, 1982), (Harmet, 1979) effects of rare earths on plants were reported. According to Pickard (1970) Pr and Nd inhibited the auxin-stimulated elongation of oat coleoptile sections while Balamani et al. (1986) found out that even low concentrations of lanthanum chloride (10 - 20 μmol/l) restricted tuber development in potatoes. Almost complete inhibition of cell division and root elongation was observed in the root tips of barley plants after colloidal lanthanum was applied (van Steveninck et al., 1990). To the contrary, rare earths were shown to promote root and shoot growth of tropical plants, such as Phaseolus radiatus and Brassica pekinensis and the development of larger green leaves and fleshier roots in Ipomea triloba, a root crop (Velasco et al., 1979). Despite an initial depression, growth response was also observed in Avena coleoptile segments treated with millimolar concentrations of lanthanum chloride (Hanzely and Harmet, 1982), (Harmet, 1979). Another report on plant growth stimulants comprising metal ions was published in the UK in 1983 (Andrew, 1983), and a patent on the application of rare earth elements to prevent soft-rotten disease of cabbage and plant blight was granted in Japan, in 1980 (Kawasaki, 1980). Along with that, rare earths were also reported to enhance plant growths. However, even to this day there is still a limited number of studies on growth effects of rare earths on plants performed in Western countries and results presented so far are controversial. As a consequence, it is not possible to make a clear statement on whether or not rare earths exert positive effects on plant growth.

After 1990, first investigations to verify Chinese results under Western conditions were performed down under as Australian scientists had abandoned themselves to an impulse given by a mission from the Australian Academy of Technological Sciences and Engineering to China in 1982. From this mission it was reported that small quantities of mixed rare earth elements in the nitrate form were used in China as trace elements to stimulate growth of a variety of crops. Information on the experimental design, Chinese test procedures and techniques as well as on the material used had been obtained from further visits to China. Yet prior to the conduction of studies, commercial Chinese rare earth fertilizers were analyzed using ICP - MS in order to obtain detailed information on the elemental composition. In accordance with Chinese reports, they were found to be composed of a mixture of nitrate salts (45 % nitrate by weight), with lanthanum (8.7 %) and cerium (12.4 %) being the most abundant rare earths measured. Other rare earth elements, namely neodymium (5.7 %), praseodymium (1.7 %) and gadolinium (0.49 %) were also presented in appreciable amounts. Additionally, 0.74 % calcium and 0.80 % chloride were measured, whereas concentrations of the remaining rare earth elements and other elements were below 0.01 % (Diatloff, 1999). A similar elemental composition was described by Asher et al. (1990), who determined 48.7 % nitrate, 9.3 % lanthanum and 15.4 % cerium, 5 % chloride and 2.2 % calcium in a Chinese rare earth fertilizer. Both results are in accordance with those obtained by Krafka (1999) (Table 11.5) after analyzing a sample of *Changle* using NAA.

Element	Concentration in mass fraction (%)	Method of analysis
	Rare Earth Elements	
La	9.8	INAA
Ce	18.62	INAA
Eu	0.00016	INAA
Nd	6.5	INAA
Sm	0.028	INAA
Tb	0.00002 (single value)	INAA
Pr	1.9	ICP - AES
Yb	0.0003 (single value)	INAA
	Other Elements	
Zn	0.006 (single value)	INAA
Ba	0.24	INAA
Ca	0.68	ICP - AES
Cr	0.25	INAA
Mn	0.015	INAA
Na	0.13	INAA
Cl^-	3.4	HPLC
NO_3^-	44.9	HPLC

Table 11.5: Elemental composition of *Changle* (Krafka, 1999).

Thus, these results demonstrated that Chinese rare earth fertilizers were mainly composed of Ce, La and Nd with the predominating anion being NO_3^-, while other rare earth elements were only presented in much smaller amounts. Based on that information, the question was raised whether the mixture of rare earth elements or the single element itself is responsible for the effects reported in Chinese literature. However, the predominating use of rare earth mixtures in fertilizers usual in the trade in China is probably rather ascribed to the fact that commercialization of mixtures is cheaper and easier compared to purified individual elements than to better effectiveness. Therefore, in order to compare their potential both single and mixed rare earth elements were applied in Western studies. But in later studies individual elements were more often used as it was suggested to be unlikely that each element has the same activity.

Preliminary experiments carried out in Australia failed to reproduce Chinese results under Australian conditions. No significant effects of rare earths applied as *Nongle* were observed in sorghum and soybean. Additionally, in a field trial performed, neither spraying nor seed dressing of rare earths on Brassica seeds showed any response. In contrast, pot trials revealed highly significant ($p < 0.01$) increases in the yields of sugar cane tops and root dry weights after the setts were dipped in either *Nongle* or a mixture of laboratory grade cerous and lanthanum nitrate (Tribe et al., 1990), (Maheswaran et al., 2001). Similarly, beneficial effects on barley growth due to the application of low concentrations of lanthanum (0.5 - 1 mg/l) to barley grown on perlite were also reported from glasshouse trials (Buckingham et al., 1995). Leaf widths and stem widths increased by 14 to 16 % and 8 to 26 %, respectively, while improvements in dry matter of plants treated with lanthanum were in the range of 48 to 90 %. In accordance with Chinese reports (Brown et al., 1990), visual differences including darker green foliage, stronger tiller and delayed senescence between plants treated with lanthanum and the control group could be observed (Meehan et al., 2001). In line with further experiments, other plant species grown on perlite were investigated. Among those tested, ryegrass and barley showed the most significant responses. Increases in dry matter of perennial ryegrass were reported to be in the range of 22 % to 78 % and 35 % to 38 % for canola (rapeseed). Information on dry matter yield for each species is given in Table 11.6.

Lanthanum (mg/l)	Barley dry weight (g)	Canola dry weight (g)	Ryegrass dry weight (g)
0	1.805	1.718	0.413
0.5	3.434*	1.728	0.858*
1	3.074*	1.934	0.632*
2	2.638*	1.866	0.566*
5	2.675*	2.380*	0.670*
10	1.802	2.331*	0.459

Table 11.6: Dry matter yield of treated and control plants for barley, canola and ryegrass in pot trials using perlite; dry weights marked with an asterisk (∗) are significantly different from control ($p < 0.05$) (Meehan et al., 1995).

Compared to the control group, the heights of perennial ryegrass was up to 60 % greater in lanthanum-treated plants as shown in Table 11.7. Visual differences in terms of advanced flowering and delayed wilting were also recorded in canola.

Lanthanum (mg/l)	Ryegrass height (mm)	Barley blade width (mm)	Barley stem width (mm)
0	151.9	10.42	2.57
0.5	273.1*	11.91*	3.23*
1	226.6*	12.11*	3.04*
2	232.8*	11.32	2.79*
5	230.2*	12.02*	2.97*
10	175.3	10.87	2.84*

Table 11.7: Comparison of several physical parameters of control and treated plants in pot trials using perlite; values marked with an asterisk (∗) are significantly different from control ($p < 0.05$) (Meehan et al., 1995).

It was further found out that the optimum level of lanthanum for plant growths differed between the plant species. While application of very low concentrations of lanthanum (0.5 - 1 mg/l) was most effective in perennial ryegrass and barley, optimum levels of lanthanum needed in canola were higher. Yet at this concentration, leaf areas were increased by 20 - 50 % in canola. Even though visual differences as well as enhanced dry matter yields were seen in all species grown on perlite, using selected Australian soils the responsiveness of the same plant species was lower than in perlite (Meehan et al., 1995). However, in contrast to Meehan et al. (1995), who did not observe any significant effects of lanthanum on plant growth under field conditions but only in pot trials, field trials conducted by Reddy et al. (2001) from 1997 to 1998 showed that barley responded to lanthanum under water limiting conditions. Within the scope of these glasshouse experiments, increases in tiller production of 33 % associated with grain yield increases of 18 - 19 % were seen after lanthanum treatment (125 g/ha to soil plus 125 g/ha to foliage) under drought conditions over the whole period of two years. Yet no significant effects were observed for both fresh and dry weight of stem. Similar results were reported for wheat at higher rates of lanthanum application (500 g/ha) with grain yield increases of 11 %. Increased grain numbers per area and improvements of the harvest index were also found for both barley and wheat. Additionally, lanthanum promoted the stomatal resistance and the water use efficiency which was 21 % higher when plants were treated with 10 kg/ha (soil plus foliar application) (Maheswaran et al., 2001). Furthermore, plants treated with lanthanum generally showed lower leaf water potentials and higher osmotic adjustment, whereas no significant differences were observed for relative water contents. As it is known that reduced leaf water potential together with high relative water contents can increase crop yield, this might be a reasonable explanation for effects observed in line with these trials.

However, beneficial effects have also been reported by Buckingham et al. (1996). Thus, applying lanthanum at a rate of 1 kg/ha increased the biomass production of a perennial ryegrass pasture grown on an Australian soil by 24 %. Quite the contrary, beneficial effects of lanthanum on plant growth were neither observed for mungbean (Phaseolus vulgaris) nor for maize (Zea mays) in nutrient solution experiments performed by von Tucher et al. (2001). It was even shown that low concentrations (20 μmol/l) of lanthanum clearly reduced shoot growth of mungbean by 60 % while the yield of maize remained unchanged. Additionally due to lanthanum treatment the mineral composition of both plants was changed (von Tucher and Schmidhalter, 2005). However, changes were more pronounced in mungbean with all measured minerals, including N, P, Ca, Mg, S, Mn, being significantly affected. In mungbean leaves, decreases in potassium contents were reported to be up to 60 % making the occurrence of deficiency symptoms conceivable. It has been further assumed that reduced potassium and calcium contents (potassium 16.1 mg/g and calcium 4.9 mg/g) found in the shoots are responsible for the decrease in shoot growth since low levels of potassium and calcium are reported to be critical for plant growth (Fageria and Baligar, 1997). In maize, significant changes were only observed for Ca, Mg and root Mn contents, which in contrast to mungbean had no impact on biomass production.

Additionally, differences in the effects of lanthanum on the mineral composition were noticed between root and shoot. While decreased contents of potassium were found in the root, the calcium content was left unchanged. Yet decreased contents for calcium were measured in the shoot (von Tucher et al., 2001), (von Tucher and Schmidhalter, 2005). It was therefore suggested that lanthanum might impair the transport of calcium from the root to the shoot while in case of potassium the uptake might be hampered. Accordingly, Sharoubeem and Milad (1968) also found decreased calcium contents in shoots of mungbean previously treated with rare earth containing nutrient solutions. Yet, contents of Na, K and N in plant shoots were found to be increased by 5 ppm due to rare earth application. Hence, effects of rare earths on the mineral composition of plants are controversial. In accordance with von Tucher et al. (2001), Liu and Hasenstein (2005) also observed decreased potassium levels in corn root protoplasts after the treatment with lanthanum. Yet this phenomenon only lasted for 30 minutes while no long-term effects were seen. In contrast, Meehan et al. (1995) described increased potassium uptake in some plants treated with lanthanum.

Another experiment demonstrated a two-fold increase in the mass of spikes produced in wheat (Triticum aestivum L.) after the addition of 390 μg lanthanum to a nutrient solution, which was used to moisten the rooting medium of wheat (Meehan et al., 1993), whereas the contrary was reported by Delhaize et al. (1993). They demonstrated that the presence of even little amounts of lanthanum of 2 μmol/l in the root environment were toxic to wheat. At a concentration of 5 - 8 μmol/l lanthanum root elongation of wheat plants decreased by 50 %. This range encompasses the values determined by Diatloff et al. (1995b), who found that 4.8 - 7.1 μmol/l lanthanum could reduce root elongation in corn. Thus corn and wheat seem to have similar sensitivities to lanthanum. However, mungbean was more sensitive as the same results could be already obtained at a concentration of 3.1 μmol/l. Similar results were found in additional studies using cerium instead of lanthanum. However, while lanthanum was more toxic to corn than cerium, the reverse was seen in mungbean.

From previous studies it was concluded that the impact of rare earths on plant development highly depends on the growth medium. On the one hand, increased dry matter production was reported for some plant species cultivated in perlite under greenhouse conditions (Maheswaran et al., 2001) while, on the other hand, in soil, plant yield was unaffected. An exception was loamy sand in which yield increases occurred under drought conditions. Yet in field experiments virtually no effect of lanthanum on the biomass production could be observed. On this basis, controversial results reported on the effects of rare earths on plant growth may be ascribed to differences in the experimental design such as growth conditions or growth media. In addition, the importance of the selected nutrient solution in experimental studies has also been emphasized by Chang (2006), who furthermore considered it to be necessary that the pH remains below 5.5. This may be further supported by the fact that concentrated nutrient solutions often contain quite high concentrations of phosphate which may even be toxic (Diatloff et al., 1995b). It is assumed that precipitation between lanthanum and phosphate may reduce these toxic effects or even lower them to nontoxic levels. Additionally, substantial amounts of lanthanides are thereby removed as well. Thus the overcoming of phosphate toxicity as well as the reduction of lanthanide concentrations provides a possible explanation for positive effects of lanthanum and cerium on plant growth when high phosphate nutrient solutions are used. Failure in recognizing rare earth phosphate precipitation has earlier already confused the interpretation of several biochemical studies (Evans, 1990).

If diluted low phosphate nutrient solutions are used, which correspond to the composition of soil solutions, no significant beneficial effects of either lanthanum or cerium on corn or mungbean root elongation were found. Moreover, both lanthanum and cerium were shown to be highly toxic even at low concentrations (3.1 μmol/l - 7.1 μmol/l) (Diatloff et al., 1995b). Based upon this information, it was assumed that agronomic benefits from rare earth application are the results of rather indirect than direct biochemical effects on plant growth controlling processes (Diatloff et al., 1995a). Furthermore, it was suggested that if rare earths have any positive effect on plant growth, they are likely to be manifested only at very low concentrations, probably below 1 μmol/l. Indeed, applying lanthanum at a concentration of less than 1 μmol/l could enhance root elongation of wheat grown in strongly acidic nutrient solutions (Kinraide et al., 1992). This coincided with further studies performed by Diatloff et al. (1995c), who demonstrated that 0.63 μmol/l lanthanum could significantly increase the dry weight of corn roots by 36 %. Similarly, increasing the lanthanum solution from 0 to 0.19 μmol/l also enhanced the dry weight of mungbean roots significantly (21 %). However, despite the increased root growth of both corn and mungbean, shoot growth or total dry matter production of either species remained unaffected. While a two fold increase of corn root growth was also seen at a concentration of 0.63 μmol/l cerium, in mungbean, 0.19 μmol/l cerium solution already caused a significant reduction in the dry weight of root (26 %), shoot (48 %) and total plant (40 %) (Diatloff et al., 1995d). Moreover, the application of a 0.63 μmol/l cerium solution to mungbeans produced small black necrotic lesions which correspond to symptoms found with manganese (Mn) deficiency. Indeed along with these symptoms quite lower concentrations of manganese (5 mg/kg) were determined compared to in the control plants (44 mg/kg). This may indicate that at higher concentrations cerium depresses the manganese content. As lower root elongation in corn was observed at pH 4.5 compared to pH 5.5 (Diatloff et al., 1995b), it was suggested that beneficial effects in wheat (Kinraide et al., 1992) and corn (Diatloff et al., 1995c) may be ascribed to the alleviation of H^+ toxicity. However, this may not explain increased root growth observed in mungbean treated with low lanthanum concentrations.

In another glasshouse trial performed on corn negative effects on the growth were presented after foliar application of rare earths (Diatloff, 1999). During this experiment, the Chinese fertilizer *Nongle* was sprayed on corn and mungbean. As the spraying instructions on the bag of rare earth element fertilizer were cryptic (Table 11.8), different concentrations on the test plants ([w/v]%): 0, 0.025, 0.05, 0.1, 0.5 and 1 % were used.

Nongle (happy farmer)
Product specifications Nongle is a product which has been tested in agricultural trials for many years. The product is harmless, easy to use and easy to distribute evenly in the soil, with good retention in soil and significant improvement in plant growth.
Application Nongle can be used for wheat, rice, peanut and soybean plants, fruit trees, vegetables and garden flowers
How to use Mix with seeds: dissolve 5 g Nongle in 100 ml of water. One kilogramm of seed should be mixed with 40 ml of 5 % Nongle solution. Sow after drying. Spray: spray with 0.06 - 0.10 % Nongle solution and 450 - 750 g Nongle per ha. Solution (2.0 - 2.5 %) used for spray by aeroplane and 0.4 - 0.5 % solution by tractor
When to use Spray at any period of plant development. Generally, spray once or twice and 12 day interval between two sprays.

Table 11.8: Product specifications and application instructions on the bag of rare earth element fertilizer (*Nongle*) obtained from China (Diatloff, 1999).

However, foliar application did not increase plant growth, moreover, it was toxic at rates of 0.5 and 0.1 [w/v]% in aqueous solution. Although shoots of corn sprayed with $<$0.1 % rare earth fertilizer appeared completely healthy throughout the experiment, plants treated with 0.5 - 1 % showed symptoms of leaf burn within one to three days of treatment whereas aggravation took place over the next five to nine days. Plants sprayed with lanthanum and cerium nitrate solutions developed symptoms similar to those observed on plants sprayed with rare earth fertilizer.

The effects of lanthanum on plant growth of mungbean (Phaseolus vulgaris L. var. nanus) were also studied by Syha (2005) in Germany. During this investigation, different concentrations of lanthanum (0.5, 1, 2 and 10 mg/kg) were applied to the soil of four experimental groups. Another experimental group received one single foliar application of lanthanum chloride. In order to assure optimum growth, a balanced nutrient solution containing N, K, Mg, P, Ca, Fe, B, Mn, Zn, Cu and Mo was also applied regularly. Neither soil nor foliar application resulted in beneficial effects on fresh or dry weight of mungbean shoots. Just as little negative effects were observed on any of the plants, although at high concentration (10 mg/kg), there was a tendency in pod weight decrease indicating that detoxification takes place in soil. In accordance with some of the previous reports, increases in root fresh weight due to soil application of low dose of lanthanum (0.5 mg/kg) were noticed whereas at high concentrations of lanthanum caused toxic effects on root development.

Similar results were obtained by Liu and Hasenstein (2005). While promoting effects of lanthanum on root growth of maize plants (Zea mays L.) were obvious at low concentrations ($< 1\ \mu$mol/l), high concentrations (10 mmol/l) resulted in root growth inhibition. Thus, elongation occurred proportional to the external lanthanum concentration. Growth promoting effects following lanthanum application at 1 μmol/l were significant after 220 min. Over a time period of four hours, with 1 μmol/l, the rates of root elongation increased by 10 %, while decreases of 28 %, 42 %, 55 % were seen at 100 μmol/l, 1 mmol/l and 10 mmol/l of lanthanum respectively. After 24 hours, roots exposed to 1 mmol/l lanthanum were swollen and peeled off, an effect that was most pronounced in the elongation zone. These effects of lanthanum have been shown to be similar to those of aluminium on maize root growth (Blancaflor et al., 1998). In line with these experiments, it was further noticed that adsorption of lanthanum was concentration-dependent with lower lanthanum concentrations resulting in faster adsorption. In roots of coconut palms, rare earth elements could promote root growth at low application rates, but at higher levels, absorption of phosphorus (P) and zinc (Zn) by the palm was reduced significantly (Wahid et al., 2000).

11.2.2 Summary

From the thirties up to the seventies of the last century, a few papers on the effects of rare earth elements on plants were published reporting both nil and positive, but also negative effects. Although positive effects were dominating only few further reports were released till the end of the eighties. It was not before the nineties that Western countries resumed work on the effects of rare earths on plants after Chinese literature on their plant growth enhancing effects became partly available. In accordance with earlier findings, controversial results including nil, positive and even negative effects were obtained by the following investigations. Within the scope of Western studies, commercially available Chinese rare earth micro-fertilizers were analyzed. They were shown to be mainly composed of cerium, lanthanum, neodymium and praseodymium, all of them in their nitrate forms. Thus in later studies effects of single rare earth elements, such as cerium and lanthanum, were investigated. In pot trials, significant yield increases were observed after a mix of lanthanum and cerium nitrate or of rare earths was applied to sugar cane. These results could be confirmed in further pot experiments. In ryegrass, increases in dry matter of 22 % to 78 % and heights of up to 60 % were observed after the plants were treated with low dose lanthanum (0.5 - 1 mg/l). Similar increases were also reported for rapeseed. Differences for the optimum levels of lanthanum were shown to vary within the plant species. The growth enhancing effects demonstrated in pot experiments using perlite as growth medium could however not be reproduced using Australian soil. This indicates that these effects may depend on the growth medium. Moreover, effects of rare earths on plants are considered to be influenced by the type of nutrient solution used. Thus growth enhancing effects seen in pot experiments might be ascribed to the alleviation of phosphate toxicity, since concentrated nutrient solution used in pot trials usually contain high levels of phosphate. In further studies it was shown that under water limiting conditions, rare earths were able to increase the yield of barley grown on Australian soil by 18 - 19 %. However, even at low concentrations of 20 μmol/l of lanthanum, reduced root growth was demonstrated in mungbean and maize plants in nutrition solution experiments. During this experiment, lanthanum furthermore caused changes in the mineral composition which were more pronounced in mungbean with potassium and calcium contents being reduced. Similar results were obtained in another study while in contrast to that, Australian scientists described increase potassium uptake due to lanthanum treatment. Other studies reported significant increases in dry weights of plant roots due to the application of lanthanum at low concentrations (< 1 μmol/l) in wheat, corn and mungbean. For corn, the same was found after cerium treatment, whereas in mungbean cerium applied at the same concentration rate caused a significant reduction in the dry weight of root and shoot. In addition, toxic effects occurred when the concentration was further increased. Further negative effects could be demonstrated after corn and mungbean were sprayed with a rare earth containing-fertilizer and similar results appeared after replacing the fertilizer by a lanthanum-cerium mixture. Regarding plant root growth, some studies on the one hand reported even toxic effects in wheat, corn and mungbean after being exposed to low dose lanthanum or cerium. But other studies on the other hand, described root growth enhancement in mungbean and maize after lanthanum was applied at very low concentrations and in coconut palm due to the application of a mixture. Yet despite increased root elongation, no effects on dry weight of mungbean could be seen. In contrast to Chinese studies, results obtained so far from Western studies are quite controversial and a definite statement as to whether rare earths may enhance plant growth or not cannot be made.

Reference	Plant species	REE ^{a} species	REE ^{a} application rate	Effect
Tribe et al. (1990)	sorghum, soybean	REE	–	no significant effects
Tribe et al. (1990)	brassica (field trial)	REE	spraying, seed dressing	no effects
Meehan et al. (1995)	sugar cane	REE	–	highly significant dry weight increases
	(pot trial)	REE	–	highly significant dry weight increases
Meehan et al. (2001)	barley	La	0.5 - 1 mg/l	48 - 90 % increases in dry matter
	(pot trial)			leaf widths increases of 14 to 16 %
				stem widths increases of 8 to 26 %
				darker green foliage, stronger tiller
Meehan et al. (1995)	perennial ryegrass	La	0.5 - 1 mg/l	22 % to 78 % increases in dry matter
	(pot trial)			heights up to 60 % greater
Meehan et al. (1995)	rapeseed	La	0.5 - 1 mg/l	35 % to 38 % increases in dry matter
	(pot trial)			advanced flowering and delayed wilting
				leaf areas increased by 20 - 50 %
Reddy et al. (2001)	barley (field trial)	La	–	yield increases of 18 - 19 %
	water stress			increased grain numbers per area
				increases in tiller production of 33 %
von Tucher et al. (2001)	mungbean	La	20 μmol/l	reduced shoot growth by 60 %
	maize	La	20 μmol/l	no effect on yield
Meehan et al. (1993)	wheat	La	390 μg	twofold increase in the mass of spikes
Delhaize et al. (1993)	wheat	La	5 - 8 μmol/l	50 % decrease in root elongation
Diatloff et al. (1995b)	corn	La	4.8 - 7.1 μmol/l	decreased root elongation
Kinraide et al. (1992)	wheat	La	$<$ 1 μmol/l	increased root elongation
Diatloff et al. (1995c)	corn	La	0.63 μmol/l	increase of 36 % in the dry weight of roots
	corn	Ce	0.63 μmol/l	increase in root growth
	mungbean	La	$<$ 0.19 μmol/l	increase of 21 % in the dry weight of roots
	mungbean	Ce	0.19 μmol/l	decreased dry weight of root (26 %)
				shoot (48 %), total plant (40 %)
Diatloff (1999)	mungbean, maize	REE	0.025 to 1 % spraying	nil to toxic effects (symptoms of leave burn)
		La, Ce nitrate	0.025 to 1 % spraying	nil to toxic effects

continued on next page

Reference	Plant species	REE ^{a} species	REE ^{a} application rate	Effect
Syha (2005)	mungbean	La	0.5 - 10 mg/kg soil	no effects on fresh or dry weight
		La	low concentrations (0.5 mg/kg)	increased root growth
Liu and Hasenstein (2005)	maize	La	< 1 μmol/l	increased root growth by 10 %
	maize	La	100 μmol/l	decreased root growth by 28 %
	maize	La	1 mmol/l	decreased root growth by 42 %
	maize	La	10 mmol/l	decreased root growth by 55 %
Buckingham et al. (1996)	ryegrass	La	1 kg/ha	increased biomass production by 24 %
Wahid et al. (2000)	coconut	La	low concentrations	increased root growth

Table 11.9: Western studies on the effects of rare earth elements on plant growth ^{a} rare earth elements.

11.3 Rare Earths Uptake by Plants and Bioavailability to Plants

Different ways and methods exist as to how rare earths may be applied to plants. However, among these soil and foliar application as well as seed dressing are mostly used in China (Peverill et al., 1997), whereas, in nutrient solution experiments, root dipping or spraying may also be employed (Guo, 1987). After rare earths are applied they are partly absorbed by the plants. Although it has been assumed for a long time that rare earth uptake predominately occurs via the plant roots, considerable assimilation through the leaves has also been reported after foliage application (Sun et al., 1994), (Chua, 1998), (Fashui et al., 2002). Information on the uptake, translocation and accumulation of rare earths in plants is very important as it may help understanding the physiological role of rare earths in plants. Moreover, along with information on the bioavailability of rare earths to plants, not only the influence of rare earths on plants but also on the environment in general may be estimated as done in Chapter 7.

Several investigations on the uptake as well as on transportation processes of rare earths from soil and solution to various plant species were performed (Quiquampoix et al., 1990), (Xiong et al., 2000) (Huang et al., 2001), (Gao et al., 2003), (Liu and Hasenstein, 2005). Main conclusions drawn from sources published before 1982, which were reviewed by Brown et al. (1990), comprise facilitated rare earth uptake following additional fertilization with high levels of nitrogen and potassium, whereas inverse effects were seen after the addition of phosphate. Furthermore, it was stated that soil chelates may influence rare earth uptake, while the Casparian strip constitutes a barrier which limits the uptake of rare earth elements via the roots. Yet to this day, it is still debated whether or not rare earths can cross the cell membrane at all (Lehmann et al., 2000), (Gao et al., 2003). The cell wall which is composed of diverse cross-linked components, including microfibrils and other cross-linked carbohydrates, pectin, proteins and ions (Cosgrove, 1997) is assumed to act as an ion exchanger with the surrounding solution. As a result, this may enable the cell wall to reduce the effective concentration of rare earths while additionally inhibiting their transport across the plasma membrane. In contrast, it was shown that lanthanum can enter the cytoplasmic phase of undifferentiated cells in root tips of barley plants. In this connection, the nucleolus presented a particular high affinity for lanthanum (van Steveninck et al., 1990). Accordingly, Gao et al. (2003) demonstrated that Eu^{3+} and La^{3+} could enter plant cells.

Nevertheless, in line with the general assumption that rare earth uptake occurs through the roots, gadolinium was shown to be taken up by root cells (Quiquampoix et al., 1990). In a similar manner, Liu and Hasenstein (2005) demonstrated lanthanum uptake by maize root protoplasts. A membrane binding component was thereby revealed which was followed by a slower concentration and time-dependent uptake. Another recent study reported that binding of lanthanum to barley roots may occur through carboxylate groups and hydration of lanthanum (Han et al., 2005). Rare earths found in soil are thought to enter the roots in ionic forms (Nagahashi et al., 1974). After the uptake, they have been reported to be absorbed into epidermal, cortical or endodermal cells before moving through the cytoplasmic continuum to the vascular tissue of the roots. From the vascular tissue, they may further transfer to the plant tops through the water flow of transpiration. Inside the vascular tissue however, rare earths may bind reversibly to non-diffusible anions (e.g. $COOH^-$) while the degree of bonding varies with their atomic number (Lauchli and Bieleski, 1983). This may explain the differences in dose-dependent accumulation of rare earths in corn observed after lanthanum and not a mixture of rare earths was supplemented (Xu et al., 2003). However, other authors assumed that rare earths cannot enter the cytoplasma since passage through neither the Casparian strip nor the plasmalemma of plant roots is reported to be possible (Brown et al., 1990). Their transport and distribution may therefore only occur through the apoplasm or along the cell wall. Similar results were obtained by Wei (2000). His study on the distribution of neodymium in solution culture of oilseed rape indicated that neodymium must be either bound to the cell wall or accumulated within the cell gap since no detectable amounts were found in the cytoplasma. After absorption from the root, neodymium mainly accumulated in the root while only little was transported upward to stem and leaflet via apoplasma route. The least was found in leaflets. These results were further confirmed in soil culture experiments. In contrast to that, results obtained from investigations on the uptake of lanthanum in root protoplasts suggested that lanthanum can cross the cell membrane. However, the situation in intact cells of roots may differ substantially (Liu and Hasenstein, 2005). In experimental results described by Huang et al. (2001), lanthanum was detected in the plasma membranes of cells of soybean roots.

Besides roots, uptake of rare earths may also occur through plant leaves. Hence, Chua (1998) demonstrated that cerium could be absorbed via the stoma and cuticle, situated on the surface of the leaves of water hyacinth. Afterwards it was distributed to various parts of the plant. Accumulation of cerium in different parts of the plant was in the order of leaves $>$ stems $>$ roots while the leaves accounted for approximately 50 % of the concentration of the entire plant. Nevertheless, assimilation of rare earths has been reported to vary with each individual element. Thus, a significant correlation between scandium and lanthanum could be observed in spruce needles (Wyttenbach et al., 1994), indicating that, with respect to the total soil concentration, the uptake of lanthanum is higher than that of scandium. Accordingly, Xu et al. (2003) found that sole application of lanthanum at relatively smaller doses compared to mixtures of rare earth elements results in a substantial accumulation of lanthanum in maize plants. This further supported the assumption that rare earth uptake by roots as well as the subsequent transport of the absorbed elements from the roots to the plant tops varies with each rare earth element.

The amount of rare earth elements taken up by plants highly depends on their bioavailability in soil. This indicates that bioavailability and uptake of rare earths are closely linked to each other hence making an independent discussion very difficult. Therefore some additional information on rare earth uptake will be provided along with their bioavailability in the following section.

Though claimed earlier, neither the total amount of rare earths in soil nor the sum extracted with sequential extraction procedures are good analogous of the actual uptake or bioavailability (Wyttenbach et al., 1998b), (Li et al., 1998a), (Krafka, 1999) (Cao et al., 2000b), (Shan et al., 2003b). Poor correlations were found between the total contents of most rare earth elements in soils and their concentration in different parts of corn and rice, which coincides with the general assumption that only a small fraction of total metals in soil is available to plants (Li et al., 1998a). Accordingly, Zhang and Shan (2001) did not observe any significant correlation between lanthanum contents in plant roots and its total concentration in the adjacent soil. Yet bioavailability of rare earth elements is influenced by many factors, while up to now there is no universally useful method for its prediction. According to the long used free ion activity model (FIA) metal bioavailability and toxicity are controlled by buffered activity of free ions in soil solutions, but not the total dissolved concentrations. However, in soil environment there is a large variety of inorganic and organic ligands and therefore only a small portion of the overall dissolved metals is present as free hydrated cations. Thus, this model probably does not reflect the real bioavailable form of metals in soil (Shan et al., 2003b). Others considered the labile forms of metals referring to metals that exist in solid phases in equilibrium with the pore water as the most easily bioavailable form (Apte and Barley, 1995), while Davies (1992) reported that different fractions of soil metals vary considerably in their chemical reactivity and bioavailability.

Accordingly, fractional sequential procedures revealed that the water soluble, exchangeable and carbonate bound fraction contained the highest amounts of rare earths bioavailable for plant uptake (Zhang and Shan, 2001). Yet, a poor correlation between rare earths found in the water soluble, exchangeable and carbonate bound as well as in the Fe-Mn oxide bound fraction was described by Wang et al. (2004a), who suggested apoplastically- and symplastically-bound rare earths as an indicator for the bioavailability. Nevertheless, water soluble and exchangeable forms of metals in soils are generally considered as the most mobile and immediately bioavailable forms in soils (Brummer, 1986). Similarly, Xu et al. (2001) assumed that the bioavailability of neodymium to wheat seedlings might be reduced by precipitation of rare earth phosphates because this might limit the concentration of exchangeable rare earths. Another study confirmed this by showing that the bioavailability of rare earths mainly depended on the exchangeable fraction of rare earths in soil (Cao et al., 2000b), (Wen et al., 2001), which in turn could be strongly influenced by the physico-chemical properties of the soil (Liang et al., 2005). This coincides with several studies which demonstrated that the bioavailability and therefore the uptake of rare earths by plants are largely affected by soil properties (Krafka, 1999), such as pH, cationic exchange capacity (CEC) (Li et al., 2001), (Jones, 1997), and organic matter (Wu et al., 2001), as well as the amount of low molecular weight organic acids (LMWOAs) found in the rhizosphere (Davies, 1992), (Yang et al., 1999), (Shan et al., 2002), (Shan et al., 2003b).

Although metals bound to carbonate are supposed to be relatively unavailable to plants (Viets, 1962), it is thought that they become easily released to solution when soil pH is sufficiently low to dissolve the carbonates (Xian and Shokohifard, 1989). The conversion of metals from precipitable forms into soluble forms favored by low soil pH further leads to the association of metals with different geochemical phases such as the exchangeable fraction found in soil solution (Harter, 1983).

Additionally, it has been established that the bioavailability of trace metal ions in soils largely depends on their concentrations in the soil solution and, furthermore, on the ability of the soil to release trace metal ions from the soil phase to replenish those removed from solutions by plants (Backes et al., 1995). Thus, concentrations of metals in soil solutions are most likely controlled by adsorption and desorption reactions, while it has been reported that adsorption of La, Y, Pr and Gd are depending on both the cation exchange capacity (CEC) and the soil pH (Jones, 1997). Soils presenting greater cation exchange capacity showed higher sorption (Li et al., 2001), while adsorption of rare earth elements further increased with rising soil pH. This was supported by Wen et al. (2002), who demonstrated increased release of La, Ce, Gd and Y with decreasing pH.

Nevertheless, the adsorption of heavy metals is often also influenced by the valence of the adsorbate and adsorbent surface charge. The low pH of zero net surface charges as found in many soils indicates an electronegative surface charge, which supports the electrostatic attraction with cationic complexes (Elliott and Denneny, 1982). This may further explain increased adsorption of rare earths under acidic conditions. Similarly Cao et al. (2001) ascribed changes in the affinity of soils for rare earths to pH dependent surface-charge density on soil colloids, thus accounting for decreased desorption of rare earths with increasing pH. In addition, pH may change the species of organic ligands and thereby affecting the release of rare earth elements.

Organic ligands may also influence the bioavailability of rare earths independently. Though after entering the soil, rare earths are expected to be bond to organic and inorganic ligands, a greenhouse pot experiment demonstrated that the addition of EDTA, an organic ligand, to soil could promote the bioavailability of rare earths to wheat by increasing their desorption from the soil (Yang et al., 1999). With increasing concentrations of EDTA, increased rare earth accumulation was observed in both roots and tops. Moreover, the content of rare earths in wheat seedlings also presented a positive correlation with the concentration of EDTA in soil. On this basis, it was assumed that instead of being absorbed and fixed on the surface of the soil which usually reduces their bioavailability to plants, rare earths are complexed with EDTA, thereby increasing the amount of dissolvable rare earths in the soil solution. Accordingly, it was described that heavy metals may not only be assimilated by plants as ions but also in terms of complexes (Guy and Ross Kean, 1980). It has further been shown that other organic ligands such as organic acids and fulvic acids (Zhimang et al., 2001) also influence the bioavailability of rare earths in soil. Shan et al. (2002) reported that organic acids may increase desorption of rare earths from soil thus boosting their mobility in the vicinity of roots and enhancing their phytoavailability to plants.

In general, it is known that low molecular weight organic acids (LMWOAs) are capable of influencing many physicochemical and biological reactions taking place in the root-soil interface, such as the mobilization of metals in soil solution, the uptake of nutrients by plants as well as plant microbe interactions and many more (Shan et al., 2003b), (Ehlken and Kirchner, 2002), (López Bucio et al., 2000). Along with carbohydrates, low molecular weight organic acids (LMWOAs) are physiologically exuded from plant roots, whereas additionally, they may result from breakdown processes of plant residues (Li et al., 1998a), (Jones, 1998). In soil pore solutions, concentrations of LMWOAs were reported to be in the range of 10^{7-} - 10^{4-} mol/l, while in the rhizosphere, even higher concentrations are found (Shan et al., 2002), (Shan et al., 2003b). The rhizosphere, a zone of increased microbial activity and biomass, has already been reported to be highly influenced by plant roots, thus by LMWOAs. Among organic acids studied, most significant effects on the decrease of rare earth adsorption were shown by citric acid while acetic acid presented the least (Shan et al., 2002). The reduction of adsorption of rare earths followed the order: citric acid $>$ malic acid $>$ tartaric acid $>$ acetic acid. This coincides with the stability constants of rare earth elements with the organic ligands. It is therefore highly probable that the formation of aqueous rare earth organic ligands complexes accounts for the observed adsorption decrease. While in the absence of organic ligands it is suggested that only electrostatic attraction and repulsion exist in the soil system which may affect adsorption of rare earth elements, a competitive effect of rare earths between soil adsorption sites and aqueous organic ligands is expected in their presence.

On this basis, it has been suggested that even though soil pH constitutes an important factor affecting adsorption and desorption processes of rare earths in soil, the amount of organic acids is might be the main controlling factor influencing rare earth desorption and therefore their bioavailability. Nevertheless, soil pH and organic acids are closely related to each other as increased amounts of organic acids consequently lower the pH of the rhizosphere. As a result, rare earths turn into more soluble forms and thus become more easily available for plant uptake (Li et al., 1998a). Accordingly, concentrations of light rare earth elements have been found to be increased by 21 - 78 % in a Chinese natural perennial fern fronds after soil was amended with organic acids (Shan et al., 2003a), while uptake of lanthanum by barley (Hordeum vulgare) (Han et al., 2005) and wheat roots (Wang et al., 2004b) has been shown to be promoted by organic acids. This is supposed to be mainly but not solely mediated by calcium channels. The enhancement order was acetic $>$ lactic $>$ tartaric $>$ malic $>$ citric acid and therefore consistent with that reported by Shan et al. (2002). Again, the lower the stability constants of lanthanum-organic ligand complexes the greater the effects, that is the more easily the lanthanum-organic ligand complex was dissociated the more lanthanum was absorbed by the roots. This indicates that free lanthanum ions were more easily available to barley roots than complexed ones. Consistently, Bell et al. (2003) showed that for organo-metallic complexes no nutrient carriers exist making their diffusion at any significant rate unlikely to occur. Yet, physiological processes in soil and plant systems are more complicated. Hence, via a purely apoplastic pathway, chelation may also increase the uptake of lanthanum into the xylem in young regions of the root where the endodermis is not fully developed to form a Casparian strip (Taiz and Zeiger, 1998). But in localization studies, it could be revealed that lanthanum diffused predominately through the apoplast of plant cells (Lehmann et al., 2000).

In conclusion, soil is a complex system and interactions between biota and soil are intricate. It is therefore difficult to predict the bioavailability of rare earths to plants (Li et al., 1998a). Yet recent studies recommended the labile rhizosphere soil solution fraction (Wang et al., 2001b) with low molecular weight organic acids LMWOAs as extractant (Shan et al., 2003b), (Wang et al., 2004a) for the prediction of the bioavailability of rare earth elements in soil pools to plants. Hence, future studies on the interactions taking place in the rhizosphere soil may provide additional information on the bioavailability of rare earth elements which is important for assessing efficacy of rare earths on plant growth as well as their environmental safety.

It has been shown that the availability of rare earths to plants not only depends on soil properties, as described previously, but also on the plant species themselves. Among different plant species considerable variations in uptake and contents of rare earths even under natural conditions that is without rare earth supplementation were reported (Ichihashi et al., 1992), (Krafka, 1999), (Fu et al., 2001) and a spread of five orders of magnitude was described for the concentration of lanthanum in leaves of various plant species in Japan (Koyoma et al., 1987). Other investigations on the concentration of rare earths in six different plant species and their adjacent soils revealed large variations between the plant species (Wyttenbach et al., 1998a), whereas the concentration of rare earths in soil remained fairly uniform as shown in Table 11.10. In addition to interspecies differences, variations in rare earth contents were also found in plants belonging to the same plant species as demonstrated in spruce trees (Wyttenbach et al., 1996). It has been suggested that variations in the transpiration rates of the individual spruce trees account for these large intrasite differences observed.

Place	La	Ce	Nd	Sm	Eu	Tb	Yb	Lu	Mean RE
I	17.5	35.6	14.6	2.79	0.508	0.382	1.51	0.208	0.996
II	18.1	36.3	15.6	2.85	0.502	0.364	1.45	0.206	0.999
III	17.8	36.9	14.9	2.74	0.498	0.379	1.38	0.188	0.976
IV	16.5	32.9	13.7	2.59	0.485	0.361	1.48	0.206	0.947
V	18.7	37.9	15.6	2.95	0.549	0.394	1.47	0.206	1.038
VI	18.2	36.8	15.5	3.00	0.536	0.404	1.55	0.214	1.044
Mean	17.8	36.1	15.0	2.82	0.513	0.381	1.47	0.205	1.000

Table 11.10: Concentrations of rare earth elements (ng/g) in soils (Wyttenbach et al., 1996).

However, the physiological processes of rare earth uptake in plants are very complex. It is known that despite their chemical similarities, chemical properties such as solubility or complexing constants may vary among the trivalent rare earths. These variations are often connected to the *lanthanoide contraction*, which comprises the slight decrease of the ionic radii along with the atomic number (Chapter 4). Chemists have early benefited from this by fractionating rare earth elements. Yet it was long unclear whether and to what extent plants may do the same in the process of uptake, translocation and deposition.

Several studies reported that there is no or insignificant fractionation between the individual members of rare earths in plants with respect to the soil (Robinson et al., 1960), (Miekeley et al., 1994), (Laul and Weimer, 1982). However, according to geological procedures, these results are usually based on the comparison of distribution patterns of rare earth elements in plants with those in soil after normalization to chondritic values. These meteorites are considered to represent the naturally occurring lanthanide abundances, undisturbed by geological and biological partitioning (Evensen et al., 1978). On this basis, two important advantages have been ascribed to chrondric normalization. Firstly, it eliminates the abundant variations between odd and even atomic number elements, whereas secondly, it allows the determination of any fractionation amongst the various rare earth elements, as no fractionation between light and heavy rare earths is reported in chondritic meteorites (Wei et al., 2001), (Xu et al., 2003). However for plants, chondrite normalization is considered to obscure the values since the adjacent soil constitutes the ultimate source for rare earths in plants which never has a distribution pattern similar to chondrites. Thus, normalization to the respective soil is rather recommended. If pertinent soil analyses are unavailable, plant concentrations should be normalized to the concentration of rare earths in the upper continental crust (UCC) as most soils present similar distribution patterns to the upper continental crust.

Evans (1990) stated that the uptake of lanthanides by plants may either occur with selective enrichment of the lighter elements or without fractionating the individual elements. Yet, first evidences on the fraction of rare earth elements in plants with respect to the soil were given by Wyttenbach et al. (1996) who reported inconstant soil-normalized values for rare earths in spruce tree needles. These results could be further confirmed in five other plant species (silver fir - Abies alba, needles; plaintree maple - Acer pseudoplastanus, leaves; ivy - Hedera helix, leaves; blackberry plants - Rubus fruticosus, leaves; and wood fern - Dryopteris filis-mas, leaves and stalks) as shown in Table 11.11. Based upon these results, it may therefore be strongly concluded that plants do not take up individual rare earth elements as equal members of a chemically homogenous group.

Particularly cerium demonstrated an irregular behavior in plants which coincides with several studies describing a lower presence of cerium compared to the other elements (Wyttenbach et al., 1998a), (Fu et al., 2001). This so-called cerium anomaly could also be detected in ferns, yet bigger anomalies were observed in stem and leaf compared to root (Fu et al., 1998).

The negative cerium anomaly indicates a reduced uptake of cerium compared to the other trivalent rare earth elements. As it is known that the chemical behavior of compounds containing cerium with a valence of four may differ from that of trivalent rare earths (Brookins, 1989), the ability of cerium to occur in the cerium IV state may account for these effects. Accordingly, Ce^{4+} is considered to be less available and/or poorly assimilated by plants (Robinson et al., 1960), (Evans, 1990), (Wyttenbach et al., 1998b), (Wei et al., 2001). Ce^{4+}, which is metastable in the presence of organic material, may be stabilized by either complexation or adsorption onto solids. Based on the information that microbially mediated redox processes affect the behavior of both cerium and manganese in seawater (Moffet, 1990), it was assumed that similar processes may

Species	La	Ce	Nd	Sm	Eu	Gd	Tb	Yb	Lu
Soil (total)^{a}	17800	36100	15000	2820	513	na	381	1470	205
Soil extract^{a,b}	1878	3425	1797	459	92.5	na	70.3	152	15.80
Maple	1078	560	544	103	20.9	106	16.6	22.2	2.80
Wood fern	637	659	239	24	3.0	8	0.8	1.4	0.18
Blackberry^{c}	336	185	141	27	5.5	27	3.9	5.0	0.62
Ivy	172	75	67	9	1.8	8	1.1	2.0	0.26
Silver fir	97	61	65	14	3.2	17	3.5	8.3	1.01
Spruce^{d}	78	60	53	13	3.0	16	3.2	7.6	0.92
Spruce^{d}	110	110	69	14	3.1	16	3.1	6.9	0.83
Blackberry^{c}	76	55	33	6	1.3	6	0.9	1.7	0.21

Table 11.11: Concentrations of rare earth elements (ng/g dry weight) in soil, soil extracts and plant leaves of various plant species; ^{a} Mean of 6 places, ^{b} extracted with 0.5 mol/l acetic acid, 0.5 mol/l NH_4 acetate, 0.02 mol/l EDTA pH 4.65, concentrations relative to the weight of the extracted soil ^{c,d} from two different sites (Wyttenbach et al., 1998a).

occur in the rhizosphere (Laurie and Manthey, 1994). Thus, manganese compounds which are found as surface coatings on soil particles may function as sinks for Ce^{4+} (Hem, 1978).

In addition, small changes of the redox potential of the rhizosphere were suggested to account for differences in the size of cerium anomaly observed among various plant species and even individuals of one species (Wyttenbach et al., 1998a). Nevertheless, cerium anomaly was even more pronounced in plants after high doses of rare earths were applied (Xu et al., 2003), whereas Krafka (1999) did not observe any difference in the cerium behavior in plants at all. Even though an europium anomaly due to Eu^{2+} is generally observed in minerals and rocks, none was seen in plants (Wyttenbach et al., 1996). This might be ascribed to the fact that under the conditions prevailing in soils, Eu^{2+} is unstable hence does not influence the uptake of europium into plants.

Yet, variations in rare earth uptake in plants grown on different soils, on the same site and moreover in plants belonging to the same species have not only been reported by Wyttenbach et al. (1998a) and Krafka (1999), but also by Zhang and Shan (2001). In addition, the distribution of individual rare earths within the same plant species varied as well as can be seen for blackberry plants in Table 11.12 and for spruce trees in Table 11.14. Hence, the ratio between two rare earth elements was neither constant among needles of spruce trees nor among leaves of blackberry plants. Yet, compared to interspecies differences, variations within the same plant species were smaller.

It has been assumed that changes in the oxidation state of Ce, which presented the largest deviations, account for some but yet not all of these effect observed. Wyttenbach et al. (1998b) reported that although in blackberry plants variation coefficients dropped from 15 to 11 % after the exclusion of cerium, the variability in plants still remained much larger than that in soils. Additionally, it was also larger than in soil extracts (Table 11.13), thereby eliminating extractability as another cause for these variations.

Surprisingly, almost identical distribution pattern were observed for two cornifers (fir and spruce). Nevertheless, they were very dissimilar from those of angiosperms, which in turn dif-

Place	La	Ce	Nd	Sm	Eu	Tb	Yb	Lu
I	362	237	116	17.5	3.15	2.48	4.00	0.464
III	244	128	112	22.8	4.63	3.54	4.24	0.500
IV	270	158	114	21.9	4.52	3.29	3.94	0.507
V	565	276	288	55.7	11.43	7.87	9.05	1.146
VI	237	126	75	16.1	3.59	2.59	3.83	0.509
Mean	336	185	141	26.8	5.46	3.95	5.01	0.625

Table 11.12: Concentrations of rare earth elements (ng/g) in leaves of blackberry plants; sample II got lost during the investigation (Wyttenbach et al., 1998b).

Place	La	Ce	Nd	Sm	Eu	Tb	Yb	Lu
I	1918	3611	1937	484	96	71	172	19
II	1826	3513	1653	428	85	66	137	14
III	1721	3013	1716	442	89	61	149	15
IV	2137	3754	1972	494	99	76	162	17
V	1730	2963	1601	423	87	70	140	14
VI	1940	3693	1906	484	99	78	149	16
Mean	1879	3425	1937	459	92	70	152	16

Table 11.13: Concentrations of rare earth elements (ng extracted per 1 g of dry soil) extracted with Lakanen Solution from the soil (Wyttenbach et al., 1998b).

fered largely from ferns collected at the same site. In Japan, different distribution patterns were also described in various plant species (Koyoma et al., 1987) implicating that they are found in different plant species throughout the world.

Anyhow, tight and regular relation between these differences and the atomic number of rare earths was described by Wyttenbach et al. (1998a). Both in spruce trees and in blackberry plants, distribution patterns showed a decrease from the lightest to the heaviest rare earths about a factor of six which indicates a substantial fractionation of light and heavy rare earths. The same has been observed in other plant species. As rare earth concentrations are quite uniform in soil, this fractionation seems to be linked to the plant itself that is it is plant species specific. Yet differences in transportation length of individual plants have been excluded as possible explanation for the variations. Until now there are no verified explanations for these large inter- and intraspecies concentration differences. However, it is very likely that complexation of rare earth elements in the rhizosphere of the plants accounts for the variations in uptake as this can vary between places and be different among plant species even when growing on the same site. Further support on this has been provided by the observation that the ratio of individual rare earths could be expressed as a linear function of the atomic number of the rare earths. Additionally, this is in accordance with several studies reporting that the bioavailability of rare earths to plants is highly influenced by complexation of rare earths to low molecular weight organic acids in the rhizosphere soil. Cao et al. (2002b) reported fractionation factors of rare earths in wheat (Triticum aestivum L.) to be negatively correlated with the soil pH value, which may also influence plant uptake of rare earths.

11.3.1 Concentration of Rare Earths in Plants

Regarding interspecies variations in uptake of rare earths by plants it is self-evident that concentrations of rare earth elements also differ within plant species. Indeed, several studies confirmed that rare earths contents in plants may vary extremely. On the one hand, mainly low contents have been reported in different parts of plants (Ichihashi et al., 1992), (Krafka, 1999) that is in the ng/g range or even smaller; on the other hand, comparatively high values were found in some plant species. Nevertheless, concentrations in plants are usually quite low (Tyler, 2004) and plant soil ratios (transfer factors) of 0.04 - 0.05 have been described, while Krafka (1999) reported even lower transfer factors of 0.02 to 0.03.

In ordinary plants lanthanum concentrations determined were in the range of 3 to 5000 ng/g. With rare earth contents of less than 10 ng/g as presented in Table 11.14 (Wyttenbach et al., 1994), spruce needles were among the lowest values measured in plant leaves. Krafka (1999) determined similar values. Particularly low values were also reported in grains (Sun et al., 1994), (Li et al., 1998a) and vegetables (Laul et al., 1979), (Bibak et al., 1999) with contents ranging from 10^{4-} to 10^{2-} μg/g. Mean concentrations are generally lower in plants compared to those in soil. A comparison between rare earth contents in wheat plants and in soil is shown in Table 11.15. In wheat, low values of rare earth element contents were determined in both parts (root and tops). For lanthanum, a light rare earth element, values of 0.009 mg/kg in root and 0.006 mg/kg in stem and leaves were measured. Even lower values ranging from undetectable in roots to 0.002 mg/kg in the plant tops were found for yttrium (Zhimang et al., 2001).

Place	La	Ce	Nd	Sm	Eu	Tb	Yb	Lu	Other RE
I	43.4	35.6	23.9	5.2	1.26	1.35	3.97	0.417	0.477
II	54.0	56.4	43.5	10.1	2.33	2.70	7.06	0.838	0.840
III	96.1	65.3	58.9	14.5	3.14	3.30	6.82	0.857	1.057
IV	73.1	62.7	58.3	15.1	3.42	3.77	9.30	1.138	1.129
V	108.2	71.6	64.7	15.4	3.51	3.96	9.82	1.193	1.248
VI	94.3	67.3	68.0	18.1	4.11	4.26	8.50	1.062	1.248
MEAN	78.2	60.2	52.9	13.1	2.96	3.22	7.58	0.917	1.000

Table 11.14: Concentrations of rare earth elements (ng/g)in needles (Wyttenbach et al., 1996).

However, a few plants may accumulate large amounts of rare earths. With rare earth concentrations in the upper μg/g range they are considered as hyperaccumulators. Among these are certain ferns (Pteridophyta) (Ichihashi et al., 1992), (Ozaki et al., 2000), (Wei et al., 2001), pokeweeds (Phytolacca) (Ichihashi et al., 1992), hickory trees (Carya) (Robinson et al., 1958), (Robinson et al., 1960) or plants from the spurge family (Euphorbiaceae). Furthermore, higher values up to 10^6 ng/g were also determined in plants grown on highly mineralized soils (Miekeley et al., 1994). In Japan, contents of about 100 μg/g of lanthanum were reported in some ferns (Koyoma et al., 1987) that is about 10^4 times more than those determined in spruce needles. Similar results were obtained for Dicranopteris linearis, a fern species, containing very high concentrations of rare earths (134 - 1754 μg/g in root, 107 - 632 μg/g in stem, 51 - 102 μg/g in petiole and 977 - 2272 μg/g in lamina) (Wei et al., 2001), whereas lanthanum concentrations of up to 1 mg/g have

	Soil		Root		Shoot	
	range	mean	range	mean	range	mean
La	13.25 - 41.05	24.20	0.73 - 8.96	4.30	0.053 - 0.22	0.11
Ce	29.45 - 87.54	50.98	4.96 - 16.5	11.29	0.87 - 0.51	0.19
Pr	3.06 - 9.89	5.62	0.17 - 1.81	1.03	0.01 - 0.06	0.02
Nd	10.75 - 36.15	19.78	0.58 - 5.57	3.53	0.03 - 0.22	0.06

Table 11.15: Concentrations of rare earth elements (μg/g) in Chinese soils and shoots and roots of wheat (Triticum aestivum L.) from the same site (Shan et al., 2003b).

been reported earlier in ferns (Ichihashi et al., 1992). Thus ferns strongly absorb rare earth elements from the soil even if they are present at relatively low concentrations (Wei et al., 2001). Yet a certain soil-plant barrier exists as the absorption weakens when rare earth concentrations become higher. On the one hand, this soil-plant barrier hampers the absorption of toxic metal ions, hence constitutes one of the main resistance mechanisms observed in plants, while on the other hand, it allows the maintenance of rare earths concentration in ferns within a certain range.

Due to the large variations of rare earths in plants even among individual plants of the same species, it is probably more reasonable to define a "normal range" comprising extreme values rather than a "normal concentration".

However, the determination of rare earths in plants entails some difficulties. Due to their extremely small concentration ratio plant/soil that is very small concentrations in plants a very sensitive, analytical technique is required (Henkelmann et al., 1997). Furthermore, already little contamination by adhering soil will fudge the results and concentrations measured will thus be higher than the endogenous plant concentration. For the complete removal, a special treatment using suitable solvents, such as $CHCl_3$, is required since water cannot sufficiently dissolve the epicuticular wax covering the leave surface under which contaminations are trapped. The mass of the terrigenous material may amount up to $>$ 100 mg/g plant. Yet the error committed by including surface contamination in the analysis of plant samples depends on the sample, the sampling situation as well as the element determined and thus has to be considered for each analysis separately. Most plant analysis are done for physiological purposes and completely wrong conclusions may be drawn if nonphysiological exogenous contribution is included. Careful interpretation of published data is therefore recommended as several investigations lack proper removal of contamination, and results from afflicted studies cannot be used in the discussion of plant uptake or of other plant physiological processes (Wyttenbach et al., 1998b), (Wyttenbach and Tobler, 1998).

Two examples are given in order to emphasize the importance of careful removal of any aerosol or soil particle from the plant surface prior to analysis. A contamination of 5 mg soil per g cheat grass was determined by Laul and Weimer (1982). Compared with the results, it was concluded that rare earth concentrations measured in grass were almost totally due to contamination by soil, thus making these values completely invalid for plant physiological analysis. In contrast to that, all external material was excluded by washing the fresh samples with toluene/tetrahyrofuran (1:1) before the contents of rare earths in Norway spruce needles (Picea abies) were determined. Concentration values found were therefore much lower than those reported in literature as shown in Table 11.16. Lanthanum concentrations measured in spruce needles of age class 1 were 44 ng/g compared to 4.9 ng/g when exogenous material was carefully removed (Wyttenbach and Tobler, 2002).

	Spruce Needles (ng/g)			Earth Crust (μg/g)
	Wyttenbach et al. (1994)		Erdtmann (1991)^b	Goering et al. (1991)
	site 1	site 2		
La	22.8	28.9	307	30
Ce	13.2	29.0	403	60
Sm	2.81	3.85	49.6	6.0
Eu	0.795	0.765	9.04	1.2
Tb	0.710	0.739	10.5	0.9
Yb	1.80	1.566	26.4	3.0
Lu	0.180	0.159	-	0.5

Table 11.16: Concentrations of rare earths in cornifer needles; ^{b} value include surface contamination.

For spruce needles, average values were 10.7 ng/g for La and 1.2 ng/g for Sc while the relative concentration of rare earth elements in the needles has been shown to be similar to that found in the earth crust.

Independently from the doses applied, rare earths accumulated strictly proportional to the needle age class with concentrations in the current year's needle (age class 1) being 5 times lower than those in age class five (Wyttenbach et al., 1996). Thus accumulation proceeds exactly with time and may therefore be characterized by the yearly increment, whereas there was no indication for a retranslocation of accumulated elements.

11.3.2 Deposition and Accumulation of Rare Earths in Plants

There is little information on the metabolic consequences after rare earths are assimilated by plants. It is still argued whether rare earths are deposited at extra or intracellular locations in plants. Regarding the similar linear time-depending accumulation behavior of the rare earths and of silicon in conifer needles (Marschner, 1986), (Wyttenbach et al., 1994), it has been suggested that rare earth elements provide similar dynamics, such as the uptake by the roots, and transport by the xylem (with the transpiration stream). Thus, it might also be possible that rare earths are deposited as hydroxides together with amorphous silica. However, a study performed on hyperaccumulating ferns showed that about 40 % of the rare earths were bound to high molecular proteins (Guo et al., 1996). Zhimang et al. (2001) demonstrated that in wheat bioaccumulation of rare earth elements was much higher in the root than on the top parts. Similarities in bioaccumulation patterns observed in roots and tops suggested that rare earths in root could be transported to the above ground parts of the plant. However, as most rare earths were assumed to be absorbed and deposited on the cell wall, penetration into the cell membrane was considered difficult (Brown et al., 1990), (May et al., 1997).

Generally, roots have been reported as the main accumulation sites for rare earths in several plant species. Consistent with that, Hong et al. (1996) reported that absorbed rare earths were predominantly accumulated in the roots (88 - 90 %) while only 10 to 12 % entered the cortex and peduncle of plants. The average ratio in root to shoot of about 10 also emphasized the much greater accumulation potential of roots for lanthanum (Zhang and Shan, 2001). Higher accumulation values of rare earths in roots compared to leaves and therefore higher concentration ratios were also reported by Wahid et al. (2003). It was further reported that high doses lanthanum efficiently enhanced the permeability of the cell membrane thus disturbing their physiological function. This consequently leads to higher accumulation of rare earth elements in the roots as further transportation to the shoots is hampered (Brown et al., 1990), (Chang, 1991).

Nevertheless, accumulation of rare earths in plant roots may also reflect the general behavior of plants responding to environmental stress. Plants tend to limit the translocation of heavy metals to their aboveground parts in order to minimize or overcome toxic effects caused by metals in soil (Foy, 1983). Limited transport of absorbed lanthanum from the roots to the plant tops was also observed by Diatloff et al. (1995b), who similarly put this down to a plant-protection function from adverse effects of lanthanum. Accordingly, Zhou and Liu (1996) demonstrated that after being absorbed, rare earths were fixed or precipitated on the cell wall of plant roots which hampered further transportation to the plant tops. In contrast to that, easy uptake of lanthanum from the root to the shoot was reported in wheat plants (Wang et al., 2001c).

However, Chen et al. (1995b) suggested that the soil pH could change the structures of the cell wall and plasmolemma of the plant as well as the osmotic pressure of the plasma inside the plant, thereby inhibiting the entrance of rare earth ions along with the fluid into the cell. The uptake of rare earths by the above-soil parts of the plant (shoot) is thus inhibited which results in lower accumulation. This is consistent with the general expectation of greater bioavailability of rare earths at lower soil pH and, hence, with the observation of a significant negative correlation between rare earth contents in roots and soil pH (Zhang and Shan, 2001). Li et al. (1998a) and Yang et al. (1999) attributed higher accumulation values of rare earths in roots than in other parts (stems, leaves and grains) observed in corn, rice and wheat to sequential distribution from the soil solution to the roots and then further to the tops. Five steps are thought to be required for the transportation of rare earths from soil to the plant system (Wei et al., 2001). First total rare earths to soluble rare earths in soil, second soluble rare earths to root, third root to stem and then further to petiole and at last from petiole to lamina. Nevertheless, accumulation of rare earths has also been shown to be influenced by the application rate. A correlation between the accumulation behavior of La, Ce, Pr and Nd and the concentration of applied rare earth-containing fertilizer was demonstrated in winter wheat (Zhang and Shan, 2001). At low fertilization rates, accumulation increased with higher concentrations, whereas the inverse was observed at high fertilization rates and remained constant over the medium rare earth range. In accordance with that, Maheswaran et al. (2001) also found higher concentrations of lanthanum in barley and wheat with higher rates of lanthanum application, particularly when applied as foliar. However, when applied at lower rates no significant differences were observed, especially when lanthanum was applied to soil. A recent study reported that there was no significant accumulation with the soil-dressing method. Furthermore, for both soil and foliar dressing methods, no distinct residues of rare earths were found in plant grains (Liang et al., 2005). As the relationship between accumulation and fertilization rates is of high importance regarding environmental effects of rare earths, it is further discussed in Chapter 7.

11.3.3 Distribution of Rare Earths in Plants

The distribution patterns of rare earth elements in native plants have been widely studied (Fu et al., 2001), (Wyttenbach et al., 1998a), (Ichihashi et al., 1992). As with most trace elements a decrease in rare earth contents has been reported to be in the order root > leaf > stem > flower, grains, fruit. The same was reported in corn and rice (Li et al., 1998a), (Xu et al., 2002). However, the uptake of rare earths from soil to roots is generally much higher than the translocation rate from root to shoot (Hu et al., 2002). Nevertheless, slight variations in the distribution pattern have been observed among the individual rare earth elements (Wei et al., 2001). In contrast to light rare earths which presented distribution patterns in the order of lamina > root > stem > petiole, heavy rare earths also presented distribution patterns of root > lamina > stem > petiole or even root > stem > lamina > petiole. Compared to light rare earths, heavy rare earths (Gd to Lu and Y) presented lower contents in stem, petiole, lamina and root. Higher accumulation values for light rare earths in both root and tops of wheat were also reported by Yang et al. (1999). This phenomenon is probably due to fractionation processes of light from heavy rare earths taking place during transportation of rare earths from soil to plants as well as within the plant. Wei et al. (2001) could verify this by demonstrating that light and heavy rare earths fractionate during the migration process from stem to petiole.

It was also reported that distribution patterns of rare earths in plants may differ with the method of application. After foliar spraying, rare earths mainly accumulated in wheat leaves although only 2.84 % of the amount sprayed were found on the wheat plant itself and most of the rare earth spraying solution using cerium nitrate was found in the soil (Hong et al., 2000b). Rare earth contents in leaves were ten times higher than in roots, 100 times higher than in stem and glume and 3000 times higher than in grain. In contrast to that, it was recently observed that after foliage dressing the contents of rare earths at the maturing stage of spring wheat were still in the order of root > leaf > stem and crust (Liang et al., 2005). Compared with the control, foliage-dressing caused higher accumulation of rare earths in root and leaf whereas no significant difference was observed in stem and crust. Additional information is provided in Chapter 7.

11.4 Effects of Rare Earth Elements on Plants

Over time, several attempts have been made trying to explain the effects of rare earths on plants such as growth enhancement. Possible explanations, which are mainly based on physiological aspects of rare earths in plants, include increased plant enzyme activity, chlorophyll content and photosynthetic rate, effects on the uptake of several nutrients such as nitrogen, potassium and phosphate as well as increased resistance to environmental stress. Studies on physiological effects of rare earths on plants will therefore be presented in this section.

11.4.1 Effects on the Physiological Function of Calcium in Plants

It is generally agreed that calcium is an essential nutritional element for plants (Hu et al., 2004). Regarding their chemical properties, a lot of physiological effects of rare earths can be attributed to the extreme resemblance of individual rare earths, especially lanthanum, to calcium (Chapter 4 and Chapter 5). Brown et al. (1990), who already reviewed the effects of rare earths on physiological functions of calcium in plants, reported that rare earths act analogous to calcium, while lanthanum was shown to inhibit many enzymes as well as functional proteins. Furthermore, lanthanum could displace calcium from extra-cellular binding sites thereby inhibiting the efflux of extra-cellular and partly intracellular calcium Chapter 5. Similar to calcium, lanthanum could inhibit K uptake in plants if applied for a short time, however long-time application resulted in accelerated K uptake (Leonard et al., 1975).

Besides influencing physiological processes involving calcium, rare earths may also affect the calcium metabolism itself. To a lesser extent, they have been shown to disturb the metabolism of magnesium, too (Nari et al., 1989). Binding to calcium sites in the outer cell membranes, lanthanum was able to affect calcium translocation (Pantoja et al., 1992). Furthermore, it may also influence calcium translocation by polarizing the cell membrane (Hodick and Sievers, 1988). Decreased calcium concentration of 41 % was found in corn roots treated with a solution of 5 μmol lanthanum per l (Diatloff et al., 1995c). Another study showed that gadolinium and lanthanum inhibited calcium uptake by plant protoplasts even to a higher extent than Al. Yet in contrast to cerium, which showed the same pattern of inhibition of calcium uptake, calcium uptake was totally unaffected by scandium (Rengel, 1994b). In accordance with Hodick and Sievers (1988), inhibitory effects of lanthanum were attributed to the introduction of positive charges into the area of Ca^{2+}-ATPase, thus altering the net charge of cell membranes (Ogurusu et al., 1991). Rengel (1994a) showed that lanthanum could inhibit calcium channels and thereby the uptake of calcium.

Paradoxically, it has been reported that the addition of lanthanum can diminish symptoms in plants caused by calcium deficiency (Weng et al., 1990). Lacking calcium usually leads to the destruction of plant cells due to malfunctioning of the cytoplasma membrane (Xing et al., 1989). However, lanthanum and cerium may alleviate calcium deficiency symptoms by replacing calcium functionally (Chapter 5). Dong et al. (1993) demonstrated that lanthanum chloride accelerated growth and root activity and furthermore improved the activity of K^+ and Mg^{2+}-ATPase in the cytoplasm membrane of cucumber under calcium deficient conditions. In soil culture experiments, it was shown that lanthanum (> 100 mg/kg) increased the calcium content in the sap of rice (Chang, 2006). Increased calcium contents were also observed in the cell wall of tobacco callus and oilseed rape seedling root after lanthanum or cerium were applied at low concentrations (0.01 - 0.05 mmol/l) whereas higher concentrations (0.10 mmol/l) caused a decrease (Zhang et al., 1999c). Nevertheless, the interference of rare earths, especially of lanthanum, with several calcium functions probably accounts for many effects observed in plants, including toxic effects (Pang et al., 2002).

11.4.2 Essential Elements for Plants

According to the concept of essentiality proposed by Arnon, three criteria need to be fulfilled by plant nutrients in order to be considered essential (Arnon, 1943).

- Plants can either not complete a function or its life cycle
- A deficiency can only be corrected by application of the specific element that is deficient
- The element is directly involved in metabolism

However, there are certain plant nutrients classified as beneficial elements which are found to stimulate plant growth though have not been shown to be essential (Asher, 1995). Due to improvements in experimental techniques, elements currently classified as beneficial may later be shown to satisfy Arnon's criteria.

In view of reasonable explanations for the effects of rare earths seen in plants, it has been taken into consideration that rare earths might be essential elements for plants. Especially the high magnitude of yield increases of 8 - 15 % (Xiong, 1995) reported in China, indicated that many of these crops would be deficient in rare earths under normal circumstances and therefore suggested essentiality of rare earths. However, no deficiency symptoms have been reported, whereas, generally, large values of concentration ratios relating the concentration of a given element in the plant (dry weight) to that in the soil are found with essential elements such as Cl, Mn, Ca, Zn, K and Mg, only small values are reported for elements that have a valence of 3+, such as rare earths, yet also for arsenic and sodium (Wyttenbach and Tobler, 1998). Furthermore, except Mn, variations are smallest for essential elements but considerably larger for nonessential elements whose uptake obviously is much less controlled by plants. For each rare earth element coefficients of variation between individual spruce trees were reported to be about 30 % and thus correspond to those often found for nonessential elements in trees from one site and are much larger than the variation of some essential elements (Wyttenbach et al., 1996). Moreover, as it is largely agreed that trivalent metals are toxic to plants (Asher, 1995) and known that lanthanides exist as trivalent cations over a wide pH range, it seems paradox to assume that they might be essential elements. But there is no evidence that any of the rare earth elements is necessary for plant growth (Pang et al., 2002), (Tyler, 2004). Nevertheless, essentiality of elements has only been studied in a limited number of plants compared to the large diversity of plants existing. Boundaries between essential and non-essential elements are not as definite as described in traditional plant physiology. A less defined group of elements is known to exist, which, regarding certain conditions, concentrations, chemical forms, may be favorable to some plant species without being essential to plant life.

11.4.3 Effects on the Mineral Nutrient Uptake and Metabolism

However, influence of rare earths on nutrient metabolism in plants including beneficial effects of rare earths on absorption, transfer and assimilation of nutrients in plants have been reported, whereas Chang et al. (1998) demonstrated promoting as well as inhibiting effects of rare earths on velocity and physics of nutrients uptake by crops.

Hence, after spraying tomato seedlings with 5 mg/l $CeCl_3$ P contents increased by 10.34 % (Tang and Tong, 1988). In rice treated with rare earth fertilizers, increased absorption of P of 12 % could be observed (Ning and Xiao, 1989). In addition, increases of P uptake of 10.9 - 12.3 % were described in wheat plants due to rare earth nitrates application (Jie and Yu, 1985), (Zhu and Hu, 1988). Furthermore, the application of rare earths increased phosphate uptake in cucumber, soybean, mungbean, tobacco and day lily flower (Wu et al., 1984), (Wu et al., 1985). Therefore Wu et al. (1985) proposed that improvements in plant growth may be attributed to a rise in phosphate uptake. Another study confirmed enhanced P uptake by lanthanum-treated plants and ascribed it to the release of phosphatase into the soil medium (Leonard et al., 1975). In barley, however, phosphate assimilation was unaffected after rare earth application (Meehan et al., 2001). Investigations in hydroponics even showed that lanthanum just as calcium was able to inhibit the phosphate and potassium uptake significantly ($>$ 0.05 mmol/l) (Chang, 2006). Lanthanum exhibited negative effects on the absorption of phosphate in the same way as calcium. This was further confirmed in soil culture experiments which also indicated that lanthanum ($>$ 100 mg/kg) highly decreased the contents of phosphate and potassium in the sap of rice. Similarly, rare earths reduced the absorption of phosphorus (P) and zinc (Zn) by coconut palm when applied at high concentrations (Wahid et al., 2000).

According to Ning and Xiao (1989) rare earth application increased the absorption of potassium by 8.5 % in rice, whereas sole application of lanthanum enhanced the concentration of potassium in barley tops by 11 - 14 % (Meehan et al., 2001). Foliar application of neodymium on rapeseed lead to a redistribution of K within the plant towards those plant parts treated with Nd (Wei et al., 1999). Cerium also enhanced the assimilation of K by willow (Li, 1995). Tomato seedlings treated with cerium chloride contained 15.42 % more potassium compared to the control (Tang and Tong, 1988). However, during the whole incubation period, decrease in K uptake was observed in rice supplied with cerium (Hu and Zhu, 1994). Within the first six hours, lanthanum also hampered K uptake whereas afterwards accelerated assimilation occurred.

Impaired mineral composition after lanthanum treatment was also demonstrated in mungbean and corn (von Tucher et al., 2001). All measured minerals, including N, P, Ca, Mg, S, Mn, were significantly affected in mungbean, while in leaves, decreased potassium contents were up to 60 %. In maize, significant changes were only observed for Ca, Mg and root Mn contents. Yet, decreased potassium contents were also reported in corn root protoplasts (Liu and Hasenstein, 2005). In addition, a manganese deficiency was revealed in mungbean plants treated with a solution containing more than 0.63 μmol/l of cerium (Diatloff et al., 1995d). Velasco et al. (1979) suggested that rare earths might displace boron from its active site thus causing boron deficiency. However, increased absorption of Zn, Mn and Mo were observed in maize plants after rare earths were applied at 5 mg/l, while at 10 mg/l inverse effects occurred (Chang, 2006).

As to nitrogen, mixing tomato seedlings with 50 mg/l, rare earths lead to higher absorption of NO_3^- by 8.13 % (Lai et al., 1989). It has been assumed that the effect of rare earths on nutrient elements depends on the method of application. Also in cotton, uptake of N was shown to be accelerated by lanthanum application in solution culture experiments (Zhu, 1986). Furthermore, both soil culture experiments (Zhu and Hu, 1988) and field trials (Jie and Yu, 1985), (Zhu, 1992) could demonstrate enhanced N uptake by wheat plants after treating them with a mixture of rare earth nitrates, whereas Jie and Yu (1985) reported improved N utilization to be in the range of 20.2 - 26.3 %. Rare earths applied to Chinese date trees increased the absorption of N and Zn (Chang, 2006). The application of rare earth containing fertilizer to rice increased its absorption of N by 16.4 % (Ning and Xiao, 1989). Additionally, sulfate absorption by soybeans was also found to be enhanced. While seed dressing with rare earth nitrates has been shown to increase the contents of NO_3^- in corn by 37.4 % (Cui and Zhao, 1994), decreased N contents were observed after the sole application of lanthanum (Diatloff et al., 1995c). Alike, noncompetitive inhibition of NO_3^- uptake as well as reduced assimilation of NH_4^+ were observed in rice after the addition of lanthanum and cerium (Hu and Zhu, 1994). In contrast to that, increased absorption of nitrates was also reported in sugarcane (Kuang, 2006). The leaf nitrogen balance was decreased after the application of rare earth nitrate containing fertilizer. Additionally, an increase in total leaf nitrogen, a fractionation from nitrate nitrogen to amino nitrogen and the free amino acid pool was observed. An accelerated transfer of N from inorganic to organic forms was also described by Pang et al. (2002). This is considered to be beneficial for both the protein synthesis as well as the regulation of nutrient balance.

Thus besides nutrient uptake, rare earths might also influence the metabolism of nutrients in plants. Enhanced nitrate reductase (nitratase) activity was noted in peanuts and tomatoes due to spraying of rare earth elements (Guo et al., 1988). Furthermore, after mixing seeds with rare earth nitrate reductase enhancements of 37 - 75 % were observed in leaves of winter wheat, while at the same time yield increased by 15.52 % (Yang and Zhang, 1986). After rare earth supply, the number of root nodules increased significantly and the activity of nitrogen-fixation was improved by 24 %. Consequently the absorption of N by legumes was enhanced significantly (Wu et al., 1984).

In addition to minerals, the content of amino acids could also be affected by rare earths. The application of 5 μmol/l lanthanum chloride increased glutamine and alanine contents by 66 % and 68 % respectively in cucumber (Cucumis sativus) (Chang, 2006). Significant increases in amino acid contents especially aspartic acid, serine and arginine were also observed in leaves of Jun Date, a Ziziphus species (Z. Jujuba Mill or Chinese Date), after rare earths were applied (Sun et al., 1998). In accordance with the dose-dependent effects of rare earths on plant growth, different concentrations may also influence their effects on nutrients uptake. Besides dose-dependency, these effects have also been shown to differ among the individual rare earth elements. While lanthanum on the one hand was able to increase N, P and K uptake in plants at low concentration, cerium, on the other hand, only increased N uptake leaving P and K uptake unaffected. Pr increased the absorption of N and P but decreased potassium uptake. While promoting the absorption of N, neodymium greatly inhibited phosphate and potassium absorption (Chang, 2006).

Effects of rare earths (La, Ce, Pr) on transport and accumulation of ions especially of Na and K have already been reviewed by Brown et al. (1990) and an increased uptake of Ce and Pr was reported in the presence of Na and K. Furthermore, rare earths were shown to disturb the transport of various monovalent ions particularly of K. These effects were ascribed to both influence on membrane stability and leakiness as well as to the strong resemblance to calcium. However, studies on the effects of rare earths on nutrient uptake and metabolism, as mentioned above, have arrived at different conclusions. These controversial results may, on the one hand, be attributed to different analytical methods employed, whereas on the other hand, they indicate the complexity of actions involved in the effects of rare earths on plant physiological processes such as nutrient uptake. Nevertheless, despite different results, it is quite obvious that rare earths have the ability to affect ionic fluxes into cells, thus their concentrations in different ways and to various extents. Changes in ionic fluxes as well as in the mineral composition may in turn affect several plant physiological processes. Yet it needs to be kept in mind that results from several Chinese studies are lacking detailed information.

11.4.4 Effects on Plant Enzymes

Changes in both activity and content of several plant enzymes have been observed in plants treated with rare earths and are therefore considered as possible explanations for the effects of rare earths on plants. Significant increases in the contents of glucose and fructose were reported in sugar beet leaves after foliar application of rare earths. Since another study which observed a decreased activity of the sucrose-transform enzyme of 34.2 - 84.7 % after sugar beet plants were sprayed with 0.1 to 500 μg/l of rare earths (Tian, 1988), (Bai and Chen, 1989), (Xiong et al., 2000), it was suggested that changes in enzyme activity account for increased sugar contents.

Stimulation of enzyme activity due to rare earth supply was also highly assumed by Zhimang et al. (2001) after noticing a good correlation between accumulation of rare earths and enzyme activity of glutamic oxaloacetic transaminase (GOT) with correlation coefficients of more than 0.922. In plants, the GOT activates the reaction α - ketoglutarate + L-aspartic acid $\rightarrow$ L-glutamate acid + oxaloacetic acid, which involves both the nitrogen and the amino acid metabolism and may changes organ functions (Xu et al., 1998). Additionally, since oxaloacetic acid contains carboxyl and hydroxyl groups (Fell et al., 1997), binding to them may faciliate rare earths uptake to the plant tops. Along with enhanced respiratory rate, Hong et al. (2000a) reported increased activities of superoxide dismutase, catalase, and peroxidase as well as decreased superoxide O_2^- in rice seeds treated with lanthanum nitrate. Thus, it was suggested that this may reduce the permeability of plasma membranes. Other studies demonstrated increased nitrate deoxidase in soybean leaves when rare earths were applied as seed dressing at the early period of seed setting or during flowering (Chief Office of Helongjiang Farm, 1985), (Chen, 1991), (Xiong et al., 2000).

11.4.5 Effects on Cytoplasmic Membranes and the Cytosceleton

Similarly to calcium, rare earths have also been shown to affect the stability and functionality of physiological membranes (Mikkelson, 1976), (Dong et al., 1993), (Qiao et al., 1993). In the review of Brown et al. (1990), which summarized the effects of rare earths on membrane stabilization, it was reported that lanthanum as well as related rare earths may restrict leakiness by altering membrane characteristics, particularly membrane fluidity.

Other studies also reported reduced penetration of electrolytes as well as increased membrane stability and integrity due to rare earth application to plants (Tian, 1990), (Shen and Yan, 2002). It was assumed that this may additionally explain enhanced cold resistance observed in treated plants. Furthermore, by decreasing the penetrability of cell membranes, lanthanum was shown to influence the proton release of cells (Qiao et al., 1993). Dong et al. (1993) suggested that rare earths might reduce penetration through cell membranes by forming stable complexes with big molecules such as phosphoglyceric acid. Similarly, Ni (1995), who observed that lanthanum chloride may decrease the permeability of plasma membranes, also attributed these stabilizing effects on the cell membrane to the interaction of rare earths with phospholipids or protein amino acid groups. It was further reported that rare earths may replace and compete with calcium for binding sites on proteins and thus affect the stability of cell membranes (Hu and Ye, 1996). However at high concentrations, rare earths could destroy the cell membrane stability hence increase cell permeability (Chang, 1991). Another study demonstrated that lanthanum and cerium supply could enhance the concentration of polar and nonpolar fat in cell membranes which was thought to prevent leaves from aging (Xing and Weng, 1991). In a similar manner, lanthanum increased contents of unsaturated fatty acids in wheat settings (Li et al., 1992b).

In addition, effects of rare earths on reactive oxygen species (ROS) as reported in Chapter 5 also lead to increased membrane stabilization as it is known that free radicals can destroy the structure of cell membranes. According to Wang et al. (2003b), rare earths may inhibit ROS-related lipid peroxidation and oxidation of membrane proteins by binding to hydroperoxides. In rice seedling roots, lanthanum chloride inhibited the electron transfer from NADH to oxygen in plasma membranes, reduced the production of active oxygen radicals and the formation of lipid peroxides (Zheng et al., 2000). Lanthanum could also efficiently overcome peroxidation of membrane lipids under osmotic stress and protect the membrane from injury of free radicals by reducing the contents of O_2^- and H_2O_2 (Zeng et al., 1999). Wile lanthanum increased the resistance of plants to osmotic stress, the normal function of membrane could be maintained temporally under these conditions.

It was furthermore demonstrated that rare earth elements may affect the activity of enzymes involved in antioxidant defense. Neodymium chloride was shown to increase the activity of superoxide dismutase (SOD) and peroxidase (POD), decrease malonyldialdehyde (MDA) contents, reduce membrane demagnification and enhance the ability of plants to remove O_2^- (An and Chen, 1994). Similar results were obtained for cerium (Wang et al., 1997a). Moreover, increased capability of cells to eliminate free radicals as well as controlled over-oxidation of fat in membranes were demonstrated in rapeseed treated with a solution of 3 μmol/l neodymium nitrate $Nd(NO_3)_3$ (Wei, 2000). Additionally, neodymium increased the activity of superoxide dismutase (SOD), peroxidase (POD) and catalase (CAT) while decreasing the penetration of cell membranes. In rape the activity of peroxidase (POD) was shown to increase gradually with increasing concentrations of lanthanum (Zeng et al., 2001).

Besides stabilizing plasma membranes, lanthanum was also reported to stabilize the cytoskeleton in root protoplasts of maize plants (Liu and Hasenstein, 2005). The cytoskeleton organization which is controlled by cellular events depends on calcium/calmodulin-related processes (Cry and Palevitz, 1995). Based upon this calcium dependency, Liu and Hasenstein (2005) hypothesized that after being taken up into plant cells lanthanum may affect growth via stabilization of the cytoskeleton. Both the rate of cell division as well as the extent of subsequent elongation, on which cell growth depends, are closely linked to microtubules. It was demonstrated that microtubules affect cell division by organizing the pre-prophase band and the formation of the cell plate. They also contribute to cell elongation by coordinating cellulose microfibrils (Giddings and Staehelin, 1991), (Wymer and Lloyd, 1996). Like microtubules, actin is involved in numerous fundamental cellular processes which include the regulation of cell-shape, cell-motility and transport. Liu and Hasenstein (2005) demonstrated that lanthanum may shift microtubule organization from random to parallel while causing the aggregation of microfilaments. Remarkable changes were also observed in the thickness of F-actin bundles which increased proportionally to the concentration of lanthanum, thus impairing the function of fine action filaments (Ketelaar and Emons, 2001). As fine filaments are associated with regions of active growth or cell repair, their aggregation, which occurred at a concentration of > 100 μmol/l lanthanum, is consistent with growth inhibition. Via actin reorganization, lanthanum may also affect the transport of ions and metabolites across the plasma membrane (Schwiebert et al., 1994). Nevertheless, studies conducted by Sun et al. (2003) on the short-term growth promoting effects of rare earths on pollen of tobacco and peach trees proposed an apoplastic mechanism. It was suggested that lanthanum may exert its promoting effects on pollen germination and pollen tube growth via endogenous apoplastic calmodulin. Accordingly, localization studies revealed that lanthanum diffused predominately through the apoplast of plant cells (Lehmann et al., 2000).

11.4.6 Effects on Resisting Environmental Stress

Furthermore, alleviation of environmental stress including draught and cold conditions, as well as acid rain or metal stress may also account for performance enhancing effects observed in plants after rare earth treatment.

Thus, significant growth enhancement was apparent when lanthanum was applied to barley under water limiting conditions (Maheswaran et al., 2001), (Meehan et al., 2001). While application of lanthanum to well-watered plants did not show any significant effects on the water use efficiency (WUE), significant increases in WUE were observed when water supply was deficient. Highest values were obtained at an application rate of 10 kg lanthanum per ha with increases of 21 %. At 5 kg/ha, lanthanum significantly promoted the tiller production by 33 %. Stomatal resistance (SR) also generally increased consistent with lanthanum application which indicates that transpiration was regulated and water conserved while photosynthesis was maintained. These physiological measurements, including WUE and SR observed in plants treated with lanthanum under drought conditions, implicated that lanthanum application enables the plants to maintain yield levels even under environmental stress. Furthermore, plants treated with lanthanum presented lower leaf water potential as well as higher osmotic adjustment whereas the relative water contents remained unchanged. It is known that high relative water contents when found with low leaf water potential may enhance crop yield (Maheswaran et al., 2001).

Field studies performed under relatively dry conditions confirmed previous results in barley with yield increases amounting up to 19 % (Reddy et al., 2001). Further experiments in which lanthanum was applied to both soil and leaves of a drought intolerant variety of wheat at rates of 500 g/ha also presented increased yield of 11 % compared to untreated control plants. Although in both wheat and barley a constant pressure was measured, differences were observed when comparing the water and osmotic potential of both plant species. Both parameters decreased in wheat, while an increase was noted for barley plants. However, the relative water content was affected in barley as well as in wheat which indicates that cell hydration was not out of order. Other investigations on the effect of rare earths on drought tolerance showed that in accordance with significant corn yield increases of 16.8 % the lowest water potential in corn leaves was measured when 1 kg seeds were mixed with 3 g rare earth nitrates (Wen et al., 1992). Furthermore, compared to the control, the electrical conductivity of wheat leaves treated with rare earth nitrates at 500 μg/l was shown to be reduced by 29.6 %. As to this reduction, it was assumed that rare earths might increase the ability of cell electrolyte leakage hence reducing damages to the cell membrane usually caused by drought (Yang and Zhang, 1986).

Rare earths might also induce their effects on water use efficiency by increasing the proline content in plants. Yu and Liu (1992) noticed higher proline concentrations in sugarcane after the plants were treated with rare earth elements. Additionally, decreased free-water contents as well as increased amounts of tied water were observed leading to a decreased free water/tied water ratio, which furthermore improves drought tolerance in sugarcane. Increased amounts of proline may therefore help plants to conserve water even during drought periods as proline exhibits a strong ability for hydration. To the contrary, Sun et al. (1998) observed that the proline content decreased due to higher temperature in Jun Date, a Ziziphus species (Z. Jujuba Mill or Chinese Date). It was supposed that the protein was damaged. Yet resistance to high temperatures was enhanced in Jun Date following rare earth application.

It has been reported earlier that growth enhancement and increase in dry weight of plants after low concentrations of rare earths were applied, are pronounced under extreme environmental conditions (Guo et al., 1988). Thus, in wheat plants grown under -8 °C, rare earths reduced the amount of electrolyte effusion and enhanced the concentration of proline in leaves and seedlings. This indicates that besides increasing drought resistance, rare earths could also enhance the ability of resisting cold in wheat seedlings. Increased proline contents were also demonstrated at low temperatures in Jun date (Sun et al., 1998) thus accounting for increased cold resistance. Furthermore, low temperature induced electrolyte leakage was also reported to be decreased in the roots of crotalaria (Crotalaria lium L.) after lanthanum and ytterbium application thus maintaining the integrity of the plasma membrane (Shen and Yan, 2002). In accordance with Shen and Yan (2002), Tian (1990) also ascribed increased resistance to low temperature adversities in plants observed after rare earth supply to their membrane stabilizing abilities which in turn prevents electrolyte losses.

In addition to increased resistance in plants to unfavorable conditions as cold and draught due to rare earth supplementation reported previously, rare earth application could also increase the resistance to acid rain (Yan et al., 1998), (Yan et al., 1999).

In a similar manner, alleviation of metal stress as reported by Zhou et al. (1998) and Zhou et al. (1999) may also attribute to growth enhancing effects of rare earths observed in agricultural plants.

According to Kataoka et al. (2002) different rare earth elements, with erbium and ytterbium being most effective, were able to stimulated the malate efflux in wheat roots. This is considered as the primary mechanism for aluminium tolerance in wheat since it is assumed that these organic anions chelate the aluminium cations in the rhizosphere to form nontoxic complexes. By activating malate efflux, rare earths may support plants to overcome aluminium toxicity. Trivalent cations have often been shown to be toxic to plants and especially aluminium toxicity has been found to be a major factor limiting crop production on acid soils (Foy et al., 1978), (Kochian, 1995). Even micromolar concentrations of aluminium are capable of rapidly inhibiting root growth if the root apex is directly exposed to aluminium ions. Toxic effects of the rare earth element lanthanum on the root elongation were described in corn, mungbean and wheat (Diatloff et al., 1995b), (Diatloff et al., 1995c). However, just as toxic effects exhibited by aluminium, inhibitory effects of erbium ions on root growth could be overcome by increasing concentrations of malate which probably forms nontoxic complexes with erbium (Kataoka et al., 2002). On this basis, it might be assumed that indirect effects such as reducing aluminium toxicity accounts for growth enhancing effects of rare earths on plants.

Additionally, it has been suggested that the antioxidant potential (Chapter 5) of rare earths might be responsible for their supporting effects on stress resistance in plants. Several studies reported enhanced antioxidant abilities of rare earths (Pang et al., 2002). Being oxidized to Ce^{4+}, Ce^{3+} may reduce O_2^- to H_2O_2; moreover, Ce^{4+} could oxidize O_2^- to O_2 while being reduced to Ce^{3+} (Wang et al., 1997a).

11.4.7 Effects on Phyto-Pathogenic Organisms

In pure culture studies, it was shown that some plant pathogenic bacteria as well as the activity of some enzymes related to pathogenesis could be influenced by rare earth elements (Tang et al., 1998c). This indicates that rare earths may protect plants from pathogenic microorganism. In accordance with that, a patent on the application of rare earth elements to prevent soft-rotten disease of cabbage was already granted in Japan, in 1980 (Kawasaki, 1980). However, the contrary was reported in older studies reviewed by Brown et al. (1990). Reports were ranging from increased disease incidence in coconut trees grown on soil containing high concentrations of rare earths (Velasco et al., 1979) to increased susceptibility of barley plants to fungus species, whereas Wang and Chen (1985) reported that the application of rare earth containing paste to the bark of rubber trees helped to control the incidence of brown bast disease. Further advances have been made over the years investigating the effects of rare earths in plant diseases as to possible anti-plant-disease abilities. It was assumed that rare earths can protect plants from diseases in two ways (Mu et al., 2003). On the one hand, they can control some phyto-pathogenes directly by reducing their virulence to the host plant, while on the other hand, rare earths may somehow increase plant resistance to diseases. Besides plant-pathogenic microorganism, low concentrations of $LaCl_3$ were found to restrict the hatching of Globodera rostochiensis, a parasitic nematode, which may damage the root of potatoes (Atkinson and Ballantyne, 1979). This was ascribed to the prevention of binding and action of molecules in the root exsudat of host potato plants which are necessary to stimulate hatching. At concentrations of 83 - 100 μmol/l, lanthanum was able to inhibit hatching by 50 %. The contrary was however reported in another study which demonstrated that lanthanum effectively stimulated hatching, whereas any apparent inhibition was only evident at high concentrations (Clarke and Hennessy, 1981).

11.4.8 Effects on Plant Photosynthesis

It has also been largely suggested that growth enhancing effects of rare earths observed in several crop species in China may be attributed to increased photosynthesis abilities.

Up to now, effects of rare earths on plant photosynthesis have exclusively been reported by Chinese scientists while publications on this are predominantly written in Chinese (Guo et al., 1988), (Xiong et al., 2000). However, mixed rare earth nitrates were widely reported to be beneficial for plant photosynthesis and effects were obvious in numerous plant species. Additionally, they seemed to be independent of the method of application. Thus, enhanced assimilation of $^{14}CO_2$ by 35.8 - 79.8 % was determined in sugar beet after foliage application of 0.01 - 0.1 % rare earth nitrates (Meng and Bai, 1989), (Xiong et al., 2000). Increases in both the chlorophyll content and the photosynthetic rate by 4.7 % and 31.8 %, respectively were observed after the seeds of sugar beets were mixed with rare earths (Xie and Chen, 1984). Several further studies also demonstrated increases in net photosynthetic rate of 11.5 - 31.2 % and increased photosynthesis intensity after the supplementation with rare earth elements to plants (Chief Office of Helongjiang Farm, 1985), (Chen, 1991), (Cui and Zhao, 1994), (Xiong et al., 2000). However, the photosynthetic rate cannot only be increased by mixtures of rare earths but also by single rare earth elements. Accordingly, sole application of cerium also increased chlorophyll contents and photosynthetic rate in spinach (Fashui et al., 2002). At concentrations of more than 15 mg/kg lanthanum, a decrease in chlorophyll contents as well as in chlorophyll a and b was observed in rape (Zeng et al., 2001). In tea plants, is was also shown that rare earth fertilizers could enhance photosynthesis (Wang et al., 2003a). Besides photosynthetic rate, rare earths could also influence the translocation of photosynthetic products. Increased translocation from the leaves to the roots of 5.6 - 8.2 % was reported by Bai and Deng (1995). According to that, a former study demonstrated that rare earths may increase the translocation of photosynthetic products by 17 - 149 % (Xiong, 1986).

However, consistent with growth enhancing effects in plants reported in Chinese literature, a dose-dependency could also be observed for the beneficial effects of rare earths on plant photosynthesis. Thus, below 50 mg/l La, Ce and Pr were able to increased photosynthesis rate in nitrogen-fixation algae, whereas inhibition occurred when their concentration exceeded 50 mg/l (Wang et al., 1985). The total chlorophyll contents of chlorophyll a and b could be improved after a rare earth containing solution of 200 - 800 mg/l was sprayed on pepper (He et al., 1998). Optimum concentrations were reported to be around 400 mg/l, whereas at very high concentrations, adverse effects of rare earths were observed. Further experiments reported concentrations of $CeCl_3$ to be in the range of 0.2 to 0.5 mg/l for optimum promotion of photosynthesis in wheat whereas 10 mg/l caused harmful effects (Chu et al., 1996). In addition, optimum concentrations of 1 - 5 mg/kg and 15 mg/l were determined for cucumber and sunflowers, respectively. In Jun date only chlorophyll a contents were increased after rare earth supply while chlorophyll b was unaffected (Sun et al., 1998). The principle of their improvements on plant photosynthesis is probably related to enhanced enzyme activity, chloroplast development as well as increased chlorophyll contents.

In tobacco seedlings, an accelerated photosynthetic light reaction as well as increased chlorophyll contents were observed after the application of lanthanum chloride (Chen et al., 2001). At low concentrations of 5 - 20 mg/l, lanthanum promoted both the Hill reaction ($2\ H_2O + 2\ A + \text{(light, chloroplasts)} \rightarrow 2\ AH_2 + O_2$, where A is the electron acceptor) and the Mg^{2+}-ATPase and, furthermore, stimulated the rate of photophosphorylation in chloroplasts. Yet inverse effects occurred at high concentrations. Accordingly, lanthanum could also increase the Mg^{2+}-ATPase and thus accelerate the Hill reaction in wheat (Sheng and Dai, 1994). In rapeseed, $Nd(NO_3)_3$ increased the activity of Mg^{2+}-ATPase at 20 mg/l by 4.4 % and at 100 mg/l by 6.4 % (Wei et al., 1999). Enhanced activities of both Mg^{2+}-ATPase and Ca^{2+}-ATPase on the chloroplast membrane were observed by Pan et al. (1998) after chloroplasts were treated with lanthanum chloride. Consistent with that, they found that lanthanum chloride could accelerate phosphorylation by activating the coupled reaction taking place in chloroplasts. Effects of rare earths on the chlorophyll contents have also been reported in soybeans (Chang, 2006). Especially at concentrations ranging from 5 to 10 μg/g, rare earths increased the contents of photosynthetic pigments of soybean chloroplasts in an aquaculture experiment. Experiments conducted by Fashui et al. (2002) reported higher contents of chloroplasts and chlorophyll in plants previously treated with cerium. It was therefore suggested that cerium could enter the chloroplast hence binding easily to chlorophyll. Furthermore, cerium might be able to replace magnesium in order to form cerium-chlorophyll. Although nitrogen is not one of the favored donor atoms (Chapter 4), coordination of Ce^{3+} to nitrogen of porphyrin rings was demonstrated using x-ray absorption fine structure methods.

Accelerated synthesis of chlorophyll a and protein following $CeCl_3$ supplementation was also reported in spirulina platensis, an algae species (Chu et al., 1996). Rare earth application has furthermore shown to increase the number of chloroplasts as well as the density of canaliculus in wheat plants (Gao and Xia, 1988). Similar to Chu et al. (1996), increased chlorophyll a and b contents were observed in wheat leaves after the plants were treated with individual rare earth elements and a mixture of light rare earths (Jie and Yu, 1985). In rapeseed, $CeCl_3$ and $Nd(NO_3)_3$ increased chlorophyll contents by 9 - 40 % (Chu, 1988) whereas, in wheat enhancements of 29.6 % (Jie and Yu, 1985), in soybean of 8 % (Chief Office of Helongjiang Farm, 1985), (Chen, 1991) and in corn of 15.2 % (Cui and Zhao, 1994) were reported after the application of mixed rare earth nitrates.

In conclusion, promoting effects on the photosynthetic rate and intensity as well as on the chlorophyll contents and activity of photosynthetic enzymes seem to be reasonable explanations for increased crop yield and quality reported in several plant species in China due to rare earth application.

11.4.9 Effects on Hormonal Balance

As it is reported that rare earths may affect hormonal binding by either direct or indirect interactions with their receptors (Enyeart et al., 2002) (Chapter 5), interactions with hormones have been proposed as one of the most important means by which rare earths may influence plant physiological processes such as plant growth (Brown et al., 1990). Additionally, it was reported that rare earths may function as potent hormone effectors due to membrane stabilizing actions.

As to plants, lanthanum was found to increase the binding of the auxin α-naphthaleneacetic acid (14C-NAA), a plant hormone, to pelletable particulates from corn (Zea mays) coleoptiles (Poovaiah and Leopold, 1976). It was suggested that alterations in the attachment of the hormone to binding sites in the cell account for this effect (Taiz and Zeiger, 1998). In addition, after the treatment with 7.5 mg/l of $La(NO_3)_3$, increased contents of indole acetic acid (IAA) could be determined in wheat seedlings (Sheng and Zhang, 1994). It is known that indole-3-acetic acid (IAA), which constitutes the main auxin found in plants, controls many important physiological processes such as cell enlargement and division, tissue differentiation as well as light responses. Another study demonstrated contents of tryptophan, which may be used for the synthesis of IAA (Leveau and Lindow, 2005), to be increased in the coleoptile of corn due to rare earth application. Furthermore, rare earths could decrease the enzyme activity for IAA decomposition thereby promoting

IAA synthesis, while lanthanum chloride was reported to enhance IAA uptake and translocation (Migliaccio and Galston, 1989), (Allan and Rubery, 1991). In line with yield increases, Kuang and Ma (1998a) noticed a decrease in indole acetic acid oxidase in sugar cane (Saccharum officinarum L.) which was previously treated with 300 ppm REE/l water.

Yet, further enzymes have also been shown to be affected by rare earths. Thus, another study described significant promotion of α-amylase induction by gibberellic acid (GA_3) due to the application of a $NdCl_3$ solution at 6 μmol/l (An and Chen, 1994). Accordingly, accelerated formation of α-amylase induced by GA_3 in the aleurone layer of wheat seed was observed after rare earths were supplied (Liu and Liu, 1985). Decreased activities of peroxidase, amylase as well as their isoenzymes were observed in lanthanum and cerium treated wheat seedlings thus promoting their growth (Hou et al., 1997). In contrast to that, an increased amylase activity was reported together with yield enhancement in sugar cane (Kuang and Ma, 1998a). Nevertheless, Lu et al. (1997) showed that low concentrations of Eu (0.001 - 1.0 mg/l) may fulfil similar functions as plant hormones. It was highly assumed that the same mechanism accounts for this as described for the regulation of protein metabolism by calcium. Furthermore, membrane-altering solutes such as lanthanum-containing solutions were shown to affect the binding as well as effectiveness of several plant growth regulators such as ethephon (2-chloroethanephosphonic acid), abscissic acid (ABA) and 1-Triacontanol (Brown et al., 1990).

11.5 Conclusions, Perspectives and Research Needs

Compared to the multitude of investigations conducted on the influence of rare earths on plants in China, only a few studies have been carried out in Western countries. Those performed so far in Australia, Germany, the United States and some other countries have not been able to present conclusive results and thus could not fully confirm the positive effects of rare earths on plant growth, yield and quality as reported in China.

Different results may on the one hand be attributed to the fact that effects of rare earths on plants highly depend on a great variety of factors such as soil properties (pH, organic matter including LMWOAs, cation exchange capacity, clay contents), rare earth contents in soil, application methods, rates and timing as well as climatic and plant conditions (species, growth stage) which was already assumed earlier by Zhang and Taylor (1988). Yet on the other hand, it may simply indicate the complexity of the whole topic as dual effects of rare earths have not only been demonstrated for plant growth but also in view of their influence on bacteria, tumor growth and as to other biochemical features (Chapter 5).

However, regarding both the apparently large-scale use of rare earth fertilizers in China and the uncertainty about the true nature of the beneficial effects, there is still a need for further well-documented and carefully conducted experiments on these elements. Details concerning experimental methods and rigorous statistical treatment of data is highly recommended in order to compare individual results. Great attention should also be paid on the use of reliable analytical methods as well as on accurate removal of aerosol contamination from plant samples before rare earth concentrations are determined. In addition, detailed information on the impact of rare earths on plants might open up agricultural use of rare earths to other countries beyond China. However, up to now there are many questions left unanswered regarding both their effects on growth and the mode of action behind as well as their physiological influence on plants in general.

Although beneficial effects of rare earths on plants have been widely reported in China over the last 30 years, experimental trials performed so far in other countries are too little in order to systematically evaluate the effects of rare earths on plant growth. Further systematic research on the agronomic effects of rare earths is therefore necessary to estimate the possibility of applying rare earths to agriculture in other countries.

In accordance with the hormesis effect which could be applied to rare earths in several aspects, it was reported that beneficial effects on plants generally occurred at low application levels whereas high doses often caused adverse and sometimes even toxic effects. Thus, the amount of rare earths not always corresponds to their actions. Various investigations have been performed on the dose-effect relationship predominantly in China. However, since the concentrations required for positive effects are quite low, the tolerance between beneficial and adverse effects is very small. Furthermore, even for very low concentrations, inconsistent results were obtained in different plant species, which may probably be ascribed to variations in susceptibility of individual plants. Thus Diatloff et al. (1995d) observed stimulating effects of cerium on root growth of corn at a concentration of 0.63 μmol/l whereas even lower concentrations of 0.19 μmol/l already reduced the dry weight of root in mungbean. The relationship between applied doses of rare earths and their effects on plants should therefore be further investigated. Detailed information on this in turn will allow the determination of optimum and toxic concentrations, while in addition, a clear understanding between the amount of rare earths applied and that available to plants for physiological effects could further help to improve their agronomic application.

Moreover, for effective application of rare earths in agriculture, effects of individual rare earth elements compared to each other as well as to their mixture need to be studied, too. In the majority of Chinese studies reporting beneficial effects on plants mixed rare earths were applied though similar results could also be obtained using single rare earths such as lanthanum and cerium (Guo and Denkui, 1998), (Fashui et al., 2002), (Chen et al., 2001), (Reddy et al., 2001), (Sun et al., 2003). Even though belonging to a chemical homologous group, it is considered unlikely that each of the rare earth series exhibits the same effects on plants. Different physiological effects of single rare earth elements such as uptake mechanism for lanthanum and cerium (Hu and Zhu, 1994) have already been reported. Furthermore differences in yield responses (Savostin and Terner, 1937), (Zhu and Zhang, 1986) (Diatloff et al., 1995c), (Diatloff et al., 1995d) but also in nutrient specific uptake (Hu and Zhu, 1994) have been demonstrated among the group of rare earth elements.

Until now, information on the effects of rare earths on plant physiological actions such as nutrient uptake as well as on biochemical processes is still very rare. Besides advancing studies on bioavailability and uptake of rare earths to/by plants, that information could also help understanding their mode of action. Yet though several possible mechanisms (effects on physiological functions of calcium, membrane and cytosceleton stabilization, effects on nutrient uptake and metabolism as well as on photosynthesis, increased resistance to environmental stress, hormonal interaction) have been proposed in order to explain the effects of rare earths observed in plants, these effects are not completely understood and thus further research is needed. Additionally it was suggested that rare earths might be essential trace elements. However, to this day there is no evidence that rare earths might be essential to either plants or animals.

Notwithstanding, besides beneficial effects on plant growth, positive effects have also been reported on animals whose diets were supplemented with rare earths (Chapter 12), whereas there are hardly any reports on the effects of rare earths on human consuming rare earth containing diets. Hence before allowing the agricultural application of rare earths in other countries than China, a thorough investigation on their effects on all parts of the food chain as well as on the environment need to be conducted. Currently available literature provides only little information on the environmental impact of rare earths including soil, plants, aquatic flora and fauna as shown in Chapter 7. Thus, environmental behavior of rare earths in both soil and water and especially their effects on soil microbial flora and nitrification as well as on aquatic plants and animals has to be investigated more efficiently.

Finally, further research should also be directed at establishing a more comprehensive data base on rare earth contents in untreated and treated plants and soils of various sites. Since this may provide additional information on the distribution and accumulation behavior of rare earths. It may also serve as reference material, thus helping to assess the environmental load due to rare earth application. As to their effects on plants, research needs are summarized and listed beneath.

- Plant responses to the application of rare earths in various countries
- Relationship between application dose and effect
- Determination of optimum concentrations
- Comparison between effects of rare earth mixtures with those of individual rare earth elements
- Physiological effects of rare earths on plants
- Effects of rare earths on the cell, sub-cell and molecular biochemistry of plants
- Identification of possible explanations for the mode of action
- Environmental behavior of rare earths and their impact on soil, ground water, aquatic flora and fauna, animals and humans

CHAPTER 12

THE APPLICATION OF RARE EARTH ELEMENTS TO ANIMAL HUSBANDRY

WITHIN the scope of researching plant growth enhancing effects of rare earths in China, it was discovered that rare earth elements may also enhance the performance of farming animals. Consequently, rare earth containing feed additives were developed and applied to animal husbandry. Today, rare earths are widely used in terms of fertilizers and feed additives in Chinese agriculture. With respect to animal production, it has been reported that low concentrated dietary supplementation of rare earth elements may improve both body weight gain and feed conversion rate in nearly all categories of farming animals, including pigs, cattle, sheep and chickens. Moreover, increases in milk and egg production due to rare earth application to dairy cows and laying hens were observed, too. However, these effects remained completely unnoticed in Western countries for a long time. This may be ascribed to an insufficient flow of information from the far East to the Western world, hence a lack of knowledge. But another reason might be that there was no need for further growth promoting feed additives, since in-feed antibiotics were largely used for that purpose. Yet, the situation has changed. In the course of heavy debates on the safety of both vegetable and animal products, antibiotic performance enhancers were urged to be excluded from the agricultural sector.

Firstly banned in Sweden, in 1986, then in Switzerland, in 1999, and in Denmark in 2002, all in-feed antibiotics have finally been prohibited throughout the European Union as of 2006 by the European court of justice by invoking the precaution principle [EU directive No 183/2003 article 11 paragraph 2]. However, antibiotic performance enhancers were proven effective for more than 50 years and the complete ban on routine inclusion of antibiotics in creep and starter feeds will seriously affect post-weaning health and performance, especially in pigs. Therefore, the prohibition of antibacterial feed additives will consequently lead to a reduction in both growth and feed conversion of farming animals, as was already demonstrated in Sweden and Switzerland. Yet, along with augmentations of the world population, increases in feed production by at least 2 % per year are necessary to assure adequate feed supply, while keeping environmental loads as low as possible. Thus, efficient use of available resources is required, which, among other things, may be achieved with feed additives. Thus, legally allowed, safe and inexpensive feed additives, which are capable of enhancing animal performance, will be needed in order to maintain the state of health of farming animals and preserve their desired performance and to guarantee efficient use of resources.

It will be argued that rare earth elements might be appropriate feed additives since they exhibit performance enhancing effects, as reported in China. However, the manner of Chinese keeping, housing and feeding conditions can hardly be compared to that prevailing in European countries, as this is generally more intensive by being based on high performance breeds and strongly optimized housing, keeping and feeding conditions. It is also known that effects on the performance of animals of economic use are more pronounced when feed additives are administered at sub-optimum environmental conditions, low states of health, low nutritional value of the diet and low performance, as reported for feed additives in general. Thus, the accreditation of rare earth-based feed additives will only be accorded in Europe if it is possible to achieve effective improvements, similar to those in China, in animal growth and feed conversion under Western conditions. So far several investigations on the performance enhancing effects of rare earths on various animal species, including pigs, chickens, quails, calves and fish, have been conducted in Western countries, predominantly in Germany and Switzerland. Although, especially in pigs and poultry, application of rare earths to animal diets has shown performance enhancing effects in many studies, there is still an uncertainty among scientists as to its efficacy and safety. Thus the utilization of rare earths as feed additive to animal husbandry is still controversial. Although several proposals have been made, which will be treated in Section 12.3, it is not clear how these effects might be achieved.

Therefore, it is the aim of this chapter to look at the complexity of the issue, first by reviewing the information drawn from Chinese studies that treated the growth enhancing effects of rare earths on animals and reported on the current application of rare earths to animal husbandry (Section 12.1). Next, an overview of currently available Western studies on the effectiveness of rare earths will be presented on the Western adoption of rare earth methods in animal production (Section 12.2). Further information will deal with animal health and the safety of animal products. Thus a full discussion of the issue will only be possible if claims of achievements are contrasted with the needs for health and safety, because only then the European Union will consider the registration of rare earths as feed additives (Chapter 13). At this point it is important to mention that a temporary permission for the use of rare earth-containing feed additives in pigs has already been granted in Switzerland, in 2003. This is highly remarkable as Switzerland is among those countries that first prohibited the use of antibiotics in animal breeding.

12.1 China

12.1.1 Rare Earth Elements Used as Feed Additives

A considerable field of research on the application of rare earths to agriculture has been developed in China over the past thirty years, which has been hardly noticed in the West (Schnug, 2003). Shortly after growth promoting effects of rare earths on plants were observed, Chinese scientists found out that rare earths may also enhance performance of several animals. Test reports on applying rare earths to animals in China are shown in Table 12.1. In present-day China, rare earths are not only widely used as fertilizers as was described in Chapter 11.1 but have also been successfully applied as feed additives to livestock husbandry and aquaculture (Xiong, 1995), (Chang et al., 1998).

Chicken	
increased body weight gain	15 - 18 %
improved egg and laying rate and size	16 %
Sheep and Goats	
increased average output of fine wool	0.25 kg
increased daily body weight gain in short period in sheep	40 %
Cattle, Horses and Pigs	
increased body weight gain	20 - 25 %
increased milk output in cattle	20 %
Fish and Prawns	
increased body weight	20 %

Table 12.1: Test reports on applying rare earths to animals, Baotou Rare Earth Feed Additive Co. Ltd. in China (Rosewell, 1995).

Growth performance enhancing effects due to dietary supplementation of rare earths at low concentrations are described for nearly all categories of farming animals, including beef cattle, sheep, pigs, rabbits, ducks, chickens, shrimps and fish (Shen et al., 1991), (Rosewell, 1995), (Duan et al., 1998), (Tang et al., 1998d), (Liu, 2005), (Yang and Chen, 2000), (Yang et al., 2005). Improvements in feed conversion rates were also observed in several animals. Moreover, it was reported that rare earths may also increase milk production in dairy cows and egg production in laying hens. Additionally, improved fertility in hens was also described (Wu et al., 1994), at the same time Hu et al. (1999) and Liu et al. (2003) even reported improvements in meat quality. The same was observed in fish (Xia and He, 1997). Regarding aquaculture, increases in output and survival rate of several fish species including grass carp, blunt-snoup carp, black carp, common carp, silver carp and prawn were observed (Tang et al., 1998d), (Tang et al., 1997b). Besides growth enhancement, improved egg hatching and naupliar metamorphosis were reported in giant tiger prawns (Xin et al., 1997).

Hence, application of rare earths to animal diets was reported in terms of increasing body weight by up to 29 % along with improved feed conversion of 24 % in several animal species (Wan et al., 1998). Increases in body weight gain of up to 22.5 % were reported for pigs fed a rare earth-containing diet, whereas at the same time, feed conversion decreased by 4.3 - 18.9 % (Shen et al., 1991), (Li et al., 1992a), (Cheng et al., 1994), (Zhu et al., 1994), (He and Xia, 1998a). Improvements in laying performance of laying hens were reported to be in the range of 8 % (Shen et al., 1991). Daily body weight increases of 8 - 10 % were described in pigs and increased body weight as well as improved quality of wool was additionally detected in sheep. In chicken, rare earth supplemented diets improved survival rate and body weight by 4.5 - 10 % and 4 - 8 %, respectively (Guo et al., 1993). Also, in fish, body weight gain improved by 29.6 % in trout and by 16 % in carps after rare earths were supplemented to their feed (Tang et al., 1997b). Similarly, hatching rates of carps raised by up to 27.5 % after rare earth application (Yang and Chen, 2002), while embryo development was also shown to improve significantly (Shao et al., 1998). Animal species treated with rare earths and the results of application are presented in Table 12.2.

Animal species	Physiological-biochemical indices and results of application
Pigs	6 - 29 % BWG increased feed utilization efficiency of 10 %
Sheep	increased wool clip of 8 % 6 - 13 % increased BWG
Table Poultry	increased survival rate of 3 - 4 % stable length and density improved increased feed returns 4 - 12 %
Egg-laying Poultry	increased survival rate of 5 - 10 % increased laying rate of 8 %
Duck	6 - 10 % increased BWG increased laying rate of 9 %
Fish (Grass Carp, Silver Carp, Carp)	3.4 - 3.7 % increased BWG increased survival rate of 5 %
Long Hair Rabbit	increased BWG 7 - 10 % increased hair yield of 7 - 9 %
Domestic Silkworm	increased digestible protein increased cocoon production per 10000 larvae of 9 % increased total cocoon weight of 3 % grade of raw silk raised

Table 12.2: Effects of rare earth elements on livestock, poultry and fishery in China (Xiong, 1995).

Rare earth products commercially available on the Chinese market mainly contain a mixture of rare earths (Chen and Xiong, 1994), (He and Xia, 2001). Both inorganic (nitrate, chloride etc.) and organic (vitamin C, citrate etc.) rare earth compounds are used as feed additives in animal production (Song et al., 2005). It has been reported that best results may be obtained using organic rare earth compounds (Chen, 1997), (Wan et al., 1997). Among organic compounds are several rare earth salts, which may be applied to animals. Earlier products, such as *SVT - 2*, mainly consist of ascorbic acid rare earths and contain 30 - 32 % rare earth oxides. *SVT - 2*, which is recommended to be applied to poultry (broiler and laying hens), pigs, rabbits and silkworm at 100 g per ton feed, may still be purchased from the Rare Earth Center for Agriculture Use in China (Fleckenstein et al., 2004). However, as ascorbic acid is quite expensive other products, such as the types *RCT - 3* and *RCT - 4*, have been developed including organic compounds. These products are presently used in Chinese animal husbandry and aquaculture (Xiong, 1995).

Rare earths may either be mixed to the feed as, e.g., mineral additives or, after being dissolved, applied to the drinking water of animals (Chang et al., 1998), (Rambeck et al., 2004), (Rosewell, 1995). Optimum concentrations have been shown to differ among animal species and type of rare earth compound, whereas performance enhancing effects were reported to occur at a dosage of 100 - 200 mg per kg feed (Böhme et al., 2002a). Yet earlier, other authors recommended lower rare earth concentrations of 5 - 40 ppm in feeds in order to enhance animal growth (Guo et al., 1993). Since rare earth concentrations may vary within different rare earth compounds, information given in Chinese feeding trials often refer to the amount of rare earth oxides. In the majority of experiments performed, different mixtures of rare earths were used, though there are some studies in which single rare earth elements were applied to animals to verify whether performance enhancing effects may also be produced by individual rare earth elements.

However, it needs to be mentioned that detailed information on both statistical significance and exact compositions of these mixtures is often lacking, while additionally, chemical compounds, organic or inorganic in nature, used in these studies may differ as to concentration and composition of individual rare earth elements. Furthermore, often only two concentration levels were compared to each other in order to determine optimum concentrations rather than critically studying the dose-effects of rare earths. Thus, these inconsistencies make a comparison of results obtained in different studies hardly possible. Nevertheless, Chinese studies on the performance enhancing effects of dietary rare earth supplementation on animals of economic importance will be presented according to animal species.

12.1.1.1 Pigs

Effects of rare earth supplementation to the diets of pigs and poultry are found to be described the most in Chinese literature. It has been reported that performance enhancing effects occur when rare earths are supplemented at a dosage of 100 - 200 mg per kg feed, while improvements observed were up to 30 % (Böhme et al., 2002a).

According to Chen (1997) and Wan et al. (1997), good performance enhancing effects were obtained using compounds in which rare earths are bound to organic acids, as can be seen in Tables 12.3, 12.4 and 12.5. Although better results were claimed for rare earth organic compounds by Wan et al. (1997), with daily body weight increases of 32 % and improved feed conversion rates of 24 %, a comparison between organic and inorganic compounds in this trial is not possible, as not only the compound but also the concentration was different. Yet comparisons as to the dose-effect relation are often not only hardly possible within one feeding trial but also between different Chinese feeding trials.

	control	RE chloride 80 mg/kg	RE chloride 160 mg/kg	RE organic acids 700 mg/kg
Effects of rare earths on body weight gain and feed conversion rate				
initial BW (kg)	46	41	49	44
final BW (kg)	69	66	72	73
BWG (g/day)	704	769	713	929
FCR (kg/kg)	2.63	2.41	2.61	2.01
Improvements compared to the control				
BWG (%)		+ 9	+ 1	+ 32
FCR (%)		- 8	- 1	- 24

Table 12.3: Effects of dietary supplementation of rare earths on body weight (BW in kg), daily body weight gain (BWG in g per day) and feed conversion rate (FCR in kg/kg) of pigs; there were no data on significance (Wan et al., 1997).

Thus, Chen (1997), for example, presented similar results as Wan et al. (1997) in another trial in which only 100 mg/kg rare earth citrate was supplemented to the feed of pigs growing from

	control	RE ascorbate 100 mg/kg	RE citrate 130 mg/kg
Effects of rare earths on body weight gain and feed conversion rate			
initial BW (kg)	50	51	51
final BW (kg)	75	76	81
BWG (g/day)	710	766	890
FCR (kg/kg)	4.23	3.91	3.44
Improvements compared to the control			
BWG (%)		+ 8	+ 25
FCR (%)		- 8	- 19

Table 12.4: Effects of dietary supplementation of rare earths on body weight (BW in kg), daily body weight gain (BWG in g per day) and feed conversion rate (FCR in kg/kg) of pigs first trial; there were no data on significance (Chen, 1997).

	control	RE ascorbate 100 mg/kg	RE citrate 130 mg/kg
Effects of rare earths on body weight gain and feed conversion rate			
initial BW (kg)	32	33	32
final BW (kg)	97	112	96
BWG (g/day)	336	360	346
FCR (kg/kg)	5.12	4.53	5.42
Improvements compared to the control			
BWG (%)		+ 7	+ 3
FCR (%)		- 12	+ 6

Table 12.5: Effects of dietary supplementation of rare earths on body weight (BW in kg), daily body weight gain (BWG in g per day) and feed conversion rate (FCR in kg/kg) of pigs, second trial; there were no data on significance (Chen, 1997).

50 kg to 75 kg. During this experiment increases in daily body weight gain of up to 25 % could be observed, whereas, increases of 8 % were reported when rare earth ascorbate was used instead at the same concentration. Both compounds also improved feed conversion by 19 % and 8 %, respectively, while better results were achieved using rare earth citrates.

Another trial performed over a longer period also showed that both rare earth ascorbate and citrate compounds were able to increase daily body weight gain by 7 % and 3 %, respectively, in pigs gaining weight from 32 to 112 kg (Chen, 1997). However, this time, rare earth ascorbate presented better results by additionally decreasing feed conversion by 12 %, whereas, an increase of 6 % was observed in rare earth citrate-treated pigs. Yet, no data on significance was available for any of the three trials described previously.

In accordance with Chen (1997), growth promoting effects were also observed in growing-finishing pigs presenting an initial average body weight of 31.5 kg. Supplementation of a rare earth mix at 75 mg/kg per kg feed for thirty days increased average body weight gain significantly by 13.0 % ($p < 0.05$) compared to the control, while feed conversion also improved significantly by 6.10 % (He and Xia, 1998b). At the same concentration (75 mg/kg feed), rare earth oxides were reported to enhance body weight gain significantly by 22.9 %, 20.3 % and 13.0 %, respectively, in rearing, growing and fattening crossbred pigs (Duroc x Landrace x Large White) (He and Xia, 2000). Furthermore, highly significant increases in body weight gain of 13.3 % ($p < 0.01$) were observed in 40 - 50 day old growing pigs fed a diet supplemented with organic rare earth compounds (*RCT - 3*) at 0.01 % for 180 days (Fan et al., 1997). Likewise, the application of *RCT - 3* at 200 mg/kg for 123 days to finishing pigs could improve body weight gain by 24.1 % ($p < 0.01$) and feed consumption by 16.4 % ($p < 0.01$) without influencing meat quality (Chen and Xiong, 1994). Performance enhancing effects of organic rare earth compounds *RCT - 3* containing approximately 33 % of rare earth oxides were however not only presented in finishing but also in suckling and weaned pigs.

Feeding trials on weaned crossbred pigs, growing pigs and pigs with an average body weight of 9.78 kg, 12.55 kg and 17.28 kg, respectively, were conducted and demonstrated that the addition of rare earth compounds at 75 mg/kg per kg feed could significantly improve both average daily body weight gain and feed conversion (He and Xia, 1998b), (He and Xia, 2001). Rare earths fed over a period of 15 days increased daily body weight gain of weaned crossbred pigs (9.78 kg) by 22.9 % ($p < 0.05$), while improving feed conversion by 7.89 %. Similar effects were also observed in growing pigs (12.55 kg) presenting improved daily body weight gain and feed conversion of 20.27 % ($p < 0.05$) and 8.20 %, respectively, after a 24 days lasting feeding trial. Slightly lower performance enhancing effects were observed in pigs with an initial average body weight of 17.28 kg, which were also fed a rare earth supplemented diet for 24 days. Yet, increases in daily body weight gain and improvements in feed conversion were still 18.07 % ($p < 0.05$) and 4.79 %, respectively. In contrast to that, rare earths were used at higher concentrations in another feeding experiment performed on weaned piglets (Hu et al., 1999). During this trial, a mixture of rare earth elements (referring to oxides, the composition was as follows 22.7 % La_2O_3, 10.42 % Ce_2O_3, 3.0 % Pr_2O_3, 2.14 % Nd_2O_3, 0.58 % Sm_2O_3, 0.09 % Eu_2O_3, 0.11 % Gd_2O_3) was applied to 35-day-old weaned pigs (8 kg) for 33 days. In line with several Chinese publications, this one did neither contain any information on the composition of rare earths applied including the anion to which rare earths were attached. However, body weight gain was increased at 200 mg by 3.97 % (n.s.) and significant increases of 8.93 % ($p < 0.05$) and highly significant increases of 32.34 % ($p < 0.01$) were reported for animals fed a 400 mg and 600 mg supplemented diet, respectively. Feed conversion also decreased by 1.66 % (n.s.), 4.65 % ($p < 0.05$) and 11.29 % ($p < 0.01$), respectively, in 200 mg, 400 mg and 600 mg treated animals. Based upon these results, 600 mg/kg was considered as optimum concentration. Effects were thought to be ascribed to an improvement in digestibility of nutrients as, along with growth performance enhancing effects, apparent digestibility of energy, crude protein as well as total essential and nonessential amino acids was also improved significantly due to rare earth supplementation at 400 mg and 600 mg. Results from this trial are summarized in Table 12.6.

In another study designed to investigate the effects of rare earth feed additives on growth performance of piglets, a liquid product of mixed rare earth elements was used in 20 day old piglets for 40 days. It was shown that body weight gain increased by 7 - 8.5 % and feed conversion improved significantly by 16.8 - 18.4 % over the whole experimental period. Specified data on the composition of this rare earth compound was however missing (Ou et al., 2000). Further studies reported that dietary supplementation of different rare earth complexes (*STV-2*: RE vitamin C, *CL-1*: RE nitrates and *CL-2*: RE chlorides) to trihybrid pigs (Duroc, Landrace pig, Shaziling) could increase daily body weight gain by 7 - 21 % (11.3 % on the average), whereas, average feed conversion decreased by 6.8 %, as can be seen in Table 12.7 (Ming et al., 1995). The feeding period could therefore be shortened by 4 - 27 days, as the final weight of 90 kg was achieved earlier in rare earth supplemented animals.

	RE 200 mg/kg	RE 400 mg/kg	RE 600 mg/kg
Improvements of performance parameters compared to the control			
BWG (%)	+ 3.97 ($p > 0.05$)	+ 8.93 ($p < 0.05$)	+ 32.34 ($p<0.01$)
FCR (%)	- 1.66 ($p > 0.05$)	- 4.65 ($p < 0.05$)	- 11.29 ($p<0.01$)
Improvements of Digestibility of nutrients compared to the control			
Energy (%)	-	+ 2.31 ($p < 0.05$)	+ 3.98 ($p<0.01$)
CP (%)	-	+ 4.51 ($p < 0.05$)	+ 6.86 ($p<0.05$)
essential AA (%)	-	+ 3.06 ($p < 0.01$)	+ 3.06 ($p<0.01$)
non essential AA (%)	-	+ 3.42 ($p < 0.05$)	+ 3.07 ($p<0.05$)
total AA (%)	-	+ 2.04 ($p < 0.05$)	+ 4.24 ($p<0.01$)

Table 12.6: Improvements of daily body weight gain (BWG %), feed conversion rate (FCR %) and digestibility of nutrients (CP: crude protein, AA: amino acids) of growing pigs due to dietary supplementation of rare earths (RE) (Hu et al., 1999).

	control	RE STV-2	RE CL-1	RE CL-2
Effects of rare earths on body weight gain and feed conversion rate				
BWG (g/day)	484	590	541	543
FCR (kg/kg)	4.30	3.84	4.13	3.98
Feeding period	148	121	128	128
Improvements compared to the control				
BWG (%)		+ 21.3	+ 11.8	+ 12.2
FCR (%)		+ 10.7	+ 4	+ 7.4
Feeding period (d)		- 27	- 20	- 20

Table 12.7: Effects of dietary supplementation of rare earths on performance, daily body weight gain (BWG in g per day) and feed conversion rate (FCR in kg/kg) of pigs; there was no significant difference among the experimental groups, CL-1: RE Nitrates, CL-2: RE Chlorides, STV-2: RE vitamin C (Ming et al., 1995).

However, not only the mixtures, but also individual rare earth elements were able to enhance growth performance in piglets. Xu et al. (1999), Wang and Xu (2003) and Liu (2005) demonstrated that lanthanum could enhance growth performance in pigs to a similar extent as rare earth mixtures. In crossbred growing pigs fed a normal diet supplemented with 100 mg/kg lanthanum for 30 days, it was demonstrated that average daily body weight increased significantly by 13.26 % ($p < 0.05$) along with average daily feed intake, which improved by 5.43 % ($p < 0.05$). Furthermore, feed conversion also improved significantly by 8.5 % ($p < 0.05$) (Xu et al., 1999). Analysis of blood samples revealed significantly increased serum levels of growth hormone, as well as of both thyroid hormones (T_3 by 36.70 % and T_4 by 28.96 %). Based on these results, it was suggested that lanthanum may stimulate the synthesis and secretion of several hormones, such as growth hormone and thyroid hormones. In accordance with Xu et al. (1999), Wang and Xu (2003) also observed significantly elevated serum levels of growth hormone in growing pigs along with significant increased average body weight gain of 13.06 % and improved feed conversion rate of 6.53 % ($p < 0.05$) due to the application of lanthanum at 100 mg/kg. As can be seen in Table 12.8, similar results were achieved after the addition of lanthanum chloride at 100 mg/kg to a normal diet based on corn and soy meal, which was fed to barrows (Liu, 2005).

	control	$LaCl_3$ 100 mg/kg
n	30	30
Effects of lanthanum chloride on body weight gain and feed conversion rate of pigs		
initial BW (kg)	54.69	54.75
end BW (kg)	74.30	76.90
BWG (g/day)	653.67^a	738.33^b
FI (kg)	2.21^a	2.33^b
FCR (kg/kg)	3.39^a	3.16^b
Improvements compared to the control		
BWG (%)		+ 6.30 ($p < 0.01$)
FCR (%)		- 10.29

Table 12.8: Effects of dietary supplementation of lanthanum chloride on body weight (BW in kg), daily body weight gain (BWG in g per day), feed intake (FI in kg) and feed conversion rate (FCR in kg/kg) of pigs; n: number of animals per experimental group; ^{a,b} values without the same superscripts differ significantly $p < 0.05$ (Liu, 2005).

Although there is no definite agreement on the concentration of rare earths recommended, which may be attributed to differences in composition of rare earth mixtures applied, the majority of studies reports doses in the range of 75 mg/kg to 200 mg/kg to be effective, whereas, organic compounds are supposed to provide better effects. It could also be demonstrated that not only the mixture of rare earths but also sole application of lanthanum to pigs may enhance animal performance. In addition to growth promotion, supplementation of amino acid rare earth compounds to diets of growing pigs could also improve the quality as well as the chemical composition of meat (Liu et al., 2003).

12.1.1.2 Poultry

According to Chinese literature, application of rare earth containing feed additives in order to promote growth is not restricted to pigs. Performance enhancing effects in terms of increased body weight, improved feed conversion but also enhanced egg production and fertilization rate of hatching eggs were reported in poultry after oral rare earth application, too (Wu et al., 1994), (Chen and Xiong, 1994). So far both inorganic and organic rare earth compounds were tested. However, due to differences in rare earth concentrations as well as chemical compounds, it is hard to make any statements as to whether organic or inorganic rare earth compounds may provide better performance enhancing effects in poultry. Additionally, even though studies generally reported ergotropic effects due to rare earth application, optimum concentrations recommended varied largely. This again reflects the impossibility to compare data obtained in different Chinese feeding trials due to variations in rare earth compounds. Furthermore, often details on the compounds are missing as it is also the case in the trial described as follows. Wu et al. (1994) reported that, with respect to all performance parameters, best results were obtained applying rare earths at a rate of 600 mg/kg, therefore being considered as optimum concentration. Within this experiment it was demonstrated that a normal diet supplemented with different concentrations of rare earths to six-month-old hens (egg laying Xingza-288 breeding hens, average body weight of 1.45 kg) improved their performance significantly. At 200 mg, 400 mg 600 mg and 800 mg rare earths per kg feed egg production was improved by 8.85 %, 3.90%, 7.25 % and 6.40 % ($p < 0.01$), respectively, while the fertilization rate of hatching eggs was also improved by 1.11 %, 3.46 %, 4.32 % and 1.54 % ($p < 0.01$). Additionally, single egg weight could be increased by 0.50 g, 1.23 g, 1.33 g and 0.61 g at 200 mg, 400 mg 600 mg and 800 mg rare earths per kg feed. For rare earth nitrates, however, an optimum concentration level of 300 mg/kg feed was assumed by Zhang and Shao (1995), who investigated the effects of inorganic rare earth feed additives on growth performance of ten-day-old broilers for 60 days. The addition of rare earth nitrates (38.7 % rare earth oxides; mainly containing La_2O_3, Ce_2O_3, Nd_2O_3) at 300 mg, 400 mg and 600 mg per kg feed improved body weight gain by 20.3 % ($p< 0.01$), 18.6 % ($p < 0.01$) and 6.6 % ($p < 0.05$), respectively, compared to the control.

In a very recent study, broilers at the age of 35 days were divided into four groups receiving 0 mg, 300 mg, 400 mg and 500 mg rare earth compounds bound to fumaric acid per kilogram normal diet (Yang et al., 2005). Besides improvements in feed conversion rates, economic benefits could be achieved in those broilers fed rare earths. Best results were obtained using 500 mg rare earths, thereby improving body weight (938 g) by 12.1 % and feed conversion rate (3.0) by 13.1 %, compared to the control (837 g). Another study, however, reported even higher optimum concentrations of 1000 mg/kg and 1500 mg/kg feed in order to increase body weight gain by 1 - 9 % and decrease feed conversion rate by 9 - 11 % in poultry (Fang et al., 1994). During this study, it was further noticed that 60 to 100-day-old chickens were particularly susceptible to rare earth supplementation. Yet, lower concentrations in the range of 100 mg/kg and 200 mg/kg were described in most of the other experiments. Hence, application of rare earths at 120 mg/kg could improve total egg production and laying rate of 75-week-old laying hens (Beijing White T.) by 8.18 % and 6.41 %, respectively (Chen and Xiong, 1994). In hen farming, it was reported that *RCT - 3* (organic rare earth compounds) supplementation at a dosage of 100 mg/kg for one month could increase laying rate by 3.4 %, decrease feed egg ratio and significantly improved both fertility and hatching rate. In contrast to Chen and Xiong (1994), dietary addition of 100 mg/kg rare earths to breeding hens during laying had no significant impact on either fertilization or hatching rate of eggs, yet laying and survival rate improved, respectively, by 4.12 % and 3.8 %. In addition, feed conversion was also reported to be improved (Duan et al., 1998).

During growing, both survival rate and feed intake have been shown to be enhanced. In breeding hens, laying rate increased by 4.7 %, while the incidence of damaged eggs decreased by 1.5 % after rare earths were supplemented at 100 mg/kg to their diet (Gong, 1996). Furthermore, fertilization and hatching rate as well as the percentage of healthy chickens increased. Improvements in laying rates of 7.1 % ($p < 0.01$) and 3.6 % ($p < 0.05$), respectively, on the one hand, were reported when rare earths were applied at a concentration of 0.03 % and 0.04 % to 53 week old laying hens (Beijing White) for seven weeks. On the other hand, individual egg weight was also significantly enhanced (Zhang et al., 1996a).

In another study, one-week-old chickens (Feng Hua Chicken) were supplemented with organic rare earth compounds at different concentrations (0 mg/kg, 65 mg/kg, 130 mg/kg, 195 mg/kg) during the period of rearing (two to four weeks) and growing finishing (five to nine weeks) (Xie and Wang, 1998). Increased average body weight gain of 6.30 % ($p < 0.01$) and 10.71 % ($p < 0.01$) was demonstrated when rare earths were applied at 65 mg/kg and 130 mg/kg feed, respectively; additionally, feed conversion was also improved compared to the control group. As can be seen in Table 12.9, best results were obtained when rare earths were supplemented at a rate of 130 mg/kg, whereas, no effects occurred when rare earths were applied at 195 mg/kg, hence indicating a dose dependency.

	control	RE 65 mg/kg	RE 130 mg/kg	RE 195 mg/kg
n	120	120	120	120
Effects of rare earths on body weight gain and feed conversion rate				
BWG (g/day)	25.24	26.82	27.94	25.21
FCR (kg/kg)	2.72	2.44	2.31	2.70
Improvements compared to the control				
BWG (%)		+ 6.30 ($p < 0.01$)	+ 10.71 ($p < 0.01$)	- 0.09 ($p > 0.05$)
FCR (%)		- 10.29	- 15.07	- 0.74

Table 12.9: Effects of dietary supplementation of rare earths on daily body weight gain (BWG in g per day) and feed conversion rate (FCR in kg/kg) of chicken; n: number of animals per experimental group; p-value: significance (Xie and Wang, 1998).

Regarding the results of studies presented, rare earth have obviously shown to improve performance of chickens in terms of increased body weight gain and decreased feed conversion rate. Nevertheless, positive effects of rare earths on poultry were not only observed in chickens but also in ducks. Application of rare earths at 180 mg/kg to the diet of meat breed ducks increased their body weight gain by 16 - 25 % (Zhou, 1994). Additionally, it advanced their sexual maturity by five to seven days. In laying ducks, 60 mg/kg rare earths could already sufficiently improve total egg production by 12 - 15 %, while also prolonging the peak of egg production and the input output ratio. A summary of Chinese feeding trials performed on pigs and poultry is presented in Table 12.10.

Reference	Animal Species	RE doses (mg/kg)	RE compound	Effect (%)	
Shen et al. (1991)	piglets	300	RE mixture	+ 12 BWG	- 11 FCR
		600		+ 14 BWG	- 14 FCR
		900		+ 7 BWG	- 6 FCR
Zhu et al. (1994)	piglets		RE mixture	+ 5.37 BWG	- 4.31 FCR
Yuan (1994)	piglets	48	RE mixture	+ 11 - 19 BWG	- 9 - 19 FCR
Wan et al. (1997)	pigs	700	RE organic acids	+ 29 BWG	- 24 FCR
		80	RE chloride	+ 9 BWG	- 8 FCR
Chen (1997)	pigs	100	RE ascorbate	+ 8 BWG	- 8 FCR
		139	RE citrate	+ 25 BWG	- 19 FCR
Xia and He (1997)	pigs	50		+ 6 - 12 BWG	- 4 - 10 FCR
		100		+ 13 BWG	- 6 - 7 FCR
		150		+ 6 - 12 BWG	- 4 - 10 FCR
He and Xia (1998a)	piglets	75	RE mixture	+ 13 - 20 BWG	- 5 - 8 FCR
Hu et al. (1999)	pigs	200	RE mixture	+ 4.0 BWG	- 1.7 FCR
		400		+ 8.6 BWG	- 4.7 FCR
		600		+ 32.3 BWG	- 11.3 FCR
Xu et al. (1999)	pigs	100	Lanthanum	+ 13.3 BWG	- 8.5 FCR
Wang and Xu (2003)	pigs	100	Lanthanum	+ 13.1 BWG	- 6.5 FCR
Liu (2005)	pigs	100	Lanthanum chloride	+ 6.3 BWG	- 10.3 FCR
Xie et al. (1991)	broiler	10	RE mixture	+ 1.4 BWG	-
		20		+ 3.8 BWG	-
Shen et al. (1991)	broiler	50 - 600	RE mixture	+ 12.0 - 12.4 BWG	- 12.4 - 12.8 FCR
Yang et al. (1991)	broiler	140 - 200	RE mixture	+ 7.9 - 10.7 BWG	- 14.8 - 20.7 FCR
Zhu et al. (1992)	broiler	100 - 900	RE mixture	+ 5.7 BWG	- 8.4 FCR
Wu et al. (1994)	laying hen	200 - 800	RE mixture	+ 3.9 - 8.9 egg yield	-
				+ 0.5 - 1.3 egg weight	-

continued on next page

Reference	Animal Species	RE doses (mg/kg)	RE compound	Effect (%)	
Zhang and Shao (1995)	broiler	300	RE nitrates	+ 20.3 BWG	-
		400		+ 18.6 BWG	-
		500		+ 6.6 BWG	-
Xia and He (1997)	broiler	130	RE mixture	+ 10.7 BWG	- 12.9 FCR
		300		+ 23.7 BWG	- 16.9 FCR
Xie and Wang (1998)	broiler	65	RE organic	+ 6.3 BWG	-
		130		+ 10.7 BWG	-
		195		- 0.1 BWG	-
Yang et al. (2005)	broiler	500	RE fumaric acid	+ 12.3 BWG	- 13.1 FCR

Table 12.10: Chinese feeding trials on pigs and poultry FCR: feed conversion rate, BWG: body weight gain.

12.1.1.3 Ruminants

Although it has been reported that supplementation of rare earths to feed of ruminants may enhance their performance (Shen et al., 1991), (Xiong, 1995), studies on these effects are hardly available. Increased wool clip of 8 % and body weight gain of 6 - 13 % were reported in sheep (Xiong, 1995). Additionally, it was described in China that dietary supplementation of rare earths to goats can improve the length of cashmere grown, while keeping the fineness below 14 μm. Cashmere wool is an expensive and exclusive fibre, which may be obtained from Kashmir goats (McGregor, 2002). Though not significant, rare earth supplementation to the drinking water of Cashmeres on a private Australian farm was also reported to improve the yield of raw material and fineness. Furthermore, Cashmeres presented more lean meat at slaughter (Rosewell, 1995). Enhanced average output of fine wool of 0.25 kg in sheep and goats and improvements of daily body weight gain of 40 % in sheep were described in test reports on applying rare earths to animals published by Baotou Rare Earth Feed Additive Co. Ltd. in China. Furthermore, increases in body weight gain of 20 - 25 % and increased milk output in cattle of 20 % were also reported.

Similarly, improvements of both body weight and feed conversion rate could be observed in six-month-old fattening cattle (average body weight of 219 kg) after their feed was supplemented with rare earth nitrates containing $\geq$ 38.0 % rare earth oxides (mainly lanthanum (22 %), cerium (45 %) and neodymium (15 %) oxides) at a concentration of 600 mg/kg (5 mg/d/kg body weight) for 76 days (Zhang et al., 1994). In dairy cattle, dietary supplementation of rare earths improved performance in terms of increased milk production. The addition of rare earth nitrates consisting of $\pm$ 38 % rare earth oxides (22 % La_2O_3, 45 % Ce_2O_3, 15 % $Nd_2 0_3$) to the feed of 9 lactating dairy cows could increase both total and individual milk production as well as milk fat percentage (Shen et al., 1991). Best results were obtained at 800 ppm. Animals from the control group produced 1467 kg milk over the period of sixty-three days, whereas, 1603 kg and 1783 kg were produced by animals fed 200 ppm and 800 ppm rare earths, respectively. Individual milk production also improved by 9.3 % and 21.5 % in animals fed 200 ppm (8.48 kg) and 800 ppm (9.43 kg) rare earths, compared to the control group (7.76 kg). The absolute milk fat percentage was 3.81 in the control group, while improvements of 4.9 % and 7.4 % were noticed when rare earths were supplemented at 200 ppm (4.10) and 800 ppm (4.20), respectively. However, this study needs to be considered carefully due to the low number of experimental animals and the lack of statistical data.

12.1.1.4 Fish and Shrimps

In China, rare earths are not only applied to livestock husbandry, but also to aquaculture, including fish and shrimps. Feeding different rare earth compounds including rare earth amino acids (50 % of rare earth methionine and lysine respectively), rare earth vitamin C, rare earth citrate, rare earth glucose and rare earth gluconic acid to carps for 60 days, improved body weight gain by $>$ 20 % in all treatment groups compared to the control though, best results were obtained in fish receiving rare earth amino acids, which could increase body weight gain by 28.9 %. For rare earth vitamin C and citrate compounds, body weight gain was shown to be enhanced by 27.2 % and 24.1 %, respectively, whereas that of rare earth glutamate and gluconic acid increased by 23.0 % and 20.1 % . Furthermore, it was described that besides promoting growth, rare earth supplementation was also able to improve egg hatching dose-dependently in carps. At low concentrations of $<$ 100 mg/kg egg embryo development was promoted, however, inhibitory effects occurred when the concentration exceeded 100 mg/kg (Shao et al., 1998). Same effects were observed applying praseodymium. Yang and Chen (2002) reported optimum concentrations of praseodymium to be in the range of 2.4 - 4.8 mg/l in order to promote egg hatching of grass carps by 18.5 - 27.5 %.

An evident dose-effect dependency of growth enhancing effects was also described in rainbow trouts and carps. Supplementation of 300 ppm rare earth amino acid compounds (containing 50 % rare earth lysine and 50 % rare earth methionine) increased body weight gain by 11.2 % in rainbow trout, yet even better improvements were obtained at higher concentrations of 400 ppm (29.6 %). Also, in carps, growth promotion of 6.3 % and 16 %, respectively, was achieved when the same rare earth compound was supplemented to their feed at 300 ppm and 400 ppm (Tang et al., 1997b). However, it is known, as for several Chinese experiments, that these studies were performed under extensive or semi-intensive conditions (Tautenhahn, 2004). Nevertheless, besides yield increases, some authors also described changes in the activity of several enzymes, such as catalase, superoxide dismutase, proteinase, lipase, amylase, in liver and/or pancreas of fish due to rare earth supplementation (Wang et al., 1999), (Shao et al., 1999). This may indicate that rare earths exert their performance enhancing effects by influencing the activity of enzymes.

In line with another study designed to investigate the effects of rare earth supplementation to fish feed optimum concentration ranges of 36.9 - 42.8 mg/kg for blunt snout bream and 54.6 - 58.9 mg/kg for grass carps were determined (Shi et al., 1990). At these concentrations, it was possible to increase yield by 17 - 18 %, survival rates by 5.4 - 8.5 % and, furthermore, improve feed conversion by 5.6 - 15.5 %. Consistent with dose dependent effects of rare earths, it was demonstrated that continuous exposure of carps (Cyprinus carpio L.) to solutions containing very low concentrations of lanthanum, gadolinum or yttrium (0.50 mg/l) over 45 days at a pH of 6.0, neither caused synergistic nor antagonistic effects (Tu et al., 1994).

Yet dose-dependent effects were not only observed in fish but also in shrimps. Hence, the application of rare earth citrates to oriental river shrimps (Macrobrachium nipponense) revealed that promoting effects on egg hatching strongly depended on the doses applied (Yang et al., 2001). While rare earth citrates could only promote the development of egg embryos when applied at 1.2 - 4.8 mg/l, no significant differences were seen at low concentrations 0.1 - 0.6 mg/l and at concentrations of $>$ 9.6 mg/l adverse effects occurred. Egg hatching was thought to be promoted due to rare earth absorption, with absorption capacities of eggs being approximately 7.9 μg/egg. Similar concentrations were determined for lanthanum absorption capacity (4.4 to 8 mol) (Yuan et al., 1999), (Xin et al., 1997). Furthermore, within the scope of studying the effects of lanthanum it was shown that not only the mixture but also sole lanthanum could promote egg hatching in prawns. Optimum lanthanum concentrations of 0.37 - 1.83 mg/l were recommended to promote egg hatching in prawns (Penaeus chinensis) by 21.7 - 52.4 % (Yuan et al., 1999), whereas 0.55 - 1.64 mg/l were suggested to improve larval metamorphosis. Slightly higher optimum lanthanum concentrations of 1.2 - 4.8 mg/l were determined to increase egg hatching by 22.8 - 27.7 % in Macrobrachium nipponense, another species of oriental river shrimps (Yang and Chen, 2000). Accordingly, Xin et al. (1997) demonstrated that lanthanum could promote egg embryo development in oriental prawns after being absorbed from seawater. Yet, it was shown that lanthanum concentrations required differed with the developmental stage of prawns (Penaeus chinensis). For monocell and dicell stage of embryo development, optimum concentrations of 0.3 - 8.8 mg/l enhanced egg hatching rates by 33.5 - 49.1 %, whereas at 0.9 - 1.8 mg/l, egg hatching rates were improved by 17.1 - 23.5 % during polycell stage. For the growths of nauplii, an optimum lanthanum concentration of 0.9 - 1.5 mg/l was recommended, thereby enhancing the metamorphosis from nauplii to protozoea by 9.4 - 11.7 %.

12.1.2 Safety of Animal Products

In conclusion, performance enhancements of rare earth containing feed additives could be achieved in a great variety of farming animals as well as in aquaculture. However, not only the effectiveness but also the safety of rare earth application has been assessed in China, prior to their commercial utilization. Rare earth feed additives were tested on two million animals while their products were analyzed by the Inner Mongolian State Technical Inspection Departments. Results showed that rare earths were nonpoisonous to either humans or animals (Rosewell, 1995). Accordingly, Ming et al. (1995) did not observe any negative effects of rare earth supplementation on either the carcass or the quality of animal feedstuffs. Between rare earth supplemented pigs and the control group there were no differences as to several slaughter indexes, including carcass weight, body length, back fat, thickness, eye muscle area, lean meat rate, meat color, pH value, water loss rate, water holding rate, meat marbling or cooked meat rate. Moreover, improvements in the quality of animal products were reported after rare earth supplementation (Xie and Wang, 1998), (Liu et al., 2003). Additionally, adverse effects for consumers may neither be expected from possible accumulation of rare earths in animal tissues as their concentration is generally reported to be low. Thus, no significant differences in lanthanum contents were observed between selected organs of lanthanum supplemented pigs and those of the control (Wang and Xu, 2003). Again, this was confirmed recently by Liu (2005) (Table 12.11).

	Control	$LaCl_3$ 100 mg/kg
n	30	30
Muscle	0.15 ± 0.01	0.29 ± 0.01
Liver	0.33 ± 0.07	0.38 ± 0.03
Kidney	0.13 ± 0.03	0.16 ± 0.04
Spleen	0.17 ± 0.05	0.15 ± 0.05
Pancreas	0.16 ± 0.03	0.18 ± 0.06

Table 12.11: Lanthanum concentrations (mg/kg) in tissues of pigs; n: number of animals per experimental group; ^{a,b} values without the same superscripts differ significantly $p < 0.05$ (Liu, 2005).

As can be seen in Table 12.12, highest concentrations of rare earths were reported in bone of pigs, which conforms with the fact that rare earths have a certain affinity to bone (Ming et al., 1995). Additionally, elimination from liver tissue occurred quickly. Meat quality of rare earth supplemented chicken was also reported to be preserved, since no significant accumulation of rare earths was found in either muscle or liver in chicken (Xie and Wang, 1998). Residues of rare earths in meat and liver of meat breed ducks were reported to be around 0.1 - 0.2 mg/kg, whereas in eggs, only trace amounts were detected (Zhou, 1994).

Low rare earth concentrations were not only detected in pigs and chickens, but also in fish fed a rare earth containing diet, thus ensuring safe consumption. Though slightly higher concentrations could be determined in bone, fin and gill, accumulation of rare earths was shown to deplete easily (Shi et al., 1990). Carps generally presented a low ability to take up rare earths after being continuously exposed to low lanthanum concentrations under experimental conditions, whereas the order of bioaccumulation was internal organs > gills > skeleton > muscle (Tu et al., 1994). Accumulation pattern in goldfish, kept in water containing different concentrations of rare earth elements (0 mg/l, 0.5 mg/l, 1.0 mg/l, 2.0 mg/l, 4.0 mg/l and 6.0 mg/l) for 20 days, was liver > gallbladder > kidney > eggs > spleen for yttrium and eggs > liver gallbladder > spleen > kidney for gadolinium (Wang et al., 1999).

	Control	RE
Heart	0.06	0.06
Liver	0.05	-
Spleen	0.02	0.06
Lung	0.07	0.1
Stomach	0.03	0.41
Kidney	0.02	0.06
Bone	2.25	3.5
Intestine	0.05	-
Muscle	0.045	-
Blood	0.02	0.03

Table 12.12: Contents of rare earths (mg/kg) in tissue samples of pigs with and without dietary rare earth supplementation (Ming et al., 1995).

12.1.3 Summary

In China, rare earths were shown to promote performance, in terms of increased body weight gain and improved feed conversion, in nearly all categories of farming animals, especially in pigs and poultry. Improvements of up to 20 % are described for both body weight gain and feed conversion rates. In dairy cows, increases have also been observed in milk production. Though both inorganic and organic rare earth feed additives have been used in several trials, better results seem to be obtained using the latter. Thus, several organic rare earth products are commercially available in China. As to feeding experiments performed in China, there is no consistency regarding optimum doses. Furthermore, variations in the digestive system between different animals implicate that optimum concentrations of rare earths supplemented to the diet, differ with the animal species. Yet concentrations of 100 - 200 mg per kg feed have been recommended for pigs and poultry. Following dietary rare earth supplementation, only little accumulation of rare earths was observed in animal tissue, at the same time meat quality was not affected at all, hence indicating consumer safety as to the consumption of animal products. Nevertheless considering information obtained from Chinese studies, it needs to be taken into account that often only abstracts were available or papers had to be translated, as most Chinese sources are still predominantly written in the native language. Furthermore, statistical evaluations and details on the experimental design are lacking in several experiments. Thus, this information may has to be treated carefully.

12.2 Europe

Growth performance enhancing effects due to rare earth supplementation as reported in China, have for a long time been unnoticed in the Western world. Yet with the ban of all in-feed antibiotics as of 2006 [EU directive No 183/2003 article 11 paragraph 2], the demand for feed additives capable of enhancing animal performance has grown. Antibiotics have been successfully used as feed additives in animal diets in several European countries for nearly half a century. They were used for both prophylaxis and sub-therapeutic purposes to improve growth and feed efficiency (Guggenbichler et al., 2004). However, debates have started on in-feed antibiotics as promoting the selection of microbial resistances, which compromise the effectiveness of antibiotics in human medicine, although it is well known that the liberal usage of antibiotics in human medicine is primarily responsible for the development of resistances. Yet due to growing concerns about the transfer of resistent bacteria from animals to humans, in-feed antibiotics were blamed as well (Lynch, 1999). Indeed, multi-drug resistances have already been observed, for example in salmonella, hence, increasing the frequency and severity of infections while limiting treatment options. In accordance with public demands, the European health authorities and the World Health Organization (WHO), therefore, recommended that antibiotics should only be prescribed by veterinarians for targeted pathogens when indicated in individual infected animals. Consequently, a new European directive was passed [EU directive No 183/2003 article 11, paragraph 2], (Qualität und Sicherheit GmbH, 2005), prohibiting the sub-therapeutic usage of all anti-microbials for growth promoting purposes in animal feed as of 2006.

However, performance enhancing feed additives are highly needed, especially in pig and poultry production, since a higher incidence of disease has been noted after the prohibition of antibiotic feed additives, especially in the rearing and post-weaning period of pigs (Wenk, 2004a), which consequently leads to reduced animal performance. Besides, efficient feed additives are also needed to assure feed supply. Along with increased population growth, it has been calculated that animal production also has to increase by at least 2 % each year. This further substantiates that natural resources have to be used efficiently while minimizing environmental loads as far as possible. New feed additives are recommended to be efficient as well as safe for humans, animals and the environment (Kahn, 2004). Searching for suitable replacements of in-feed antibiotics, attention has been drawn to China, where rare earths have been used as feed additives in animal production for approximately 25 years, successfully enhancing performance of farming animals.

But under highly optimized feeding and keeping conditions, animals especially those belonging to high performance breeds are less susceptible to performance enhancing substances. Thus, livestock conditions in Europe or the United States differ greatly from those prevailing in China and may therefore not be compared at all. It is generally agreed that the efficiency of growth promoting agents highly correlates with keeping, housing, hygienic and feeding conditions (Wenk, 2004b). Furthermore, genetic variations may lead to differences in enzyme activities. Likewise, keeping conditions may affect the composition of microbial populations within the gastrointestinal tract. In fact, it was discovered that numerous Chinese investigations on performance enhancing effects of rare earths were performed under extensive to semi-intensive conditions (Tang et al., 1998d), (Tang et al., 1997b), (Wan et al., 1998), (Shao et al., 1998). Moreover, animals used in Chinese feeding trials often present lower proficiency levels, compared to those found in European animal husbandry (Schuller, 2001). Based upon this information, it was hypothesized that rare earths may only promote animal performance under suboptimum conditions.

Yet the contrary was also demonstrated in several Western studies; and a temporary permission for the use of rare earths as feed additives in pig production has already been granted in Switzerland, in 2003 (Rambeck and Wehr, 2004), (Sanopharm, 2006). At present, rare earth containing feed additives may be purchased from the Swiss company *Zehentmayer*, as either *Lancer*® for feedstuff companies or as *Sanocer*® for farmers (Zehentmayer, 2006), (Meier, 2003). On this basis, it is also intended to register rare earths as feed additives in Europe. Preparations are currently in progress (Süss, 2004).

Also Swiss price calculations show that financial efforts follow the use of rare earths in agriculture. Currently, approximately five US $plus transportation have to be paid for one kg rare earths (Bayerischer Rundfunk, 2003), while according to recommended amounts of rare earth elements, only 250 mg rare earths need to be supplemented to one kilogram animal feed. Additional costs for farmers resulting from rare earth application are therefore less than one Swiss franc per 100 kg food (Zehentmeyer, 2006), which is equal to 0.65 € and 0.78 US$ (Oanda, 2006). This is in the same range as other feed additives such as phytobiotics which are supposed to cause additional costs of 0.62 € per 100 kg feed (Reinecke, 2006), while potassium diformate amounts up to 1.50 to 2.70 € per 100 kg pig feed. As for probiotics, additional costs of approximately 0.50 € per 100 kg pig feed were reported (Sommer and Bunge, 2006).

12.2.1 Feeding Trials

Several feeding studies have been designed in Germany and Switzerland since 1999, investigating to what extent rare earths may enhance body weight and feed conversion under Western conditions. Pioneer work on researching the effects of rare earths on several farming animals has thereby been conducted by W. A. Rambeck, U. Wehr and several doctoral students at the University of Munich. Similar studies on rare earth performance enhancing effects have also been carried out at other German institutions, including the Agriculture Research Institute (FAL - Bundeforschungsanstalt für Landwirtschaft) at Brunswick under the direction of G. Flachowsky and at the University of Berlin under the direction of O. Simon. Beyond that, research has also been performed in Switzerland, (at the ETH Zurich and University in Zurich), where antibiotic performance enhancers were already prohibited in 1999. Feeding experiments conducted on pigs (Rambeck et al., 1999a), (He et al., 2001), (Kessler, 2004), poultry (Halle et al., 2002a), (He et al., 2006a) and rats (He et al., 2003a) were able to prove that rare earths can also improve body weight gain and feed conversion of high performance animals that are kept under optimized housing and feeding conditions. Moreover, results have been shown to be reproducible.

Hence, positive results with improved body weight gain and feed conversion rate of 2 - 5 % and 7 %, respectively, were noticed in piglets after rare earth chloride application (Rambeck et al., 1999a). Even better effects in terms of increased body weight gain of 12 - 19 % ($p < 0.05$) and improved feed conversion of 3 - 11 % ($p < 0.01$) were described in growing pigs and could be proven statistically (He and Rambeck, 2000), (Rambeck et al., 1999b), (He et al., 2001), (Borger, 2003). Fattening pigs that received rare earth citrates, presented significant higher body weight gain of 851 g, which was improved by 8.8 % compared to the control group's weight gain (782 g). Additionally, the final weight of 104 kg was shown to be achieved nine days ahead of control animals (Kessler, 2004). Significantly decreased feed conversion rate of 7 - 9 % was demonstrated in piglets (8 to 40 kg) treated with rare earth citrates (Prause et al., 2004). Similarly, improvements in feed conversion of 3.6 - 5.5 % were also reported in piglets (8 - 30 kg) in another feeding trial using rare earth citrate along with increased body weight gain of 3.7 - 25 % (Knebel, 2004). However, performance enhancing effects were not only demonstrated under controlled experimental conditions, but also in field trials. Thus, rare earth chlorides were shown to improve body weight gain and feed conversion rate by 10 % and 2 %, respectively, in pigs that are kept under field conditions (Zehentmayer, 2002), (Eisele, 2003). In the meantime, positive effects of rare earths on pig performance have not only been published as scientific reports, but also in newsletters, magazines and on television in order to inform the public (Mavromichalis, 2001), (Azer, 2003), (Süss, 2004), (Bayerischer Rundfunk, 2003).

Besides pigs, significant growth promoting effects were also observed in growing rats. Dietary supplementation of rare earth chlorides improved their body weight gain and feed conversion by 4 - 7 % and 3 - 11 %, respectively (He et al., 2003a). In addition, rare earths were also shown to have ergo-tropic effects in terms of increased end weights of 7 % ($p < 0.05$) on broilers (Halle et al., 2002a), while feed conversion was improved by 1 - 3 % ($p < 0.05$). A recent study further reported performance enhancing effects in veal cattle after rare earths were supplemented to milk substitute (Meyer et al., 2006).

Yet, there are also studies, in which performance enhancing effects after dietary supplementation of rare earth elements could not be observed (Kraatz et al., 2004), (Böhme et al., 2002a), (Eisele, 2003), (Schuller, 2001), (Gebert et al., 2005), (Miller, 2006). Therefore, a detailed description of currently available studies conducted under Western conditions will be given according to the animal species. Also, studies using inorganic compounds will be presented prior to that applying organic rare earth compounds since it is assumed that performance enhancing effects of rare earth elements may vary with the anion bound.

It might be of interest that, due to legal policy and procedures in Germany, a special governmental authorization is required before investigations on growth promoting effects of rare earths can be performed in animal experiments, since, at present, utilization of rare earths as feed additives to animals has to be licensed. Experimental diets containing rare earths may, therefore, only be applied following a special permit.

As to the source of rare earth elements, the researches performing studies, have purchased their rare earth samples either from China (Baotou area, Anhui Agricultural University) or from Switzerland (E. Zehentmayer AG Brühl 8 CH-9305 Berg SG), while pure lanthanum samples applied in some of the studies were bought from the German Company Merck.

Regarding rare earth concentrations used in feeding trials, it has to be considered that the amount of individual rare earth elements within different rare earth compounds, such as chlorides or citrates, does not necessarily have the same weight; that is, 100 mg/kg rare earth citrates does not equal to 100 mg/kg rare earth chlorides. Furthermore, the composition of rare earth mixtures may also vary as to the contents of individual rare earth elements within the feeding trials. Thus, a consistent basis is required to compare these investigations with respect to their concentrations. In China, such rare earth concentrations are therefore often declared as *total rare earth oxides* (TREO). Indeed, the content of total rare earth oxides (TREO) is supposed to provide a standard basis as to the comparison of results obtained in feeding trials in which different rare earth compounds are used. A brief description on the conversion of rare earth contents to total rare earth oxides is therefore given in this format: TREO refer to the concentration of rare earth oxides in percent, which comprises oxides (La_2O_3, CeO_2, $Pr_{11}O_6$, Nd_2O_3, Sm_2O_3, Tb_4O_7) originating from pyrolyzing corresponding hydroxide, oxalate, carbonate, acetate salts in the present of dry air (oxygen). Given the concentration of individual rare earth elements, such as La, Ce, Pr, Nd and Sm determined by analytical methods (ICP - MS or NAA), total rare earth oxides may be calculated using the following multiplication factors (Richter, 2006), (Richter and Schermanz, 2006).

- 1.1723·[% La] = [% La_2O_3]
- 1.2285·[% Ce] = [% CeO_2]
- 1.2077·[% Pr] = [% Pr_6O_{11}]
- 1.1669·[% Nd] = [% Nd_2O_3]
- 1.1601·[% Sm] = [% Sm_2O_3]

Contents of other rare earth elements can be neglected and the total rare earth oxides (TREO) are calculated by the addition of the amount of individual rare earth oxides (% TREO = % La_2O_3 + % CeO_2 + % $Pr_{11}O_6$ + % Nd_2O_3 + % Sm_2O_3 + % Tb_4O_7)

Conversion of individual rare earth salts to rare earth oxides requires the multiplication of rare earth salts by the percentage of the oxide content in percent included in different salts. The product than has to be divided by 100. The concentration of oxides within different rare earth salts are summarized consecutively in Table 12.13.

On this basis, contents of TREO have also been calculated for comparative evaluation of feeding trials performed under Western conditions, and results are presented in Table 12.19. Additionally, a more detailed discussion as to optimum concentrations and the influence of anion bound to rare earths on their effect on animals will be provided in Chapter 13.

12.2.1.1 Pigs

To this day, the majority of investigations on rare earth performance enhancing effects has been performed on pigs at different periods of growth, including rearing, growing and fattening. This is probably due to the loss of in-feed antibiotics and the fact that feed additives exerting growth promoting effects are especially needed for pig production. An overview of feeding trials conducted on pigs until now is given in Table 12.14, whereas experiments are listed according to the type of rare earth compound used.

Within the scope of these first studies, the growth promoting effects of rare earths, as reported previously in Chinese literature, could already be confirmed for pigs kept under Western conditions. During this feeding trial, which lasted for five weeks, 72 pigs (crossbred German Landrace pig x Piétrain pig) with an average body weight of 7.2 kg were fed a complete diet (52.7 % barley, 20 % wheat, 18.8 % soybean, ME 13 MJ/kg, digestible crude protein 184 g/kg, fat 44.94 g/kg) supplemented with inorganic rare earth compounds (Rambeck et al., 1999a), (He and Rambeck, 2000). Besides the control group, there were four experimental groups receiving pure $LaCl_3$ (99.7 % $LaCl_3 \cdot 6H_2O$; TREO 44.3 %) and a mixture of rare earth chlorides ($RECl_3 \cdot 6H_2O$; 38 % $LaCl_3 \cdot 6H_2O$, 52.1 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$ and 10 % of other rare earth chlorides; TREO 46.0 %), respectively, at low (75 mg/kg) and at high (150 mg/kg) concentrations. Positive effects achieved over the whole experimental period comprised improved body weight gain and feed conversion of 2 - 5 % and 7 %, respectively ($p > 0.05$) (Rambeck et al., 1999a), (He and Rambeck, 2000). Only slight differences were noticed in feed intake among the experimental groups. Regarding body weight gain, best results of 299.4 g were achieved when lanthanum chlorides was supplemented at 150 mg/kg, followed by the supplementation of lanthanum at 75 mg/kg and the mixture of rare earths at 75 mg/kg (291.7 g). By comparison, with respect to feed conversion, those animals receiving 150 mg/kg rare earth chlorides presented the lowest ratio (1.89), which was still improved by 7 % compared to the control (2.02). Animals treated

RE salts / compounds	% RE - oxide (% TREO)
Chlorides (hydrate)	
$LaCl_3 \cdot 6H_2O$	46.1 % La_2O_3
$CeCl_3 \cdot 6H_2O$	48.5 % CeO_2
$PrCl_3 \cdot 6H_2O$	47.9 % $Pr_{11}O_6$
$NdCl_3 \cdot 6H_2O$	46.9 % Nd_2O_3
$LaCl_3 \cdot 7H_2O$	43.9 % La_2O_3
$CeCl_3 \cdot 7H_2O$	46.2 % CeO_2
$PrCl_3 \cdot 7H_2O$	45.6 % $Pr_{11}O_6$
$NdCl_3 \cdot 7H_2O$	44.7 % Nd_2O_3
Chlorides (anhydrous)	
$LaCl_3$	66.4 % La_2O_3
$CeCl_3$	69.8 % CeO_2
$PrCl_3$	68.8 % $Pr_{11}O_6$
$NdCl_3$	67.1 % Nd_2O_3
Nitrates (hydrate)	
$La(NO_3)_3 \cdot 6H_2O$	37.6 % La_2O_3
$Ce(NO_3)_3 \cdot 6H_2O$	39.6 % CeO_2
$Pr(NO_3)_3 \cdot 6H_2O$	39.1 % $Pr_{11}O_6$
$Nd(NO_3)_3 \cdot 6H_2O$	38.4 % Nd_2O_3
Nitrates (anhydrous)	
$La(NO_3)_3$	50.1 % La_2O_3
$Ce(NO_3)_3$	52.8 % CeO_2
$Pr(NO_3)_3$	52.1 % $Pr_{11}O_6$
$Nd(NO_3)_3$	50.9 % Nd_2O_3
Acetates (hydrate)	
$La(CH_3COO)_3 \cdot 1.5H_2O$	47.5 % La_2O_3
$Ce(CH_3COO)_3 \cdot 1.5H_2O$	50.0 % CeO_2
$Pr(CH_3COO)_3 \cdot 3H_2O$	45.8 % $Pr_{11}O_6$
$Nd(CH_3COO)_3 \cdot 3H_2O$	44.8 % Nd_2O_3
Citrates (hydrate)	
$La(C_6H_5O_7) \cdot 3H_2O$	42.6 % La_2O_3
$Ce(C_6H_5O_7) \cdot 3H_2O$	44.9 % CeO_2
$Pr(C_6H_5O_7) \cdot 3H_2O$	45.0 % Pr_6O_{11}
$Nd(C_6H_5O_7) \cdot 3H_2O$	44.1 % Nd_2O_3
Ascorbate ( )	
$La(C_6H_7O_6)_3$	24.52 % La_2O_3
$Ce(C_6H_7O_6)_3$	25.86 % CeO_2

Table 12.13: Calculation of total rare earth oxides (TREO) (Richter, 2006).

Reference	RE compound	Concentration
Inorganic Compounds		
Rambeck et al. (1999a)	$LaCl_3$, $RECl_3$	75 mg/kg and 150 mg/kg
He et al. (2001), Borger (2003)	$RECl_3$	300 mg/kg
Eisele (2003)	$RECl_3$	200 mg/kg, 300 mg/kg
Recht (2005)	$LaCl_3$, $RECl_3$	300 mg/kg
Organic Compounds		
Kessler (2004)	RE - citrate	200 mg/kg
Knebel (2004)	RE - citrate	50 mg/kg, 100 mg/kg, 200 mg/kg
Kraatz et al. (2004)	RE - citrate	200 mg/kg
Recht (2005)	RE - citrate	200 mg/kg
Prause et al. (2006)	RE - citrate	150 mg, 300 mg
Miller (2006)	RE - citrate	300 mg/kg
Förster et al. (2006)	RE - citrate	100 mg/kg, 200 mg/kg, 400 mg/kg
Gebert et al. (2005)	RE - citrate	150 and 300 mg/kg
Both		
Böhme et al. (2002a)	RE - citrate, ascorbate $RECl_3$, $RENO_3^-$	100 mg/kg 100 mg/kg

Table 12.14: Feeding trials performed under western conditions on pigs; RE: rare earths.

with 75 mg/kg and 150 mg/kg lanthanum chloride and 75 mg/kg rare earth chlorides, respectively, presented feed conversion rates of 1.93, 1.95 and 1.97, which, compared to the control, were also improved by 5 %, 3 % and 4 % ($p > 0.05$), as illustrated in Figure 12.1.

As can be seen from Table B.1, growth promoting effects of rare earths were more pronounced during the first two weeks of the experiment. With respect to determined performance parameters, the supplementation of the mixture of rare earths at 150 mg/kg (69.0 mg/kg TREO) showed the best results. Thus, this pilot trial strongly has indicated growth promoting effects of dietary rare earth supplementation, although not significant.

Significant positive results in terms of improved body weight and feed conversion of 19 % ($p < 0.05$) and 10 % ($p < 0.01$), respectively, were noticed in a proceeding feeding trial (He and Rambeck, 2000), (He et al., 2001), (Borger, 2003). In fact, this trial, which comprised the growing and fattening period, presented similar results as those reported in Chinese literature (He and Xia, 1998a) and even better ones than those described for former antibiotic performance enhancers (Rambeck et al., 2004). Again, a similar mixture of rare earth chlorides (38 % $LaCl_3 \cdot 6H_2O$, 52.1 % $CeCl_3 \cdot 6H_2O$, 3.0 % $PrCl_3 \cdot 6H_2O$ and 6.9 % of other rare earth chlorides; TREO 44.3 %) was added at 300 mg per kg feed (132 mg/kg TREO) to a complete feed of 7 piglets (German Landrace pig x Piétrain pig, average body weight 17.5 kg). The diet provided all nutrients at or above requirements (MI: 13.7 MJ/kg and CP 173 g; MII: 13.8 MJ and 164 g crude protein) (He and Rambeck, 2000), (He et al., 2001), (Borger, 2003). During the whole growing period the body weight gain of animals treated with rare earths was 755 g ($p < 0.05$), and thus significantly higher

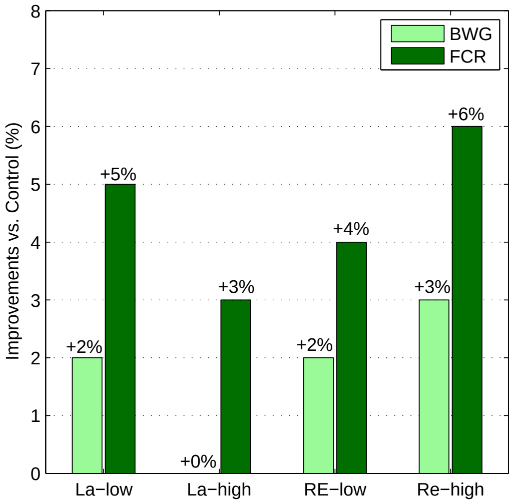


Figure 12.1: Improvements of body weight gain (BWG) and feed conversion rate (FCR) (%) in rare earth (RE) chloride treated pigs versus control animals; La-low: lanthanum chloride at 75 mg/kg, La-high: lanthanum chloride at 150 mg/kg, RE-low: rare earth chlorides at 75 mg/kg, RE-high: rare earth chlorides at 150 mg/kg (Rambeck et al., 1999a).

(19 %) than that of the control (635 g). Additionally, at 2.13 kg/kg feed conversion, which was 2.38 kg/kg in the control group, was significantly improved by 10 % ($p < 0.01$) in the treatment group.

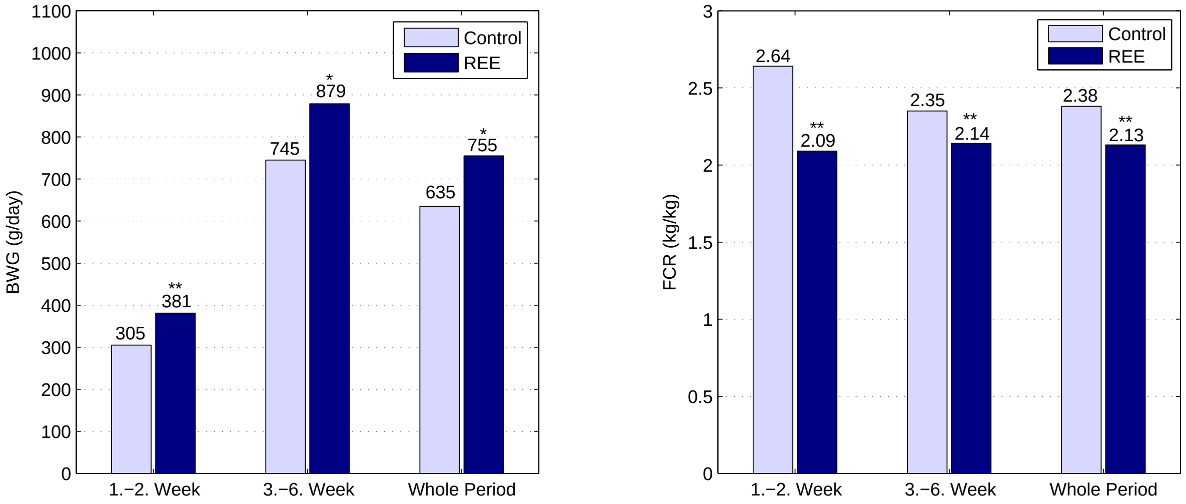
In accordance with the previous trial, growth promoting effects of rare earths on piglets were more evident during the first two weeks of the growing period compared to the later period. Hence, highly significantly improved daily body weight gain of 25 % ($p < 0.01$) and feed conversion rate of 21 % ($p < 0.01$) were observed during the first two weeks (Table B.2). Furthermore, increased daily body weight gain of 18 % ($p < 0.01$) and improved feed conversion rate of 9 % ($p < 0.01$) were reported for the last six weeks of growing as illustrated in Figure 12.2.

At the end of the fattening period, increased body weight gain of 12 % and decreased feed conversion of 3 % ($p > 0.05$) were noticed. Over the whole period of twelve weeks, body weight gain was enhanced by up to 19 % and feed conversion was improved by 11 %. The results of the growing and fattening period are presented in Tables B.3 and B.4 and Figures 12.3 and 12.4. Furthermore, feed intake was increased by 7 % (total intake 90 kg) and 8 % (total intake 69 kg), respectively. Thus improvements were in the same range as those reported for rare earth supplementation at 150 mg/kg feed (66.5 mg/kg TREO).

Results from these two experiments proved that rare earths can also improve body weight and feed conversion of pigs kept, fed and housed under Western conditions. Furthermore, it could be shown, that effects were in a similar range or even better than those achieved by formerly used in-feed antibiotics.

Further studies were performed within the scope of doctoral thesis (Eisele, 2003), (Recht, 2005), demonstrating the performance enhancing potential of rare earth elements on pigs.

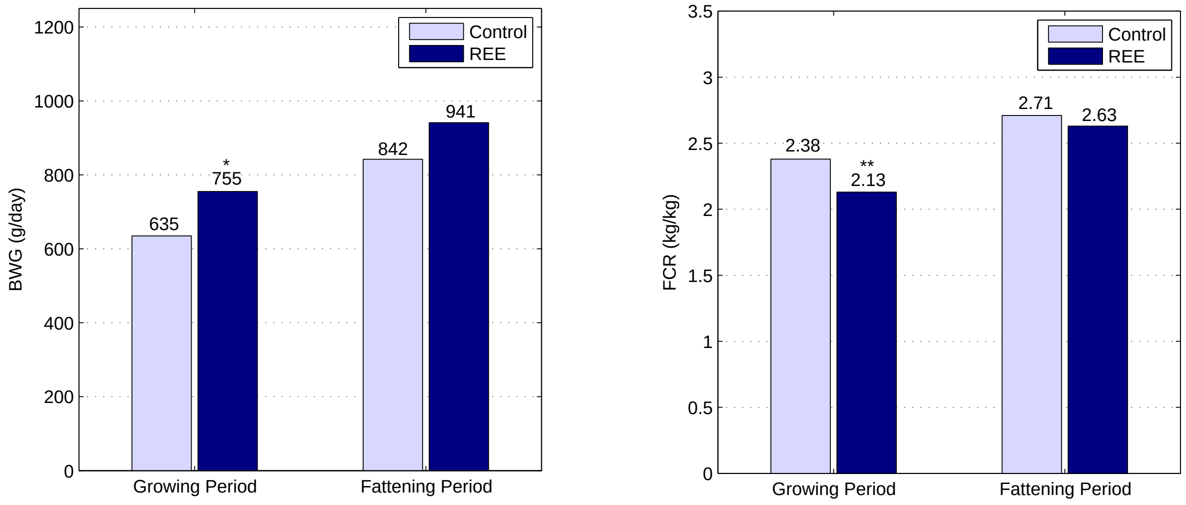
Hence, one feeding trial was conducted on 48 growing and fattening pigs (German Landrace pig x Piétrain pig, 15 - 75 kg), which were allotted into four experimental groups whose feed



(a) Body Weight Gain

(b) Feed Conversion Rate

Figure 12.2: Effects of rare earth (RE) chlorides on body weight gain (BWG in g/day) and feed conversion rate (FCR in kg/kg) of pigs; values with an asterisk ($*$) differ significantly $p < 0.05$ and values with two asterisks ($**$) differ significantly $p < 0.01$ (He and Rambeck, 2000).

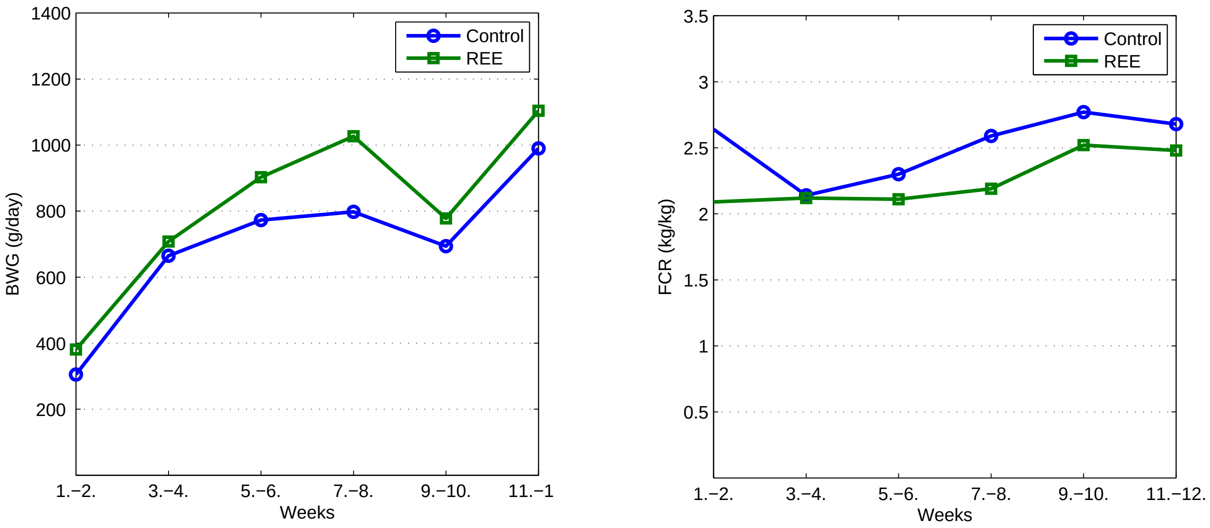


(a) Body Weight Gain

(b) Feed Conversion Rate

Figure 12.3: Effects of rare earth (RE) chlorides on body weight gain (BWG in g/day) and feed conversion rate (FCR in kg/kg) of pigs; values with an asterisk ($*$) differ significantly $p < 0.05$ and values with two asterisks ($**$) differ significantly $p < 0.01$ (He et al., 2001), (Borger, 2003).

was supplemented with 0 ppm (group 1), 300 ppm rare earth chloride (38.00 % $LaCl_3 \cdot 6H_2O$, 52.01 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$ and 6.97 % of other rare earth chlorides; TREO 44.2 %) (group 2), a mixture of 100 ppm $LaCl_3$ and 200 ppm $CeCl_3$ (99.9 % $LaCl_3 \cdot 7H_2O$ and 99 % $CeCl_3 \cdot 7H_2O$; TREO 45.4 %) (group 3) and the last group 200 ppm $LaCl_3 \cdot 7H_2O$ and 100 ppm $CeCl_3 \cdot 7H_2O$ (TREO 44.5 %) (group 4) per kg feed (Eisele, 2003). Though being lower than



(a) Body Weight Gain

(b) Feed Conversion Rate

Figure 12.4: Effects of rare earth (RE) chlorides on body weight gain (BWG in g/d) and (FCR in kg/kg) of pigs presented as line graph (He et al., 2001), (Borger, 2003).

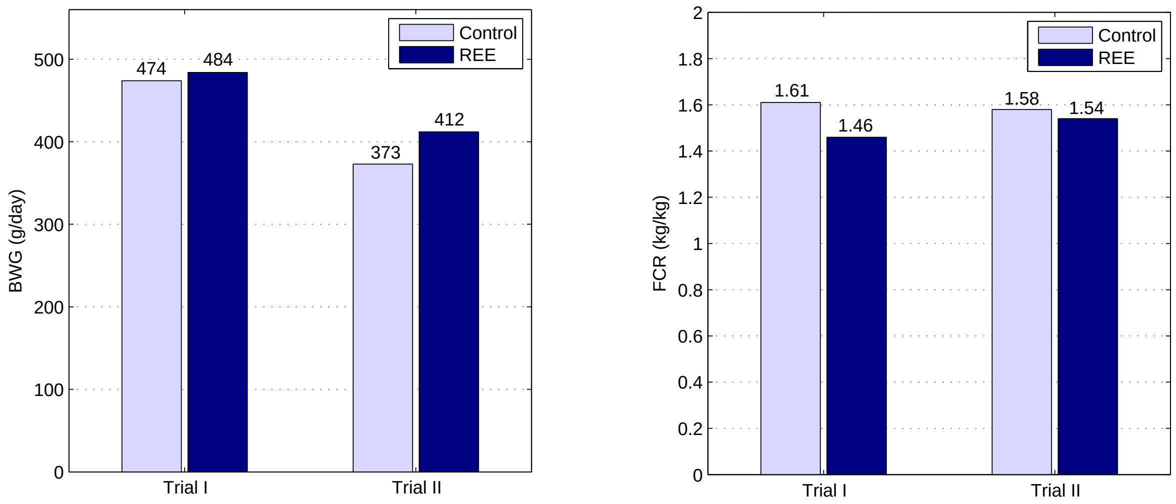
those of previous trials, increases in body weight gain of 4 - 5 % could be observed along with decreases in feed conversion rate of up to 2 % ($p > 0.05$), as shown in Table B.5. Over the whole experimental period, animals of Group 2 presented the highest feed intake, which was 1587 g, thus 3.5 % higher than the control (1529 g). Best results regarding body weight gain were obtained in animals of Group 3, which presented increased daily body weight gain by 5 % (747 g), compared to the control (711 g). At 2.12, Group 3 and 4 had the best feed conversion rates over the whole experimental period, thus being 1.9 % higher than that of the control (2.16).

Considering performance parameters over the whole fattening period, including the period in which rare earths were not supplemented, lowest feed intake and daily body weight gain were observed in animals belonging to the control group, whereas increased feed intake of 5 % was noticed in animals supplemented with 300 ppm rare earth chlorides. Animals of group 4 presented the highest body weight gain, which was 5 % better than the control, while only slightly differences were noticed in feed conversion. However, these results could not be verified statistically.

Nevertheless, performance enhancement was also observed in another feeding experiment (Recht, 2005), in which 48 crossbred piglets (German Landrace pig x Piétrain pig, average initial body weight of 8.3 kg) were divided into four experimental groups: one control group and three treatment groups receiving a diet, which was supplemented with different mixtures of rare earth chlorides at 300 mg/kg feed RE A (99.7 % $LaCl_3 \cdot 6H_2O$; TREO 46.0 %) and RE B (38.0 % $LaCl_3 \cdot 6H_2O$, 52.01 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$; 44.3 %). Consistent with Eisele (2003), increases in feed intake of 3.6 - 4.6 % were observed in animals receiving RE B for ten weeks. Furthermore, after the first seven weeks, body weight of animals belonging to group RE B was increased by 5.9 %. Yet, as can be seen in Table B.6, in contrast to other studies (Rambeck et al., 1999a), (He et al., 2001), (Knebel, 2004), hardly any differences were observed among the experimental groups at the end of the trial.

After performance enhancing effects of rare earth elements were demonstrated under experimental conditions, they could also be confirmed in two field trials conducted on piglets (Swiss throughbred pig) in a basic breeding unit (Zehentmayer, 2002). Increased body weight gain of up to 10 % and improved feed conversion rate of up to 3 % were reported (Eisele, 2003). In both trials, rare earth chlorides were supplemented at 200 mg/kg (38.00 % $LaCl_3 \cdot 6H_2O$, 52.01 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$ and 6.97 % of other rare earth chlorides; TREO 44.2 %) to the diet (weaned feed: 13.2 MJ/kg, 165 mg copper and 300 mg phytase, starter feed: 13.6 MJ/kg, 165 mg copper).

During the first experiment, which lasted sixteen days, both feed intake and feed conversion decreased by 8.0 % and 9.3 %, respectively, in animals supplemented with rare earths, whereas body weight gain increased by 2.1 %. Growth promoting effects were also seen during the second trial, which started right after weaning (initial body weight of 8.3 kg) and ended after thirty days. Body weight gain and feed intake were shown to be improved by 10.2 % and 7.6 %, respectively, while feed conversion decreased by 2.5 %, as presented in Table B.7 and Figure 12.5. Thus, ergotropic effects of rare earths could not only be reproduced in high performance pigs under controlled experimental conditions (Rambeck et al., 1999a), (He et al., 2001), but also under practical field conditions. Additionally, feed conversion was also improved due to rare earth supplementation.



(a) Body Weight Gain

(b) Feed Conversion Rate

Figure 12.5: Effects of rare earth (RE) chlorides on body weight gain (BWG in g/day) and feed conversion rate (FCR in kg/kg) of pigs (Eisele, 2003).

In further studies performed on the effects of dietary rare earth supplementation to pigs, organic compounds have been used. There are two reasons for replacing inorganic rare earths compounds by organic ones. Firstly, this was done because of better handling, since application of rare earth citrates turned out to be easier (Knebel, 2004). Due to their hygroscopic properties, rare earth chlorides only occur as solids in rocks, a fact that complicates their processing since they have to be dissolved in water prior to dietary supplementation. In contrast, rare earth citrates are already available as powders and can be mixed easily with animal feed. Yet there is also another reason. Against the background of better performance enhancing effects of organic rare earth compounds, such as ascorbates or citrates observed in China, it was assumed that the ligand, that is the anion bound to rare earths, may affect growth enhancing effects of rare earths.

On this basis, a study using rare earth citrates in growing pigs (German Landrace pig x Piétrain pig, 8 - 30 kg) was designed to assess the effects of rare earths on performance, in order to evaluate if changing the ligand has any impact on these effects (Knebel, 2004). Indeed better results were obtained when organic rare earth compounds were applied. In contrast to first feeding experiments, which reported increased body weight gain of 5 - 19 % after the supplementation of rare earth chlorides (Rambeck et al., 1999a), (He et al., 2001), Knebel (2004) was able to demonstrate increases in daily body weight gain of 8.6 - 22.6 % in rearing piglets fed a rare earth citrate supplemented diet. With respect to these results, the low number of experimental animals (28 piglets) and thus the lack of significance has to be taken into account.

During this trial, a complete feed was formulated, according to recommendations of the German Agriculture Society (DLG), to which rare earth citrates were added at 0 mg, 50 mg 100 mg and 200 mg per kg feed (5.94 % La, 16.29 % Ce, 3.015 % Pr, 0.32 % Nd; TREO 31.0 %), respectively. A dose-dependent increase in the performance of rearing piglets could be demonstrated over the whole experimental period of six weeks. Feed intake was increased by 4.9 % and 17.2 %, respectively, in piglets receiving rare earth citrates at 100 mg/kg and 200 mg/kg, as shown in Table B.8. Results obtained at 200 mg/kg were significant, however, animals treated with 100 mg/kg rare earth citrates also presented significant increases after the first five and a half weeks. In contrast, those animals receiving rare earth citrates at 50 mg/kg presented similar feed intake and body weight as the control, whereas, highest body weight was again recorded for pigs supplemented at 200 mg/kg rare earth citrates. Compared to the control, rare earth supplementation at 100 mg/kg also increased body weight. Body weight gain was improved by 8.6 - 25.3 %, apart from the low dose group. Best results in daily body weight gain of 8.6 % (568 g) and 22.6 % (641 g), respectively, were reported at 100 mg/kg and 200 mg/kg compared to the control (523 g). In contrast to that, hardly any differences were noticed at an application rate of 50 mg/kg. Results are illustrated in Figures 12.6, 12.7 and 12.8.

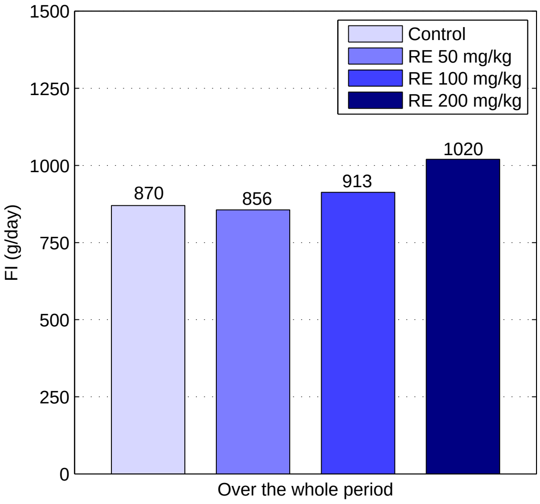
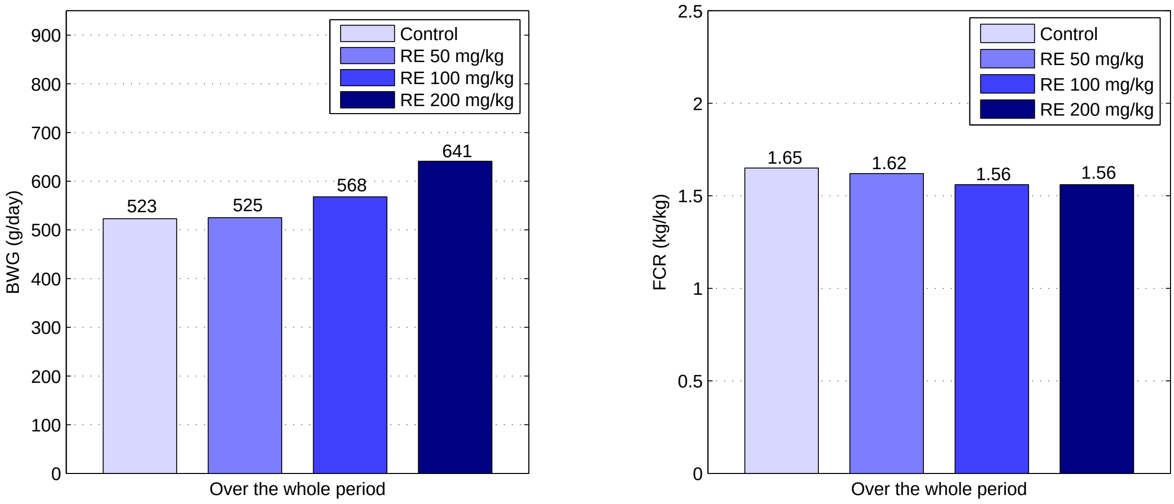


Figure 12.6: Effects of rare earth (RE) citrates on feed intake (FI in g/day) of pigs (Knebel, 2004).

Feed conversion, which describes the amount of feed necessary in order to gain one kilogram body weight, was also calculated in order to find out if increases in body weight were only due to increased feed intake. Improved feed conversion could be demonstrated in all rare earth supplemented groups, whereas, highest improvements of 5.5 % were noticed after supplementation of



(a) Body Weight Gain **(b)** Feed Conversion Rate

Figure 12.7: Effects of rare earth (RE) citrates on body weight gain (BWG in g/day) and feed conversion rate (FCR in kg/kg) of pigs (Knebel, 2004).

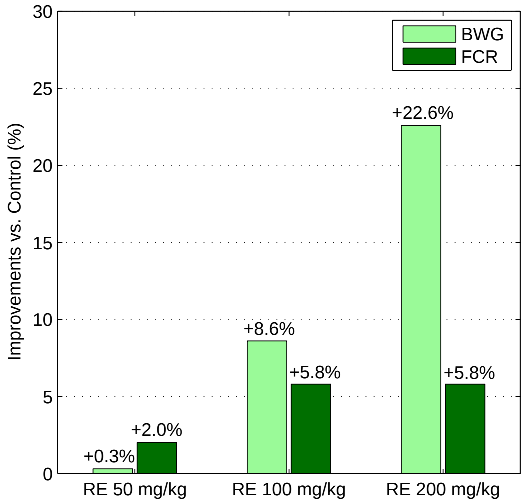


Figure 12.8: Improvements of body weight gain (BWG) (%) and feed conversion rate (FCR) (%) in rare earth (RE) citrate treated pigs versus control animals (Knebel, 2004).

both 100 mg/kg and 200 mg/kg rare earth citrates (1.56), compared to the control (1.65). However, feed conversion could only be calculated as an average of the whole group due to group housing. Thus, individual differences in feed intake may largely affect the total result, thereby reducing significance. Results of this study highly indicate that performance enhancing effects are dose-dependent, as previously reported by Chinese scientists. Slightest improvements, on the one hand, were recorded at 50 mg kg feed, whereas, best results, were achieved when rare earth citrates were applied at 200 mg per kg feed (62.0 mg/kg TREO). The lack of significance caused by high standard deviations is very likely to be due to the low number of experimental animals.

As reported above, feed additives containing rare earth citrates have been granted temporary permission in Switzerland and can be purchased from the company *Zehentmayer* AG, CH - 9305 Berg (Zehentmayer, 2006) as *Lancer*® containing 50 % lanthanides (Miller, 2006). Its composition is described in Table 12.15.

RE-Citrate					
TREO 32,2 %	CeO_2/TREO 66,6 %	La_2O_3/TREO 20,1 %	Pr_6O_{11}/TREO 12,3 %	Nd_2O_3/TREO 1,0 %	
	Ce/material 17,46 %	La/material 5,52 %	Pr/material 3,28 %	Nd/material 0,28 %	Na/material 15,6 %

Table 12.15: Rare earth contents according to total rare earth oxides (TREO) in RE citrate used for the production of *Lancer*®.

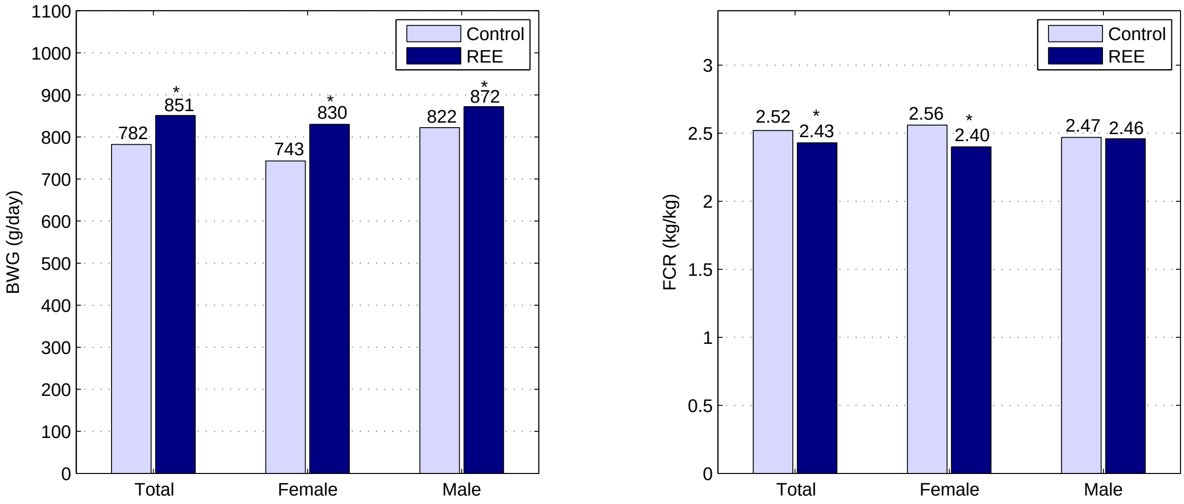
Several farmers, who have already applied *Lancer*® to the feed of their pigs for some time, reported improvements in fecal quality, increases in appetite, state of health as well as in body weight as a result of rare earth supplementation (Zehentmayer, 2004). Furthermore, female fattening pigs seemed to be more relaxed, while growing regular and steady during fattening, whereas in the past, sows used to present a slight performance collapse around 60 kg. Though, these observations are merely subjective, they may still indicate a tendency towards improved animal performance due to rare earth containing feed additives.

Consistent with that, performance enhancing effect were also demonstrated in another investigation on the effects of rare earth citrates, in which *Lancer*® was applied to fattening pigs.

Though demonstrating performance enhancing effects Eisele (2003) and Recht (2005), could not prove their results statistically. However, Kessler (2004) was able to prove significant performance enhancing effects in 24 fattening pigs (German Landrace pig x Piétrain pig), whose diet was supplemented with organic rare earth compounds over the whole fattening period from 25 to 104 kg (Kessler, 2004). Pigs treated with 200 mg/kg feed rare earth citrates, as *Lancer*® 500 (TREO 32.2 %), achieved their final weight of 104 kg within 93 days, whereas animals in the control group needed 102 days, hence, fattening period was shortened by 8 % ($p < 0.05$). Furthermore, average body weight gain was improved by 11 %, being 851 g/d versus 782 g/d in the control, and feed conversion rate, which was 2.4 in the rare earth citrate group, decreased by 4 %, compared to the control (2.5). All differences observed could be proven statistically.

Highly significant values ($p < 0.01$), in terms of decreased fattening period and increased daily body weight gain, were obtained for female pigs, whereas a significance of $p < 0.05$ was reported for barrows. Results are presented in Table B.9 and illustrated in Figure 12.9. A significant ($p < 0.05$ for females and $p < 0.1$ for males) decrease in feed consumption was also observed in both males and females.

Additionally, it could be demonstrated that rare earth citrates increased slaughter yield in males, whereas a slight reduction occurred in females. Yet the amount of valuable meat pieces was increased in females, whereas there was no difference in males. Surprisingly, effects in female animals were more obvious being roughly twice as high as those in barrows, which may indicate that rare earths possibly act on hormonal basis, whereas, on the other hand it may just reflect the fact that performance enhancement in male pigs has already achieved a higher standard compared to that of female pigs.



(a) Body Weight Gain

(b) Feed Conversion Rate

Figure 12.9: Effects of rare earth (RE) citrates on body weight gain (BWG in g/day) and feed conversion rate (FCR in kg/kg) of pigs; values with an asterisk ($*$) differ significantly $p < 0.05$ (Kessler, 2004).

Further investigations on the effects of rare earth citrates were conducted on 40 crossbred piglets (German Landrace pig x Piétrain pig) over a period of 138 days subdivided into rearing, growing and fattening (Miller, 2006). These trials were designed by following Kessler (2004) who observed more pronounced effects on female pigs. Thus, according to weight and sex, piglets were allotted to four experimental groups with ten animals each group receiving experimental diets either with or without rare earth supplementation. Based on barley, maize, wheat and soy meal, a complete diet was fed supplying nutrients at or above requirements (rearing feed: CP 197,8 g, during growing: CP 192,1 g, fattening feed: CP 173,8 g).

During fattening, rare earth citrates (TREO 32.2 %), applied at 300 mg/kg feed could increase body weight in male pigs by 3.4 %, whereas body weight of female did not differ from animals without supplementation, though female pigs presented increased body weights of 4.4 % during the rearing period. Thus, these results could not confirm the sex-dependency described by Kessler (2004). However, increases in body weight of 10 % were found in pigs after the first seven weeks and body weight gain of male pigs was higher than that of the control at any time of the experiment. As shown in Table B.11, increases in body weight gain of 6.1 % ($p < 0.05$), 32.4 % ($p < 0.05$), 7.6 % ($p > 0.05$) were observed during the last three weeks of rearing, the first half of fattening and the whole fattening period, respectively. Females presented increased body weight gain of 18.7 % ($p > 0.05$) at the beginning of the fattening period, whereas no effects of rare earth citrates on body weight gain were observed over the whole fattening period. During rearing, however, increases in body weight gain of 10.9 % and 3.1 % were noticed in both male ($p > 0.05$) and female pigs ($p > 0.05$) (Miller, 2006). The calculation of feed conversion required for scientific purposes was not possible in this experiment, as accurate feed intake per animal could not be determined due to technical difficulties. Nevertheless, the addition of rare earth citrate (TREO 32.2 %) at 300 mg/kg to the diet of piglets could also increase feed intake by 9 % in another study. However, results need to be considered carefully as heavy diarrhoea caused by E. coli occurred during this experiment (Recht, 2005).

Yet another study was performed, applying a mixture of rare earth citrates (TREO 32.2 %) at 200 mg/kg to a commercial diet of piglets (initial body weight of 8.75 kg) for seven weeks. Pigs treated with rare earths presented decreased feed intake over the whole experimental period, while body weight and body weight gain were increased, compared to the control ($p > 0.05$). For feed conversion, best effects were obtained during the second and third week with improvements being in the range of 12.4 to 17.4 %. Over the whole experimental period, feed conversion was still improved by 8.1 %, compared to the control ($p > 0.05$) (Recht, 2005). The results on body weight gain and feed conversion are summarized in Table B.12.

Furthermore, a recent feeding experiment was also focused on investigating growth performance enhancing effects of rare earths on 80 piglets (40 female pigs and barrows, respectively), which were weaned at the age of three weeks. Additionally to a soy-corn-based diet (15.4 MJ ME, 20.4 % crude protein), rare earth citrates (30 % lanthanum, 55 % cerium, 5 % praseodymium and 10 % neodymium; TREO 44.2 %) were applied at 0 mg/kg, 100 mg/kg, 200 mg/kg, 400 mg/kg and 800 mg/kg to piglets over an experimental period of five weeks (Förster et al., 2006). Consistent with dose-dependent effects observed by Knebel (2004), performance in terms of weight gain of piglets was only increased at low concentrations (100 mg rare earth citrates per kg feed, 32.2 mg/kg TREO), whereas inverse effects occurred at high concentrations ($>$ 100 mg) (Förster et al., 2006). As can be seen in Table B.13, piglets supplemented with 100 mg/kg rare earths presented increased daily body weight gain of 6.3 % and an increased final body weight of 3.5 %, compared to the control. Yet at concentrations of more than 100 mg/kg, decreases in daily body weight gain ranging from 4.3 to 10.2 % were observed.

Accordingly, performance enhancing effects of rare earths on pigs were also described to be dose-dependent in another feeding trial performed on 40 barrows (8 - 40 kg, mean age 33 d) (Prause et al., 2005b). During this trial, a commercial diet based on maize, barley, wheat, oats and soy (ME: 14 MJ/kg, CP: 176 g/kg feed) was supplemented with 100 mg sodium-citrate (control), 150 mg rare earth citrates (low dose) and 300 mg (high dose) rare earth citrates. Just as Kessler (2004), Prause et al. (2005b) applied rare earth citrates as *Lancer*® 500 (TREO 32.2 %). Feed conversion rate was shown to be decreased significantly by 9 % in the low dose (150 mg rare earths) and by 7 % in the high dose (300 mg rare earths) (Figure 12.10, Table B.14) group (Prause et al., 2004). It has been suggested that these significant changes may be ascribed to either improved digestibility of nutrients or enhanced absorption as the digestibility of both energy and nitrogen were slightly higher in both treatment groups compared to the control (Table D.1). Best effects were achieved at a concentration of 150 mg/kg feed (48.3 mg/kg TREO).

Over the whole experimental period, however, in contrast to several other studies on pigs (Rambeck et al., 1999a), (He et al., 2001), (Knebel, 2004), (Eisele, 2003), no differences between rare earth supplemented pigs and those in the control group were observed regarding daily body weight gain (Prause et al., 2004). Until now, there is no reasonable explanation as to why body weight gain was not affected in this trial, while feed conversion was significantly improved.

Though several studies demonstrated performance enhancing effects of rare earths on pigs, there are also some trials in which only little or no effects were observed after rare earths were added to the feed of pigs (Böhme et al., 2002a), (Eisele, 2003), (Kraatz et al., 2004), (Gebert et al., 2005). Thus, growth performance enhancing effects of rare earths have not always been obvious.

According to Eisele (2003), only little differences in body weight gain and feed conversion

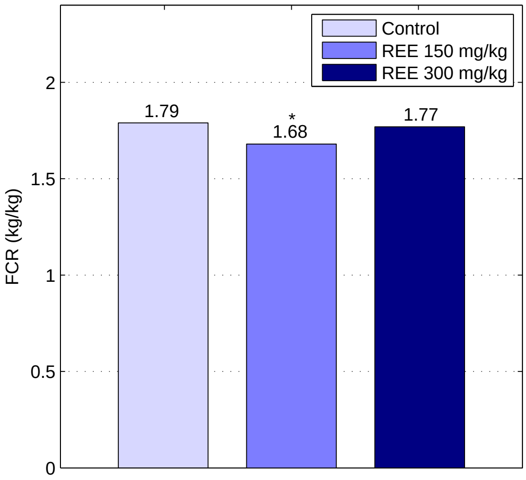


Figure 12.10: Effects of rare earth (RE) citrates on feed conversion rate (FCR in kg/kg) of pigs; with an asterisk ($*$) differ significantly $p < 0.05$ (Prause et al., 2005c).

could be noticed after rare earth chlorides were supplemented at 0 mg (group 1), 300 ppm rare earth chloride (38.00 % $LaCl_3 \cdot 6H_2O$, 52.01 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$ and 6.97 % of other rare earth chlorides; TREO 44.2 %) (group 2), a mixture of 100 ppm $LaCl_3$ and 200 ppm $CeCl_3$ (99.9 % $LaCl_3 \cdot 7H_2O$ and 99 % $CeCl_3 \cdot 7H_2O$; TREO 45.4 %) (group 3), and the last group 200 ppm $LaCl_3 \cdot 7H_2O$ and 100 ppm $CeCl_3 \cdot 7H_2O$ (TREO 44.5 %) (group 4) per kg feed to the feed of piglets (German Landrace pig x Piétrain pig). Small changes were observed over the first five weeks, yet from the seventh week until the end of the trial, feed intake of pigs supplemented was increased by up to 8 %. Increased feed intake by 3.5 %, 3.2 % and 2.5 % ($p > 0.05$), respectively, were recorded in group 2, 3 and 4 over the whole experimental period.

Similar results were obtained regarding body weight gain. During the first four weeks highest body weight gain was determined in the control, whereas in the fifth to sixth week group 3 and 4 presented increased body weight gain of 1.8 % and 5.2 %, compared to the control, while in group 2 body weight gain decreased by 4 %. In week seven and eight, group 2, 3 and 4 showed increases in body weight gain of 5.9 %, 6.1 % and 5.2 %, compared to the control and similar increases of 4.3 %, 6.6 % and 5.9 % in week nine and ten. Better improvements of 16.2 %, 15.3 % and 13.9 % compared to the control were reported for group 2, 3 and 4 in week eleven to twelve, as can be seen in Table B.15. Increases in body weight gain of 4 %, 5 % and 4 % were noticed over the whole experimental period, for group 2, 3 and 4, respectively. Yet, results were not significant at any time of the experiment. However, this might be ascribed to the fact that piglets needed to be treated with antibiotics first due to diarrhea.

Two further feeding experiments were performed to assess the impact of rare earth citrate on growth performance of rearing piglets at high proficiency level (feed conversion rates of 1.4). In both trials, a complete diet based on wheat (62 %) and soy meal (30 %) was formulated providing an energy content of 13.2 MJ per kg feed and crude protein of 21 %. For six weeks, rare earth citrates, were supplemented at 200 mg per kg feed (TREO 32.2 %) to the diet of 22-day-old rearing piglets (Kraatz et al., 2004).

A tendency towards improved growth with respect to all performance parameters was noticed in rare earth treated piglets over the first four weeks of the first trial. Yet, these effects could not be verified statistically over the whole experimental period. Results are shown in Table B.16. At the end of the experiment, a significant increase in feed conversion was observed in animals, whose diet was supplemented with rare earth citrates. However, performance enhancement, as shown during the first four weeks in experiment 1, could not be reproduced in the second trial, which included an additional control group receiving sodium citrate at 200 mg per kg feed to assess whether this organic acid may have any effects. No significant differences between rare earth citrate and sodium citrate supplemented animals could be observed at any time of the experiment, while performance levels were nearly as high as during the first trial (Table B.17).

Hence, efficient effects of rare earths on performance of piglets, as described in former studies (Rambeck et al., 1999a), (He et al., 2001), (Borger, 2003), (Knebel, 2004), (Kessler, 2004), (Eisele, 2003), could only partly be shown during the first experiment conducted by Kraatz et al. (2004), while a reproduction in line with a second experiment was not possible. This may, on the one hand, be ascribed to very high proficiency levels already prevailing in this experiment, whereas, unusually high concentrations of crude protein (21 %) presented in the diet may also account for it. It is generally agreed that protein to energy ratios in diets play a major role in animal nutrition as to optimum growth. Yet, as protein constitutes the most expensive source of energy in feed and commercial feed production, its contents in standard feed are, therefore, often kept as low as possible to maintain optimum growth and feed conversion (Pillay, 1990). Thus, protein contents of 21 % are not generally found in commercially available feed. Therefore, it may be assumed that they would hamper growth promoting effects of any performance enhancing agent. According to Kamphues et al. (1999), crude protein concentrations of 112 - 184 g/kg feed are recommended for four to seven week-old piglets, while, crude protein concentrations of diets used in former trials were usually in the range of 17 - 19 % (Eisele, 2003), (Knebel, 2004), (Prause et al., 2005b), (Miller, 2006).

However, no significant growth promoting effects were also observed by Gebert et al. (2005) after rare earth citrates (*Lancer*® TREO 32.2 %) were applied at 150 mg/kg and 300 mg/kg feed to weaned piglets (initial body weight 8 kg to 22 kg) kept under experimental conditions for five weeks. While no positive effects could be achieved on feed intake and body weight gain, feed conversion was positively influenced by rare earths (Prause et al., 2005c).

Additionally, no effects on animal performance were reported in another feeding experiment performed on 15 fattening barrows (German Landrace pig, 42 - 90 kg) Böhme et al. (2002a). Consistent with other studies, different rare earth concentrates, which were mainly composed of lanthanum and cerium, were imported from China and supplemented at low dosage to the feed of pigs, while results were compared to a negative control. A complete diet based on cereals and soy meal was formulated in compliance with DLG recommendations (Deutsche Landwirtschafts Gesellschaft - German Agriculture Society, ME 14.5 % and CP 18 %) (Halle et al., 2003a) to which rare earths, as different rare earth compounds including nitrates, citrates and ascorbates, were applied at 100 mg/kg. However, the concentration of 100 mg rare earths was calculated on the basis of lanthanum and cerium contents with the sum of both elements being 100 mg/kg feed. Based on the information provided in Table 12.16, contents of TREO ranging from 30.7 to 46.3 % were calculated. Additionally, pure lanthanum chloride ($LaCl_3 \cdot 7H_2O$), manufactured by the German company Merck, was also applied to one experimental group.

	RE ascorbate	RE citrate	RE nitrate	La chloride	control
Concentrations in rare earth concentrates (%)					
La	8.5	9.7	12.3	39.7	-
Ce	16.8	15.7	21.7	-	-
La and Ce	25.3	25.4	34.0	39.7	-
Concentrations in experimental feed (mg/kg)					
La	34.8	30.7	38.8	60.9	0.8
Ce	63.1	58.7	61.8	1.9	1.9
La and Ce	97.9	89.4	100.6	62.8	2.7

Table 12.16: Concentrations of lanthanum and cerium in Chinese rare earth concentrates, manufactured lanthanum chloride samples and in experimental feed (%) or (mg/kg) (Böhme et al., 2002a).

Over the whole experimental period, no improvement of either body weight gain or feed conversion rate was observed (Table B.18). This, however, might be ascribed to the low dosage of only 100 mg/kg feed applied in this trial (Böhme et al., 2002a). According to Chinese studies, only accurate amounts of rare earths presented in the animal diet can improve body weight gain and feed conversion (Rambeck and Wehr, 2005).

Additionally to this trial, balanced tests were performed. Yet none of the rare earth compounds used had any significant effects on the digestibility of nutrients (Böhme et al., 2002b).

Nevertheless, consistent with Chinese reports, significant performance enhancing effects of low dose rare earth supplementation, both inorganic and organic compounds, to the diet could also be demonstrated for pigs under Western conditions. For rare earth chlorides, best results in terms of increased body weight of 19 % and decreased feed conversion rate of 11 % were obtained at a concentration of 300 mg/kg feed (He et al., 2001), whereas for rare earth citrates, increases of up to 22.5 % could be achieved at 200 mg/kg feed (Knebel, 2004). Thus, organic rare earth compounds presented slightly better improvements. Presently, rare earth citrate concentrations of 200 mg/kg feed are recommended for *Lancer*® (200 mg/kg feed RE citrates are included in 400 mg/kg feed *Lancer*®) (Meier, 2003).

12.2.1.2 Poultry

Based on encouraging results achieved in pigs, studies on broilers (Halle et al., 2003b), (Schuller, 2001), (He et al., 2006a) and Japanese quails (Schuller et al., 2002), (Halle et al., 2002b) were performed to verify if these ergo-tropic effects may also occur in poultry. Chinese studies had already described positive effects on broilers, laying and breeding hens (Xia and He, 1997), (Xie and Wang, 1998).

So far, fewer studies have been carried out on poultry than on pigs. However, similar effects, in terms of significant performance enhancement due to dietary supplementation of rare earth compounds, could be observed in broilers (Halle et al., 2003b), (He et al., 2006a). Increases of finial body weights of 7 % were reported in chickens after organic rare earth compounds were supplemented (Feldmann, 2003), (Vetcontact, 2003), (Flachowski, 2003), (Schnug, 2003).

Positive effects, however, could not be achieved in another study in which inorganic rare earth compounds were added to the feed of broilers and Japanese quails (Schuller, 2001), thus indicating the importance of the chemical compound applied. Yet, a very recent study demonstrated that both organic and inorganic rare earth compounds were able to improve growth performance in broilers after oral application at low dosage (He et al., 2006a). Significant improvements of more than 5 % for both feed intake and body weight gain were noticed over the whole experimental period. Thus, in accordance with experiments performed on pigs, performance of chickens could also be enhanced in chickens due to dietary rare earth supplementation. This section will attempt to give a more detailed description of individual trials performed on the effects of dietary rare earth supplementation on poultry.

The effects of rare earths on poultry on possible performance enhancement were first investigated by Schuller (2001) in growing broilers and Japanese quails during both rearing and laying period. In the course of this investigation, which lasted for six weeks, 300 broilers were allotted to one control and four experimental groups, whose diet (ME 12.62 MJ, CP 195.1 g/kg) was supplemented with rare earths in terms of lanthanum chloride (99.7 % $LaCl_3 \cdot 6H_2O$; TREO 46.0 %) or rare earth chlorides (38.0 % $LaCl_3 \cdot 6H_2O$, 52.01 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$ and 6.97 % other rare earth chlorides; TREO 44.3 %) at 150 mg/kg and 300 mg/kg, respectively.

A similar design was used in Japanese quails, to which a rare earth supplemented diet was applied over a period of eight weeks including growing and laying (Schuller, 2001). Rare earths were added as either lanthanum chlorides (99.7 % $LaCl_3 \cdot 6H_2O$; TREO 46.0 %) or as mixed rare earth chlorides (38.0 % $LaCl_3 \cdot 6H_2O$, 52.01 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$ and 6.97 % other rare earth chlorides; TREO 44.3 %) at 75 mg/kg, 150 mg/kg and 300 mg/kg, respectively to the feed (feed during growing period: ME 11.33 MJ, CP 281.8 g/kg; feed during laying period: ME 11.44 MJ, CP 244.9 g/kg), whereas results obtained were compared to a negative control.

The state of health of chickens and quails was not impaired at any time of the experiment and only mild accumulation was determined by NAA in liver and bone. However, neither lanthanum chloride nor the mixture of rare earth chlorides was able to enhance performance in these animal species, as shown in Table B.19 (Schuller, 2001), (Schuller et al., 2002). Hence, no significant effects were observed on either growth or productivity. However, a slight reduction in performance was demonstrated in quails receiving high-supplemented diets 300 mg/kg during the first half of the experiment. Thus, in contrast to positive effects of rare earths on performance of poultry reported in China, during this experiment no effects could be demonstrated on broilers or quails. The absence of positive effects may be attributed to differences in concentrations, as it was reported that only distinct amounts of rare earths supplemented to the diet may cause any effects. Furthermore, variations in animal species, fattening period or keeping and feeding conditions may also play a role. Further investigations using different breeds at different growth stages and intensity were therefore suggested.

In accordance with Schuller et al. (2002), no positive effects of rare earths on fattening performance of turkeys could be either revealed in another feeding trial (Rambeck, 2006a). Yet, studies using organic compounds at very low concentrations instead of inorganic ones, as Schuller (2001) did, were able to prove significant performance enhancing effects in chickens (Halle et al., 2003b), (He et al., 2006a).

In the course of two feeding trials lasting 35 days, it was demonstrated that the supplementation of different rare earth compounds could improve both body weight and feed conversion by 7 % and 3 %, respectively, whereas, improvements in feed conversion of animals receiving rare earth ascorbate were significant, as illustrated in Figures 12.11 and 12.12 (Halle et al., 2002a).

During the first trial performed on 308 one-day-old male broilers, an experimental feed, con-

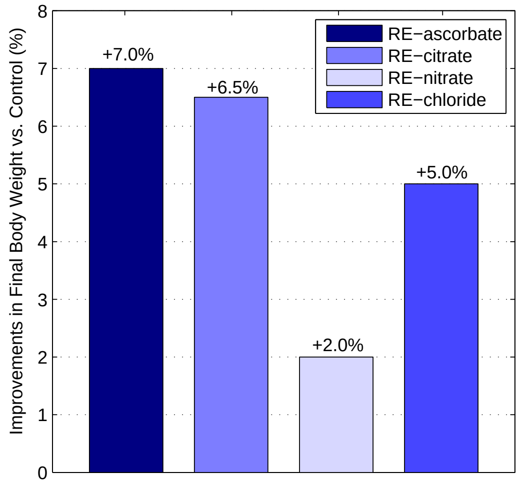


Figure 12.11: Improvements of body weight (BW) (%) in rare earth (RE) treated broilers compared to control animals (Halle et al., 2002a).

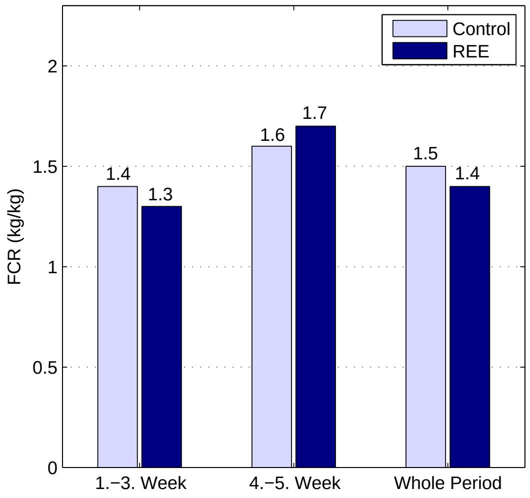


Figure 12.12: Effects of rare earth (RE) ascorbate on feed conversion rate (FCR in kg/kg) of broiler (Halle et al., 2002a).

taining three different rare earth compounds: rare earth ascorbate, rare earth citrate, rare earth nitrate as well as purified lanthanum chloride (44.5 % lanthanum), was applied to the feed. Rare earths were added at a concentration of 100 mg per kg feed (Table 12.17), based upon the sum of lanthanum and cerium, with different rare earth compounds being imported from China and pure lanthanum chloride ($LaCl_3 \cdot 7H_2O$) manufactured by the German company Merck. Thus, following the conversion of rare earth concentrations to total rare earth oxides, contents of TREO were in the range of 30.7 to 52.2 %.

The basal diet applied was based on soy bean and meal, wheat providing all nutrients at or above requirements (ME 12.8 MJ/kg, CP 202 - 213 g/kg). In Table 12.18 the concentration of individual rare earth elements in the experimental diets before and after rare earth supplementation are presented.

	RE ascorbate	RE citrate	RE nitrate	La chloride
La	8.5	9.7	12.2	44.5
Ce	16.8	15.7	21.7	-
La and Ce	25.3	25.4	33.9	44.5

Table 12.17: Analysis of Chinese rare earth samples and of lanthanum chloride, concentrations in %, first experiment (Halle et al., 2002a).

	Control	RE ascorbate	RE citrate	RE nitrate	Lanthanum chloride
First experiment					
La	0.3	45	46	28	94
Ce	0.3	80	85	41	2.6
Pr	0.05	8.16	10.3	4.7	0.28
Nd	0.2	24	2.3	7.3	0.5
Second experiment					
La	0.41	33	35		98
Ce	0.64	63	71		2.7
Pr	0.09	6.50	8.50		0.33
Nd	0.32	20	2.3		0.33
Sm	0.060	0.056	0.041		0.035

Table 12.18: Contents of rare earths (RE in mg/kg) in feed samples with and without supplementation (Fleckenstein et al., 2004).

Performance levels were generally high with body weights of > 2 kg in all treatment groups at the end of the trial and feed consumption of less than 1.5 kg feed per kg increased body weight (Halle et al., 2002b), (Flachowski, 2003). Body weight increases of 7 %, 5.6 %, 2 % and 5 %, respectively, were achieved in animals whose feed was supplemented by rare earth ascorbate, citrate, nitrate and lanthanum chloride. Thus, best performance enhancing effects were achieved in chickens treated with either rare earth ascorbates or citrates. Final body weights in these experimental groups were significantly increased by 5 - 7 %, while feed conversion was improved by 1 - 3 % ($p < 0.05$) (Table B.21). Additionally, feed intake was increased in both treatment groups ($p < 0.05$) (Halle et al., 2002a). A tendency towards increased feed intake, body weight gain and feed conversion was also noticed in lanthanum chloride treated chickens, whose body weight increased significantly by 5 %. Least improvements were presented in those animals supplemented with rare earth nitrates. Hence, dietary supplementation of rare earth elements could improve both body weight and feed conversion significantly in broilers under Western feeding and housing conditions (Fleckenstein et al., 2004). Furthermore, no influence was observed on the composition of the carcass and, compared to the amount of rare earths applied through feed, only little transfer to animal organs occurred. Rare earth contents in animal tissue were below 100 μg/kg, hence three to four magnitudes lower than the amount of rare earths applied through the diet (Flachowski, 2003). Based upon these results, it was concluded that both the type of chemical compound and the concentration of rare earths supplemented seem to have a great impact on their efficiency, since no effects on final weight were noticed after the supplementation of 50 mg rare earth nitrates per kg feed (Halle et al., 2002a).

Also, during the second trial different rare earth compounds were incorporated at a level of 100 mg lanthanum plus cerium per kg feed into the basal diet of one-day-old chicks and tested against a negative control (Halle et al., 2004). However, this time, rare earth nitrates were substituted by another negative control, as this compound did not show any significant effects during the first experiment. Performance level was slightly lower with final weights being decreased by 5 - 10 % compared to the first trial. Furthermore, average feed intake was also lower, which explains lower daily body weight gain and final body weights (Halle et al., 2003c). Consistent with the first trial, body weight was improved significantly by 3 % in chickens supplemented with rare earth ascorbate. Yet, no significant results were achieved in rare earth citrate and lanthanum chloride treated animals ($p > 0.05$). As shown in Table B.20, a tendency towards improved feed conversion was observed in all supplemented groups (Halle et al., 2003c). As to these results, it might be concluded that particularly rare earth ascorbates are able to influence growth of broilers positively with effects being most pronounced on feed conversion (Halle et al., 2003c), (Halle et al., 2003a).

In conclusion, well marked growth enhancing effects of rare earths on broilers could be demonstrated in the first trial with body weights and feed conversion of broiler being improved by 5 - 7 % and 1 - 3 %, respectively, ($p < 0.05$) at the end of fattening. Significant improvements of feed conversion were also observed during the second experiment. Thus, growth promotion in broilers following rare earth supplementation were shown in both studies. Yet effects of rare earths, particularly ascorbate and citrate bounded compounds, seemed to be most pronounced on feed conversion.

Accordingly, He et al. (2006a) also demonstrated performance enhancing effects of rare earths on broilers. Both feed intake and body weight gain were significantly improved by more than 5 % over the whole experimental period. During this experiment, a complete diet based on corn, wheat, soy beans and meal (ME 12.7 MJ/kg, CP 20.8 %) was supplemented with low dosed rare earth compounds originally purchased from China and Switzerland, while the experimental period lasted for five weeks. As presented in Table B.22, both rare earth chlorides ($RECl_3 \cdot 6H_2O$) (14.9 % La, 20.6 % Ce, 1.2 % Pr; TREO 44.3 %) at 40 mg/kg (17.72 mg/kg TREO) and rare earth citrates, *Lancer*®, (5.5 % La, 17.5 % Ce, 3.28 % Pr; TREO 31.9 %) at 70 mg/kg (22.4 mg/kg TREO) were able to enhance performance of broilers. Body weight achieved at the end of the trial was more than two kilogram in all experimental groups, with increasing order of control < rare earth chloride group < rare earth citrate group. Significantly higher body weights were recorded in animals treated with rare earths, compared to the control. During the last two weeks of the trial feed intake and body weight gain were improved significantly by 4.2 % and 4.9 % ($p < 0.05$) in broilers supplemented with rare earth chlorides, whereas over the whole period, improved feed intake and body weight gain of 3.1 % and 3.6 %, respectively, were noticed ($p > 0.05$). In accordance with Halle et al. (2004), better results were achieved due to the application of organic rare earth compounds. Significantly improved feed intake and body weight gain of 5.4 % and 5.0 %, respectively, were noticed over the whole experimental period after rare earth citrates were applied. An illustration is given in Figure 12.13, whereas even better improvements of 6.9 % in feed intake and 6.6 % in body weight gain were observed during the last two weeks of the experiment. Yet, only small differences were noticed with respect to feed conversion rate.

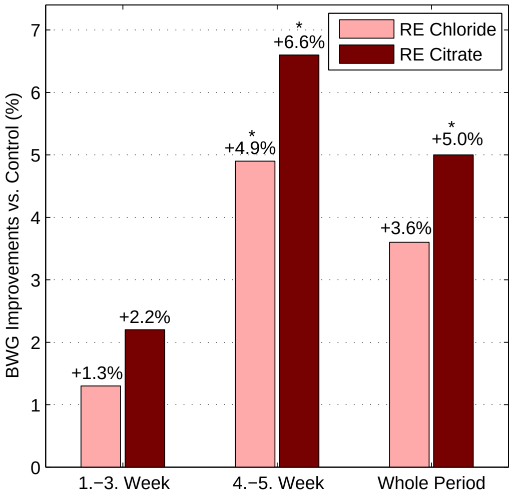


Figure 12.13: Improvements of BWG (%) in rare earth (RE) treated broilers compared to control animals; values with an asterisk ($*$) differ significantly $p < 0.05$ (He et al., 2006a).

Thus it was also possible to demonstrate performance enhancing effects of rare earth application on broilers during this study. As feed conversion rates were not affected, it might be suggested that performance enhancing effects in broilers achieved in this trial may be mainly due to increased feed intake. Yet Halle et al. (2004) reported performance enhancing effects of organic rare earth compounds on broilers to be most obvious on feed conversion rates.

Another study has recently been performed on Japanese quails, whose feed was supplemented with different concentrations (0 ppm, 50 ppm, 100 ppm, 200 ppm, 400 ppm) of rare earth citrates (Zohravi, 2006). However, results have not been completely evaluated yet and can therefore not be presented in this study.

In conclusion, though no effects were observed in pioneer studies performed on broilers (Schuller et al., 2002), other studies have been able to demonstrate performance enhancing effects of rare earth elements on poultry kept under Western conditions. It was noticed that both concentration and chemical form of rare earth compounds seem to play a major role regarding efficiency.

12.2.1.3 Ruminants

Since, in China, performance enhancing effects have been reported for nearly all categories of farming animals (Shen et al., 1991), including beef cattle and dairy cows, feeding trial have also been performed on ruminants under Western conditions particularly veal cattle. Yet, results obtained so far are controversial. Meyer et al. (2006), on the one hand, reported increases in body weight gain and total feed intake of 14.6 % and 7.8 % ($p > 0.05$), respectively, after the addition of rare earth citrates at 200 mg/kg to milk substitute of veal cattle (initial body weight of 44 kg, one-week-old). On the other hand, no effects were reported after rare earth application in another feeding trial performed on veal cattle (initial body weight of 83 kg, average age of 44 days) (Miller, 2006). However, due to different age classes addressed in these two trials, results are not completely comparable to each other. Within the scope of investigating the mode of action, furthermore no effects of rare earths were noticed on ruminal fermentation under RUSITEC conditions (Wehr et al., 2005b).

In this section an overview of these studies will not only introduce the various studies but also permit a brief analysis of these results. In the course of a field trial, a mixture of rare earth citrates was supplemented at 400 ppm *Lancer*® per kg dry matter, that is 200 mg/kg rare earth citrates (64.4 mg/kg TREO), to the milk substitute of 44-day-old veal cattle (312 male calves, red pied cattle or spotted mountain cattle), which was applied by transponder-regulated feeding system (Miller, 2006). In addition to that, a basal diet compromising rearing feed, maize silage, concentrates, soy meal and hay was fed. The rare earth concentration applied was chosen following studies performed on pigs, as there were no recommendations available in either Chinese or Western literature. In accordance with several other animal feeding trials (Schuller, 2001), (Knebel, 2004), (Eisele, 2003), (He et al., 2003a), which reported low oral toxicity, the state of health of calves was not impaired over the whole experimental period as to rare earth application. However, in contrast to reports about performance enhancing effects in pigs, poultry and rats, no effects could be observed in calves due to dietary rare earth supplementation (Miller, 2006).

The lacking of ergo-tropic effects in this trial may be attributed to several factors including conditions under which the trial was performed, the concentration of rare earths applied and the fact that cattle, in contrast to pigs and rats, are not monogastric. Calves were kept under highly optimized feeding and housing conditions with the farm being well organized. It is generally agreed that the effectiveness of several performance enhancing substances highly depends on feeding, keeping and housing conditions. Furthermore, performance enhancing effects due to rare earth supplementation, both in China and Europe, were reported to be dose-dependent. Thus, it might be possible that other concentrations, especially lower ones, are required for ruminants. Yet the absence of performance enhancing effects may also be attributed to the fact that ruminants are not monogastric, thus bearing several differences regarding the digestive system. Accordingly, rare earths have not been able to affect the microbial composition of the rumen. Effects on ruminal fermentation was performed following the assumption that rare earths may exert their performance enhancing effects by influencing the micro flora of the gastrointestinal tract since only very small amounts are absorbed (Evans, 1990). Yet, in ruminants, concentrations of 150 ppm, 750 ppm, 3750 ppm rare earth citrates (TREO 32.2 %) did not influence ruminal fermentation in a in-vitro study using an artificial rumen (RUSITEC - rumen stimulation technique) (Wehr et al., 2005b), (Knebel, 2004). This may indicate that rare earths are not able to affect microbial organisms in the gastrointestinal tract of animals at all. But it may reflect the inability of rare earths to enhance the performance of ruminants under Western conditions. Although significant effects could be demonstrated for pigs and poultry, it might be possible that rare earths may not improve performance in ruminants kept under highly standardized conditions, as shown for veal calves.

Yet, in contrast to that, a tendency towards improved growth due to rare earth supplementation was observed in another trial performed on younger animals. In addition to hay and pelleted concentrates, 24 one-week-old preruminant female Holstein calves were fed 600 g milk substitute (23 % crude protein, 15 % crude fat) at a concentration of 100 g/l water per animal and day supplemented either with or without 200 mg/kg rare earth citrates for six weeks (Meyer et al., 2006). Between the two treatment groups, no difference was observed as to the intake of either milk substitute (consumed at 11 % of body weight, 24.1 kg in the control versus 24.4 kg) or concentrates (7.5 kg in the control versus 7.7 kg). Though not significant, higher average daily body weight gain of 52 g/d (14.6 %) and decreased total feed intake of 69 g/d (7.8 %) were observed in those animals whose milk substitute was supplemented with rare earth citrates (Table B.23). Additionally, the average amount of hay consumed decreased significantly by 45 % (82 g/d) along with rare earth supplementation. A study aiming at reproducing these results is presently in preparation.

Furthermore, effects of rare earths on the performance of dairy cows kept in loose housing on a research farm have currently been investigated in the course of a doctoral thesis. According to race, age and stage of lactation, animals were randomized and allotted to different experimental groups. Rare earths were applied at a concentration of 150 mg/kg concentrates, whereas performance parameters, in terms of milk production, composition of milk and feed conversion rates, were determined over the whole experimental period (Rohn, 2006). This investigation is, however, not yet finished and results may therefore not be presented in this study.

12.2.1.4 Fish

In Chinese literature, performance enhancing effects have also been reported for a great variety of aquatic animals including several species of fish and shrimps (Tang et al., 1998d), (Tang et al., 1997b), (Yang and Chen, 2000), (Shao et al., 1998), (Yang and Chen, 2002). Accordingly, investigations applying rare earths to the feed of farmed fish in pisciculture have also been performed in order to assess their efficiency on growth promotion under high performance conditions (Tautenhahn, 2004), (Renard, 2005). Up to now, it is not possible to reproduce performance enhancing effects of either inorganic or organic rare earth compounds on fish under Western conditions. However, the trials will be introduced briefly.

The effects of rare earths on growth of juvenile Nile tilapia (Oreochromis niloticus) (22-week-old, initial mean weight of 15 g) were investigated over a period of eight weeks (Tautenhahn, 2004). A mixture of rare earth chlorides (46.18 % of total rare earth oxides (TREO) containing 24.7 % La_2O_3, 52.3 % CeO_2, 5.7 % Pr_6O_{11}, 17.2 % Nd_2O_3, 0.1 % Sm_2O_3) was supplemented at 0 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg per kg feed to a vitamin premix, which afterwards was mixed to a commercial crumb trout diet (containing 35 % protein and 12 % fat), while water quality was monitored regularly. No significant differences were noticed between treatment groups and control, indicating that rare earths may not affect fish growth under Western conditions. However, increases in body weight of 18.7 % and decreases in feed conversion 13.3 % were described over the first five weeks after rare earths were applied at a concentration of 50 mg/kg ($p > 0.05$). Yet this result has to be considered carefully, as it is only attributed to very high growth rates observed in one single tank. This tank had to be restocked completely after the first week of the experiment due to deaths following excessive stress and bullying of male fish. Furthermore, it is assumed that missing acclimatization, stocked fish, which presented lower average sizes, were underfed. Thus, compensatory growth probably accounts for increased body weights observed in this tank. Along with the fact that no significant differences were observed in any other treatment group, it can, therefore, be concluded that rare earths did not affect fish growth during this experiment. Nevertheless, feeding rare earths did just as little impair fish health in any way, which corresponds to results obtained in several other feeding studies (Knebel, 2004), (He et al., 2003a), (Schuller et al., 2002), (Zhu et al., 1995), (Lu et al., 2000), (Tang et al., 1998d), (Tang et al., 1997b) and no significant effects were noticed on the body composition.

Consistent with Tautenhahn (2004), performance enhancing effects of rare earths were neither observed in feeding trials performed on carps (Cyprinus carpio L.) and trouts (Oncorhynchus mykiss) chosen as representatives for fresh water fish (Renard, 2005). These trials were conducted in cooperation with the Institute of Fishing of the Bavarian Regional Office of Agriculture. Different concentrations (0 ppm, 100 ppm, 200 ppm, 400 ppm) of rare earth citrate, *Lancer*® (TREO 32.2 %), were added to a commercial diet, which was fed to 800 rainbow trouts (average initial body weight of 145 g) growing from 150 g to 350 g for 12 weeks. The diet chosen was suboptimum regarding its fat content (CF 12 %), as effects of performance enhancing substances are known to be more pronounced under suboptimum conditions. However, though feeding was not optimized, performance enhancing effects, as to body weight gain (average 1.11 %/d) and feed conversion (average 1.24), were not achieved (Reiter, 2005), (Renard, 2005), (Wedekind et al., 2004). Furthermore, no significant differences were observed in fish filet weight, pH value, meat color or fish texture between rare earth supplemented fish and the control.

During the second trial, a commercial pelleted diet for carps (CP 20 %, CF 6 %) was supplemented with 400 ppm rare earth citrates and fed to 3050 carps (initial body weight of 30 g) over two months (June to September). Yet, consistent with previous results, no significant influence of dietary rare earth supplementation was observed on either final body weight or feed conversion. However, it needs to be considered that values of body weight gain and feed conversion varied largely, hence, making a definite statement difficult (Renard, 2005), (Reiter, 2005). Nevertheless, on this basis, performance enhancing effects of dietary supplemented rare earths were achieved in neither rainbow trouts nor in carps.

Improvements in body weight gain of 11.2 - 29.6 % and feed conversion rate of 24 %, as reported in trouts by Chinese scientist (Tang et al., 1997b), could not be reproduced in fish kept under Western conditions. The absence of performance enhancing effects may be attributed to several factors. First of all, feeding trials in China were often conducted under extensive or semi-intensive conditions. Accordingly, initial average body weight of trouts (53 g) (Tang et al., 1997b) was almost 100 g lower than that of trouts used in Western feeding trial (Renard, 2005). Furthermore, feed conversion rates (2.0 - 2.4) in Chinese trials were twice as high compared to Western trials (1.2), that is twice as much feed is necessary to achieve similar weight gain, indicating that feed used in Chinese aquaculture is by far not up to the mark of modern high-performance feed used in Western studies. However, feed quality and especially protein is known to play a major role in fish nutrition, yet, contents are often kept low as protein constitutes the most expensive source of energy in feed (Pillay, 1990). Feed used in Western trials contained quite high protein contents of 40 % (Renard, 2005) suggesting that the absence of positive effects might also be attributed to this. Moreover, as the chemical type of rare earths also seems to be important regarding growth enhancing effects, this may additionally explain the lack of performance enhancing effects. While rare earth chlorides and citrates were used in previous studies (Tautenhahn, 2004), (Renard, 2005), a mixture containing 50 % rare earth methionine and 50 % rare earth lysine was used by Chinese scientists (Tang et al., 1998d), (Tang et al., 1997b). Differences in growth promoting effects due to variations in rare earth compounds have already been described in other Western studies (Halle et al., 2002a), (He et al., 2006a). As a result of both unconsumed feed and faecal excretion, rare earths may also accumulate in intensive recirculating systems. Thus, especially highly soluble compounds, such as chloride, may spread throughout the whole circulating system, hence, affecting results enormously. However, it might also be possible that proficiency levels are already highly advanced in European pisciculture, thus hardly allowing further performance enhancements due to rare earth application.

12.2.1.5 Rats

Yet, in contrast to fish, significant growth promoting effects were achieved in growing rats whose feed was supplemented with rare earths. Feeding trials on rats were conducted following the demonstration of ergo-tropic effects of rare earths in pigs kept under Western conditions (Rambeck et al., 1999a), (He et al., 2001).

It is generally agreed that reproducing these effects in rats would help to establish small rodents as a suitable model in order to further investigate performance enhancing effects of rare earth in animals, including optimum concentrations, effects of different chemical compounds as well as the mode of action.

Both lanthanum and a mixture of rare earths were able to promote body gain weight and feed conversion in growing rats, as shown in a feeding trial performed on four-week-old Wistar rats (average initial body weight of 93 g). Within the scope of this trial, 50 rats were allotted to five experimental groups: one control, two receiving a mixture of rare earth chlorides (38 % $LaCl_3 \cdot 6H_2O$, 52 % $CeCl_3 \cdot 6H_2O$, 3.0 $PrCl_3 \cdot 6H_2O$, 7 % other rare earth chlorides; TREO 44.6 %) at 75 mg/kg (REE low) and 150 mg/kg (REE high), respectively, and another two receiving pure lanthanum chloride (99 % $LaCl_3$; TREO 44.2 %) at either 75 mg/kg (La low) or 150 mg/kg (La low) (He et al., 2003a). Rare earths were supplemented to a complete diet which provided all nutrients at or above requirements (18.1 % crude protein, 4.3 % crude fat, 4.9 % crude fibre). Increases in body weight gain of up to 9 % ($p > 0.05$), compared to the control, were achieved in rats receiving a rare earth containing diet for 18 days. Additionally, feed conversion was improved by 6 - 8 % ($p < 0.01$) using lanthanum chloride at both concentrations (75 and 150 mg/kg feed), whereas, decreases of 3 - 11 % were observed in rats whose diet was supplemented with rare earth chlorides at 75 and 150 mg/kg. Furthermore, a significant increase in feed intake was noticed after rare earth supplementation at 75 mg/kg. In contrast, animals receiving either lanthanum chloride at 75 mg/kg and 150 mg/kg or the mixture of rare earths at 150 mg/kg presented decreased feed intake of 3 %, 3 % and 6 %, respectively, compared to the control. An illustration of the results obtained during this trial is provided in Figure 12.14.

A comparison of these results revealed (Table B.24) that rare earth chlorides were somehow more effective as to growth promotion than sole lanthanum application. It was therefore suggested that the impact of rare earths on animal growth differs with individual elements. Though rare earths are reported to be a chemical homogenous group sharing a great variety of biochemical characteristics, there are still differences among the individual elements. Lanthanum, for example, unlike cerium, is a cation missing unpaired f-electrons, whereas, cerium may assume two oxidation states, Ce^{3+} and Ce^{4+} (Chapter 4).

In addition, blood samples were taken in line with this study, so as to gain information on the mode of action. Though all biochemical blood parameters were within the physiological range, serum glucose was significantly decreased. Additionally, urea and creatine were increased in animals supplemented with rare earth chlorides, which might indicate a possible impact of rare earths on protein metabolism (He et al., 2003a). Yet, total cholesterol, total protein and albumin were unaffected. Furthermore, significant increases in liver enzymes were reported in all supplemented

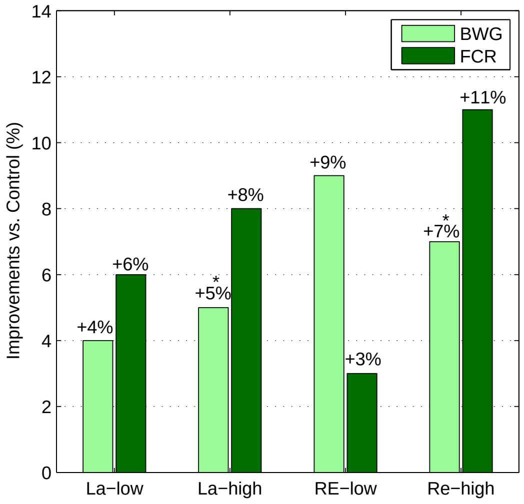


Figure 12.14: Improvements of body weight gain (BWG) and feed conversion rate (FCR) (%) in rare earth (RE) chloride treated rats versus control animals; La-low: lanthanum chloride at 75 mg/kg, La-high: lanthanum chloride at 150 mg/kg, RE-low: rare earth chlorides at 75 mg/kg, RE-high: rare earth chlorides at 150 mg/kg; FCR values of both high supplemented groups were highly significant: $p < 0.01$ (He et al., 2003a).

animals. Enhanced ALP activity due to rare earth supplementation was significant in rats supplemented with rare earth chlorides at 75 mg/kg, whereas those receiving rare earths at 150 mg/kg presented an increased ALP activity of 20 % ($p > 0.05$). This information may help to understand effects of rare earths on animals as shown in Section 12.3. With respect to the reproducibility of performance enhancing effects of dietary supplemented rare earths in growing rats, they have been proven suitable for the study of the effects of orally applied rare earths on animals and hence were chosen for further research projects.

Following reports of better growth enhancement due to the application of organic rare earth compounds instead of inorganic ones (Knebel, 2004), (Kessler, 2004), (Halle et al., 2004), it was suggested that both bioavailablility and performance enhancing effects of rare earths might be affected by the chemical form used, that is the anion bound. Thus, feeding trials on rats were recently performed in order to investigate as to how the anion, to which rare earths are bound, may affect the efficiency of rare earths regarding performance enhancement (Kaplirz, 2006), (van Gemmeren, 2008). In line with these trials, various rare earth compounds, including rare earth citrates, carbonates and chlorides, were supplemented at different concentrations to the diet of four-week-old rats (Wehr et al., 2005a). Though studies are not completely evaluated yet, it has been shown that orally supplemented rare earths were able to improve both body weight gain and feed conversion. However, effects differed with both type and concentrations. This strongly supports previous assumption that both type and concentration constitute two important factors influencing the magnitude of performance enhancing effects in animals.

In contrast to previously conducted studies, no effects on body weight and feed intake were reported in recently performed feeding experiments on four-week-old mice, whose diet was supplemented with cerium at 20 mg/kg and 200 mg/kg (Kawagoe et al., 2005).

Further experiments using rats as small animal models in order to investigate optimum concentrations, effects of the chemical type as well as the mode of action of rare earths are currently conducted at the University of Munich (Kaplirz, 2006), (van Gemmeren, 2008). However, studies are either not completed or not fully evaluated at this time, hence, results may not be presented in this study. As information on the mechanism underlying performance enhancing effects are still patchy, it is expected that further studies will provide additional details. Current proposals as to how rare earths may exert their effects are discussed in Section 12.3.

To sum up all animal feeding experiments conducted under Western conditions, it could be demonstrated that rare earths were capable of enhancing animal performance, though not in all animals species. A summary of Western feeding trial performed on farming animals and rats is presented in Table 12.20. However, coinciding with Chinese reports, organic compounds seem to provide better results than inorganic ones. Possible explanations for this are given along with information on absorption and bioavailability of rare earths in animals in the next section. In addition, the composition of individual rare earth elements within the supplementation may also affect performance enhancement of rare earths, as Rambeck et al. (1999a) and He et al. (2003a) presented better results when a mixture of rare earth chlorides (La, Ce, Pr, Nd) was applied instead of pure lanthanum chloride. Furthermore, a comparison between results obtained and concentrations applied, as shown in Tables 12.19 and 12.20, reveals that optimum concentrations vary with the animal species. Thus, for pigs best results were achieved at concentrations of approximately 65 mg/kg feed referred to TREO, whereas lower amounts may be recommended for poultry (20 mg/kg to 30 mg/kg feed TREO). Yet, a more thorough comparison on concentrations with respect to the anion is given in Chapter 13.

Reference	Animal species	RE species	RE doses (mg/kg)	TREO (mg/kg)
Pigs				
Rambeck et al. (1999a)	piglets	La - Chloride (TREO 46.0 %)	75	34.5
			150	69.0
		RE - Chloride (TREO 44.2 %)	75	33.2
			150	66.3
He et al. (2001), Borger (2003)	pigs	RE - Chloride (TREO 44.2 %)	300	132.6
Böhme et al. (2002a)	pigs	RE - Chloride (TREO 46.3 %)	100	46.3
		RE - Nitrate (TREO 41.1 %)	100	41.1
		RE - Ascorbate(TREO 30.6 %)	100	30.6
		RE - Citrate (TREO 30.7 %)	100	30.7
Eisele (2003)	piglets	RE - Chloride (TREO 44.2 %)	300	132.6
		La and Ce Chloride (TREO 45.4 %)	100 + 200	136.1
		La and Ce Chloride (TREO 44.5 %)	200 + 100	133.4
	pigs	RE - Chloride (TREO 44.2 %)	200	88.4
Kessler (2004)	pigs	RE - Citrate (TREO 32.2 %)	200	64.4
Knebel (2004)	piglets	RE - Citrate (TREO 31.0 %)	50	15.5
			100	31.0
			200	62.0
Prause et al. (2004)	piglets	RE - Citrate (TREO 32.2 %)	150	48.3
			300	96.6
Kraatz et al. (2004)	pigs	RE - Citrate (TREO 32.2 %)	200	64.4
Recht (2005)	pigs	La - Chloride (TREO 46.0 %)	300	138.0
		RE - Chloride (TREO 44.2 %)	300	132.6
		RE - Citrate (TREO 32.2 %)	200	64.4
Miller (2006)	pigs	RE - Citrate (TREO 32.2 %)	300	96.6
Förster et al. (2006)	piglets	RE - Citrate (TREO 44.2 %)	100	32.2
			200	64.4
			400	128.8
			800	257.6

continued on next page

Reference	Animal species	RE species	RE doses (mg/kg)	TREO (mg/kg)
Poultry				
Schuller (2001)	broiler	RE - Chloride (TREO 46.0 %)	150	69.0
			300	138.0
		RE - Chloride (TREO 44.2 %)	150	66.3
			300	132.6
	Japanese quails	RE - Chloride (TREO 46.0 %)	75	34.5
			150	69.0
			300	138.0
		RE - Chloride (TREO 44.2 %)	75	33.2
			150	66.3
			300	132.6
Halle et al. (2002a)	broiler	RE - Chloride (TREO 52.2 %)	100	52.2
		RE - Nitrate (TREO 41.1 %)	100	41.1
		RE - Ascorbate (TREO 30.6 %)	100	30.6
		RE - Citrate (TREO 30.7 %)	100	30.7
He et al. (2006a)	broiler	RE - Chloride (TREO 44.2 %)	40	17.7
		RE - Citrate (TREO 31.9 %)	70	22.4
Fish				
Tautenhahn (2004)	fish Nile tilapia	RE - Chloride (TREO 46.2 %)	50	23.1
			100	46.2
			200	92.4
			300	138.6
			400	184.8
Renard (2005)	rainbow trout	RE - Citrate (TREO 32.2 %)	100	32.2
			200	64.4
			400	128.8
	carps	RE - Citrate (TREO 32.2 %)	400	128.8

continued on next page

Reference	Animal species	RE species	RE doses (mg/kg)	TREO (mg/kg)
Ruminants				
Miller (2006)	calves	RE - Citrate (TREO 32.2 %)	200	64.4
Meyer et al. (2006)	Holstein calves	RE - Citrate (TREO 32.2 %)	200	64.4
Rats				
He et al. (2003a)	rats	RE - Chloride (TREO 44.6 %)	75	34.2
			150	68.5
		La - Chloride (TREO 44.1 %)	75	33.1
			150	66.2

Table 12.19: Western feeding trials as to rare earth concentrations including total rare earth oxides.

Reference	Animal Species	RE species	RE doses (mg/kg)	effect (%)	
Pigs					
Rambeck et al. (1999a)	piglets	RE - Chloride	75	+ 2 BWG	- 4 FCR
			150	+ 5 BWG	- 7 FCR
		La - Chloride	75	+ 2 BWG	- 5 FCR
			150	+ 0 BWG	- 3 FCR
He et al. (2001), Borger (2003)	piglets	RE - Chloride	300	+ 19 BWG	- 11 FCR
	pigs	RE - Chloride	300	+ 12 BWG	- 3 FCR
Böhme et al. (2002a)	pigs	RE - Chloride	100	- 3.6 BWG	-
		RE - Nitrate		- 3.6 BWG	-
		RE - Ascorbate	100	- 3.4 BWG	-
		RE - Citrate		- 1.1 BWG	-
Eisele (2003)	piglets	RE - Chloride	300	+ 4 - 5 BWG	-
	pigs	RE - Chloride	200	+ 3 - 10 BWG	- 2 - 9 FCR
Kessler (2004)	pigs	RE - Citrate	200	+ 8.8 BWG	- 3.6 FCR
Knebel (2004)	piglets	RE - Citrate	50	+ 0.4 BWG	- 1.8 FCR
			100	+ 8.6 BWG	- 5.5 FCR
			200	+ 22.6 BWG	- 5.5 FCR
Prause et al. (2004)	piglets	RE - Citrate	150	+ 0 BWG	- 9 FCR
			300	+ 0 BWG	- 0 FCR
Kraatz et al. (2004)	piglets	RE - Citrate	200	- 3 BWG	- 1 FCR
				+ 1 BWG	+ 3 FCR
Recht (2005)	piglets	RE - Chloride	300	+ 4.6 BWG	- 2.6 FCR
		La - Chloride	300	+ - 9.3 BWG	- 4.4 FCR
		RE - Citrate	200	+ 3.5 BWG	- 7.0 FCR
Gebert et al. (2005)	piglets	RE - Citrate	150	- 4 BWG	- 1 FCR
		RE - Citrate	300	- 4 BWG	- 4 FCR
Miller (2006)	pigs	RE - Citrate	300	+ 11 BWG	-
Förster et al. (2006)	piglets	RE - Citrate	100	+ 6.3 BWG	-
			200 - 800	- 4.3 - 10.2 BWG	-

continued on next page

Reference	Animal Species	RE species	RE doses (mg/kg)	effect (%)	
Poultry					
Schuller (2001)	broiler	RE - Chloride	150, 300	no effect on BWG	or FCR
	Japanese quails	RE - Chloride	75, 150, 300	no effect on BWG	or FCR
Halle et al. (2002a)	broiler	RE - Chloride	100	+ 5 BW	-
		RE - Nitrate	100	+ 2 BW	-
		RE - Ascorbate	100	+ 7 BW	-
		RE - Citrate	100	+ 6.5 BW	-
He et al. (2006a)	broiler	RE - Chloride	40	+ 4.2 BWG	-
				- 4.9 FI	-
		RE - Citrate	70	+ 5.4 BWG	-
				- 5.0 FI	-
Fish					
Tautenhahn (2004)	fish Nile tilapia	RE - Chloride	50	+ 18.7 BWG	- 13.3 FCR
			100 - 400	no effects	-
Renard (2005)	rainbow trout	RE - Citrate	100, 200, 400	no effects on BWG	or FCR
Renard (2005)	carps	RE - Citrate	400	no effects on BWG	or FCR
Ruminants					
Miller (2006)	calves	RE - Citrate	300	no effects on BWG	or FCR
Meyer et al. (2006)	Holstein calves	RE - Citrate	200	+ 14.6 BWG	- 7.8 FCR
Rats					
He et al. (2003a)	rats	RE - Chloride	75	+ 9 BWG	- 3 FCR
			150	+ 7 BWG	- 11 FCR
		La - Chloride	75	+ 4 BWG	- 6 FCR
			150	+ 5 BWG	- 8 FCR

Table 12.20: Western feeding trials; FCR: feed conversion rate, BWG: body weight gain.

12.2.2 Safety to Animals and of Animal Products

12.2.2.1 Oral Toxicity

Dietary application of rare earths did not impair or harm the state of health of any animal tested within the scope of European feeding trials (Rambeck et al., 1999a), (He et al., 2001), (Schuller et al., 2002), (Eisele, 2003), (Knebel, 2004), (Fleckenstein et al., 2004), (Miller, 2006), (Meyer et al., 2006). This coincides with reports from Chinese literature as well as with general literature on oral toxicity of rare earth elements (Durbin et al., 1956), (Ji et al., 1985b), (Evans, 1990), (FairweatherTait and Dainty, 2002), (Fiddler et al., 2003a). It is known that the toxicity of rare earths highly depends on the way of administration and, furthermore, varies with the chemical compound applied. While high toxicity has been reported after intra-venous injections, oral toxicity is considered to be very low (Durbin et al., 1956), (Haley, 1965), (Hutcheson et al., 1975), (Ji et al., 1985b). According to the Hodge-Sterner classification system, rare earths are generally regarded as substances of low toxicity (Haley, 1979).

Along with the wide-spread use of rare earths in several technical areas (Chapter 9) over the last 50 years, various studies were performed investigating whether rare earths may impair human or animal health so as to assure their safe application. Yet, further studies on rare earth toxicity were conducted with the introduction of rare earths for medical purposes (Chapter 10). Detailed information on rare earth toxicity is provided in Chapter 6.

Regarding oral application, toxicological studies revealed that rare earths pose a similar health risk as sodium chloride, that is usual table salt (Wald, 1990), hence, already indicating the safe use of rare earths as feed additives in animals. Low oral toxicity could also be confirmed in numerous experiments conducted on various animal species, including rats (Durbin et al., 1956), (Ji et al., 1985b), (Cochran et al., 1950), mice (Haley, 1965), (Hutcheson et al., 1975), Shimomura et al. (1980), (Ji et al., 1985b), guinea pigs (Ji et al., 1985b), apes (Hutcheson et al., 1975) and other mammals (Venugopal and Luckey, 1975). According to Cochran et al. (1950) and Bruce et al. (1963), no toxic effects were observed in rats after oral administration of either rare earth oxides at 1000 - 10000 mg/kg body weight or rare earth sulphates at 5000 mg/kg body weight, while oral LD_{50} of 0.9 - 1.75 g/kg body weight was described for rare earth nitrates in rats (de Boer et al., 1996) and no observed adverse effect levels (NO(A)EL) of 300 mg/kg body weight per day were determined for rats.

Similar LD_{50} of 4200 mg/kg and 4500 mg/kg were reported for lanthanum chloride in rats (Cochran et al., 1950) and praseodymium chloride in mice (Haley, 1965). Likewise, several other studies also reported LD_{50} of rare earth compounds to be beyond 1 g/kg body weight (Venugopal and Luckey, 1975), (Ji et al., 1985b). Yet, it has to be considered that oral toxicity varies within the chemical form, in which rare earths are applied (Evans, 1990). Thus, even 10 g/kg La_2O_3 or 5 g/kg lanthanum sulfate per body weight did not cause any toxic effects, while lanthanum ammonium nitrate was a little more toxic, yet still presenting an oral LD_{50} of 3400 mg/kg. Nevertheless, it can be concluded that oral application of simple rare earth compounds (oxides, chlorides, nitrates, sulphates, acetates etc.) is of low toxicity with LD_{50} ranging from 830 mg/kg to 10 g/kg body weight (Richter, 2003). A summary of LD_{50} values determined in various studies is given in Table 6.1. In contrast to high LD_{50} values after oral application, LD_{50} values of 10 - 100 mg/kg body weight were reported for intravenous application of rare earth elements. However, low toxicity of orally applied rare earths was not only reported in comparatively older literature going back to the 1950s, but also confirmed in various recently performed feeding trials. According to Feng et al. (2002), no death and only minor deviations in blood parameters occurred in rats after

La_2NO_3 was orally applied at 0.1 mg/kg, 0.2 mg/kg, 10 mg/kg, 20 mg/kg for three to six months. To that effect, a safety dose of 0.1 - 0.2 mg/kg body weight was suggested for lanthanum nitrate. Furthermore, comprehensive toxicological long-term studies, performed within the scope of registering lanthanum carbonate as new phosphate binding agent in human medicine, reported that oral intake of up to 3 g lanthanum carbonate per person per day was well tolerated over a period of four years, not presenting any adverse or toxic effects (Joy and Finn, 2003), (Harrison and Scott, 2004), (Locatelli et al., 2003), (Ritz, 2004). Thus, in conclusion, compared to LD_{50} values of more than 1 g/kg body weight, application of rare earths as feed additives to animals, regarding concentrations of 200 mg/kg feed, is considered to be safe.

12.2.2.2 Absorption of Rare Earth Elements by the Gastrointestinal Tract

Low oral toxicity of rare earths is probably attributed to poor gastrointestinal absorption, as it is known that only tiny amounts of rare earths are absorbed from the gastrointestinal tract of adults (Hamilton, 1949), (Cochran et al., 1950), (Durbin et al., 1956), (Haley, 1965), (Haley, 1979), (Eisele et al., 1980), (Ji et al., 1985b), (Evans, 1990), (Fiddler et al., 2003a), (D'Haese et al., 2003), (Rambeck et al., 2004), (Hutchison and Albaaj, 2005), hence, only a very small amount is physiological available. Historical papers (Baehr and Wessler, 1909) already described low absorption rates of rare earths after oral application. Consistent with that, retention values below 0.05 to 0.4 % of orally administered doses were determined in rats (Hamilton, 1949), while poor gastrointestinal absorption was also described in mice after intra-gastrical application of cerium chloride (Stineman et al., 1978). According to Norris et al. (1956), 90 % of orally single-dosed $^{91}YCl_3$ was found in the feces within the first three days of a rat feeding experiment, whereas complete elimination occurred after one week. Daily application of $^{91}YCl_3$ for six months revealed retention values of 0.4 % of the total administered dose, thus being in the same range as those reported by Hamilton (1949). Similarly, Cochran et al. (1950) described a total retention of 0.3 % for orally applied doses of lanthanum chloride in rats. Insignificant absorption was also observed after rare earths were supplemented with feed to rats, whereas, less than 0.1 % of the administered dose was shown to be absorbed by the gastrointestinal tract (Durbin et al., 1956). Durbin et al. (1956) suggested that the insolubility of lanthanum at physiological pH might be an important factor contributing to difficult absorption. Thus, for rats in general, gastrointestinal absorption of rare earths is supposed to be less than 0.05 % (Arvela, 1977).

Similar results could be obtained in dogs (Hutchison and Albaaj, 2005), chickens (Mraz et al., 1964), (Fleckenstein et al., 2004) and quails (Robinson et al., 1978). Hutchison and Albaaj (2005) reported that only 0.00005 % of orally applied lanthanum carbonate was absorbed in the canine gastrointestinal tract, whereas, approximately 94.5 % and 1.14 %, respectively, were detected in feces and urine, while in rats, 99.36 % of the administered doses was recovered in feces. An absorption factor ranging from 10^{-3} to 10^{-4} was determined in line with a feeding trial performed on chickens (Fleckenstein et al., 2004), as in relation to the total sum of 300 mg rare earths digested, only small rare earth contents were detectable in animal tissues. However, minimum systemic absorption was not only observed in animals but also in humans. Fiddler et al. (2003a) demonstrated very low plasma levels of less than 1 ng/ml after a cumulative dose of 15 g lanthanum carbonate was orally applied. Accordingly, negligible absorption from the gastrointestinal tract, in terms of less than 0.001 %, was described for lanthanum carbonate given with food (Steward and Frazer, 2002). Similar results were reported in subsequent studies (Joy et al., 2003), (Locatelli et al., 2003), (De Broe and D'Haese for the Lanthanum Study Group, 2004), (Harrison and Scott, 2004), (Behets et al., 2004b). In addition to poor absorption, Pennick et al. (2004) suggested that extensive binding of absorbed lanthanum to plasma protein further limits its potential for adverse effects as well as its distribution to tissues.

12.2.2.3 Bioavailability of Rare Earth Elements

Absorption of ionic rare earths has been reported to occur in the small intestine, particularly in the ileum (Kostial et al., 1989), (Sullivan et al., 1984). The existence of special absorption mechanisms in stomach and intestines was demonstrated for metals (Tallkvist et al., 2001), but not particularly for rare earth metals. However, it has been suggested that cerium and lanthanum may be swallowed or phagocytosed by cells in form of particles or macromolecule bound species, thereby crossing the cell membrane (Szasz et al., 1978), (Cheng et al., 1999). Following poor absorption, only tiny fractions of rare earths are considered to be physiological available. Yet, variations as to both absorption and bioavailablity may occur with the chemical form of rare earths applied as well as with the age of the animal.

Since better performance enhancing effects were achieved by rare earth citrates compared to rare earth chlorides, it has been proposed that organic compounds may be better assimilated than inorganic ones. Ji et al. (1985b) suggested that water-soluble rare earth compounds, on the one hand, were almost completely hydrated within the digestive tract, hence, forming hydroxide colloids, which were hardly absorbed, whereas, complexed rare earth compounds, on the other hand, may have presented slightly higher absorption rates. As to current knowledge, there are no studies available on the impact of the chemical compound on rare earth bioavailability in animals, whereas conflicting results were reported as to better bioavailability of other organic metal compounds, such as e.g. zinc. Hence, zinc, originating from organic sources, was described to be less (Schell and Kornegay, 1996), equal (Hill et al., 1986) or more available (Matsui et al., 1996) compared to zinc sulfate in pigs. Though Ammerman et al. (1995) reported different bioavailability values for chelates and complexes of various elements, no advantages were observed for organic zinc sources. Accordingly, no significant differences were observed between organic and inorganic zinc compounds in chicks and lambs (Cao et al., 2000a). For cupric compounds, it is known that cupric sulfates provide a higher bioavailability than cupric oxides and carbonates.

However, bioavailability is not an inherent characteristic of a specific source of any mineral element. It describes the absorbed fraction of ingested nutrients from a particular source that reaches system circulation, thus being available to animal metabolism (Ammerman et al., 1995). Bioavailability is therefore reflected by experimentally determined values, which strongly depend on both the condition of a specific test situation and the animal tested (Guo et al., 2001).

Nevertheless, reports of greater bioavailability of organic compounds compared to inorganic ones, such as in case of zinc (Spears, 1989), (Wedekind et al., 1992), lead to increased use of organic forms in feed industry. This may also explain enhanced application of organic rare earth compounds in China. Yet, not only the anion itself but also the strength of bonding seems to influence rare earth bioavailability. As to rare earth chemistry (Chapter 4), it has been reported that, despite their high affinity for ionic binding, rare earth complexes, especially chelates, constitute stronger compounds. Complete dissociation is therefore expected to occur for ionic compounds under acidic conditions as, e.g., found in the stomach of animals, thus, leaving ions, which may either form other compounds or be absorbed by the gastrointestinal tract. But solubilities of salts of light rare earths may differ from those of heavy rare earths (Möller, 1963). Dissociation of rare earth complexes, on the contrary, is less likely to occur, hence, hampering both gastrointestinal absorption and interaction with other biological molecules. Accordingly, a quick passage has been reported for highly stable chelator-rare earth complexes after oral application, therefore, being excreted unchanged in the feces (Evans, 1990), (Hirano and Suzuki, 1996). Similar results were obtained by Kostial et al. (1989), who found that chelating agents may reduce the retention of ^{141}Ce from the gastrointestinal tract of rats, indicating that rare earth chelates are absorbed to a lower extent.

Organic chelates may be classified as strong, moderate and weak chelates with most proteinates used in commercial diets being weak chelates. Moderately strong chelating ligands, such as amino acids, have been suggested to improve the bioavailability of transition metals. However, present techniques may neither determine the degree of chelation and complexation of mineral elements to organic ligands in commercial samples, nor trace the absorption and metabolic fate of minerals in organic products. Yet, the degree to which organic ligands remain bound to the metal as well as the behavior under physiological pH conditions are considered most important as to determine the physiological function of chelated and complexed metals. Experiments revealed that chelation effectiveness decreases at lower pH values. Most metal chelates involving amino acids or proteins dissociated at a pH of either less than 3 or greater than 9, hence, becoming similar in behavior to inorganic materials. On this basis, it is unlikely that organic metal products remain chelated under pH conditions prevailing in the gastrointestinal tract (Holwerda et al., 1995), (Cao et al., 2000a), (Guo et al., 2001). PH values of 0.5 to 2.5 and 3.0 to 7.2, respectively, are determined in gastric juice and intestine (Leach and Patton, 1997), while the stomach of pigs presents a pH of 4.5 ± 0.3 (Dintzis et al., 1995). In rumen pH values range from 7.0 (on forage) to 4.6 (on high grain diet) (Hoover and Miller, 1991), whereas diets leaving the abomasum of cattle have a pH of 2 - 3 (Church, 1969).

Moreover, continuous addition of drinking water, saliva and other digestive juices promotes the dilution of metal compounds within the intestines, thus, increasing solubilization. It is therefore assumed that only a small amount of free ions is available in the gastrointestinal tract, as there are so many ligands on-hand for (re)chelation, while in order to be absorbed, organic metal sources also have to become soluble prior to reaching absorption sites (Guo et al., 2001). Additionally, it must be considered that products may, on the one hand, be quite soluble, while, on the other hand, still remain complexed or chelated, which, theoretically, improves absorption by animals and, thus, provides greater bioavailability. Finally, no binding statement may be made at present as to whether organic rare earth compounds are more available than inorganic ones.

However, several studies reported higher absorption rates for rare earths from the gastrointestinal tract of neonates rats compared to adults (Sullivan et al., 1984). Absorbed amounts of ^{147}promethium determined in newborns were between 4 and 1000 times higher than in adults. After oral application of ^{144}Ce, 91 % of the administered dose were shown to be absorbed from the digestive system of newborn pigs (Mraz and Eisele, 1977), (Haley, 1979). In contrast to that, no absorption of rare earths was observed from the gastrointestinal tract of suckling rats (Marciniak et al., 1996). Yet, Eisele et al. (1980), who investigated the uptake of ^{144}Ce from the gastrointestinal tract of neonatal mice, rats and pigs, also found that, though poorly absorbed by adults, cerium was absorbed to a considerable extent by neonates of all three species. The group of mice and rats dosed within the first six hours after birth presented initially greater absorption and retention than those supplied between six and twenty-four hours. Yet, differences disappeared with time, being minimal after three weeks. These findings are in accordance with general observations of higher intestinal absorption of metals in sucklings (Kostial et al., 1978), (Eklund et al., 2004).

A possible explanation might be that, due to higher nonspecific phagocytic activity, epithelial intestinal mucosa cells of neonates incorporate rare earths to a greater extent (Evans, 1990). Radiochemical measurements performed on neonatal piglets and rats revealed highest retention levels of promethium in the ileum (Sullivan et al., 1984). Kostial et al. (1978) also described the lower part of the small intestine, that is the ileum, as the site of metal accumulation. However, the magnitude of absorption by newborns may vary within the animal species. For actinides, values obtained in piglets were 1000 times higher, whereas neonatal dogs, guinea pigs and rats absorbed only 100 times more than adults (Sullivan and Gorham, 1983). Furthermore, the gastrointestinal tract of infants was not nearly as permeable to macromolecules as that of pigs. In contrast to that, mice were shown to absorb and retain the most of orally applied cerium compared to rats and pigs, which absorbed the least (Eisele et al., 1980).

Besides age or chemical form, there are also other factors, such as gastrointestinal contents, diets, nutritional status or genotype, which may influence gastrointestinal absorption of metals (Diamond et al., 1997). Accordingly, Sullivan et al. (1986) described increased absorption of ^{147}promethium from the intestinal tract of fasting rats. Further increases were achieved by the addition of mild oxidizing agents, indicating that higher oxidation states may be more readily absorbed. Though ^{147}Pm is unlikely to convert to different oxidation states under conditions prevailing, other lanthanides such as cerium may be more susceptible. Marked increases in transit time of ^{141}Ce and its uptake by the gastrointestinal tract were reported in adult male rats due to milk feeding, compared to fasting or grain feeding (Sagan and Lengemann, 1973).

12.2.2.4 Concentrations of Rare Earth Elements in Animal Tissues

Though absorption and uptake of rare earths may be influenced by several factors, rare earth contents detected in animal tissues after rare earth supplementation were generally low, even if supplemented at early age. According to this, low tissue concentrations were determined in chickens after feeding a rare earth containing diet over the first five weeks of their lives. Slightly higher concentrations were observed in kidney, liver and fat tissue compared to those in breast and thigh muscle as well as heart. However, as to lanthanum concentrations of 45 to 98 mg/kg feed presented in the diet (Table C.2) and a total sum of 300 mg digested, accumulation is considered negligible since tissue concentrations were three magnitudes lower (30 - 50 μg/kg dry matter) (Tables C.1, C.2, C.3). An absorption factor of only 10^{-3} to 10^{-4} could be calculated based on this information.

Even lower concentrations in the range of 1.0 - 53.4 μg/kg dry weight were determined in another feeding trial performed on chickens, whose feed was supplemented with 150 - 300 mg rare earths per kg feed for six weeks (Schuller, 2001) (Table C.5). However, in untreated animals, tissue concentrations of lanthanum and cerium were found to be in a similar range (1.1 - 52 μg/kg dry weight). Thus, even long-term application of orally substituted rare earths did not show any tendency to accumulate rare earths in muscle, liver, kidney or bones of chickens. Consistent with that, little accumulation of rare earth elements was also observed in feeding trials performed on pigs (Rambeck et al., 2004), (He et al., 2001), (Borger, 2003) (Böhme et al., 2002a) (Table C.7), (Eisele, 2003).

Most experiments focused on the determination of lanthanum and cerium, since these light rare earths constitute the main part of rare earths presented in experimental diets as shown in Tables C.6, C.9 and C.10. Kraatz et al. (2004) revealed that lanthanum and cerium accounted for 91 %. Values measured for rare earth contents in animal tissues were shown to be of the order of the limit of detection, hence are very low. Lanthanum concentrations of 2.1 μg/kg to 12 μg/kg, for example, were determined in liver tissue of supplemented pigs. For muscle tissue, which is of special interest regarding food safety, rare earth contents ranged between 4.6 μg/kg and 8.3 μg/kg, thereby being close to or even below those determined in the muscle of control animals (7.7 μg/kg) (Rambeck et al., 1999a), (He and Rambeck, 2000) (Table C.4). Lanthanum contents of 19.0, 53.4 and 22.3 μg/kg dry matter, respectively, were determined in muscle, liver and kidney of pigs in line with another feeding trial (He et al., 2001), (Borger, 2003) (Table C.6). Though lanthanum concentrations were shown to be increased by a factor of 6.3, 19.1, and 7.4, respectively, in muscle, liver and kidney of rare earth supplemented animals, compared to the control, they were still low ranging from 2.8 to 3 μg/kg. Surprisingly, higher cerium contents were detected in the liver of control animals compared to those receiving rare earth elements. The same was reported for lanthanum, with higher concentrations found in muscle tissue of untreated animals (Eisele, 2003) (Table C.8), which strongly indicates that, compared to normal feed, hardly any additional accumulation takes place following rare earth supplementation.

In general, rare earth concentrations detected in muscle and liver were below those reported in vegetables and fruits (Krafka, 1999) as well as those determined in the feed of control animals, suggesting that rare earths are harmless for both animals and consumers of animal products. Additionally, no correlation was observed between lanthanum contents in feed and those in muscle tissue (He and Rambeck, 2000), (Eisele, 2003). Hence, the amount of rare earths taken up by consuming lettuce and vegetable products, e.g. roast potatoes or dumplings, is higher compared to that following the consumption of meat products obtained from rare earth supplemented animals, e.g. knuckle of pork. Furthermore, lanthanum concentrations in kidney of animals fed a rare earth containing diet were as low as those in liver and muscle, while similar concentrations were determined for cerium (He and Rambeck, 2000), (He et al., 2001). Slightly higher values obtained in liver tissue are in accordance with earlier reports describing liver, spleen and bone of rats as main accumulation sites, while reporting low concentrations in kidney, pancreas and heart. Moreover, rare earths were not detected in muscle and blood (Haley, 1965), (Ji et al., 1985b), (Nakamura et al., 1991b), (Nakamura et al., 1991a). The same, that is low rare earth contents in blood, muscle, liver and heart, was also reported in Chinese feeding experiments (Xie et al., 1991), (Xie et al., 1995).

Low tissue accumulation may, on the one hand, be ascribed to poor gastrointestinal absorption, whereas, the fact that rare earths occur ubiquitous, thus also in soil and plants (Krafka, 1999), probably also accounts for it. Accordingly, lanthanum and cerium concentrations of 0.2 mg/kg and 0.3 mg/kg, respectively, were found in standard pig feed (He et al., 2001) and similar values were also reported by Eisele (2003). As a result, rare earths are also taken up through commercial diets (Meier, 2003). According to Evans (1990), concentrations of rare earths of μg/kg - mg/kg body weight were determined in tissues of humans and animals receiving a normal diet, whereas a similar range was reported for rare earths in vegetable edibles (Table 12.21).

A possible daily intake of 2.10 - 2.50 mg/person/d has been calculated for humans based upon a common food basket (Su et al., 1993), which provides a proxy estimate of individual feed intake of a population according to affordability and accessibility, established to assess food security (Lareo et al., 1990), (Nathoo and Shoveller, 2003). Including a safety factor of 100, acceptable daily intake (ADI) for rare earth oxides of 0.1 - 1.0 mg/kg body weight (0.2 - 2.0 mg/kg body weight for rare earth nitrates), has been reported for humans (Ji et al., 1985b). Similar values have

	RE contents	reference
grain	0.41	Su et al. (1993)
wheat	1.0 - 2.0	Ji et al. (1985b)
rice	0.5 - 1.0	Ji et al. (1985b)
vegetables	0.23	Su et al. (1993)
vegetables	< 0.50	Ji et al. (1985b)
fruits	0.19	Su et al. (1993)
fruits	< 0.50	Ji et al. (1985b)
beans	0.83	Su et al. (1993)
potato	0.66	Su et al. (1993)
tea	1.76	Su et al. (1993)
meat	0.07	Su et al. (1993)
eggs	0.07	Su et al. (1993)
aquatic animals	0.52	Su et al. (1993)

Table 12.21: Rare earth (RE) contents in vegetables, fruits, animal products (mg/kg) and drinking water (μg/l) (Su et al., 1993).

also been described in a recent paper (12 - 120 mg/d per person for rare earth nitrates) (Song et al., 2005), whereas, slightly higher concentrations of 2.5 mg/kg/d were reported as maximum allowable intake for rare earth chlorides (Tian et al., 1992). Nevertheless, this limitation range greatly exceeds both concentrations determined in animal tissue, especially in muscle (1.8 - 30 μg/kg) (Ji, 1990), (He and Rambeck, 2000), (He et al., 2001) as well as possible daily intake (Su et al., 1993). Thus, it is obvious that there is no risk for humans as to rare earth accumulation through the uptake of animal products.

Moreover, it was shown that neither carcass nor meat quality were affected by long-term application of rare earths with feed (Miller, 2006), (Rambeck et al., 2004), (Borger, 2003). Various parameters, including pH values, meat brightness, electrical conductivity or meat fat ratio, were determined at the end of several feeding trials in order to assess meat quality. No significant differences could be revealed between animals, whose diet was supplemented with rare earths, and the control group, for either pH_1 and pH_{24}, which are considered to provide a high significance on meat quality in terms of identifying PSE (pale, soft and exudative) and DFD (dark, firm and dry) meat. Furthermore, none of the other parameters was influenced either (Miller, 2006), (Rambeck et al., 2004), (Borger, 2003), (Eisele, 2003). This indicates that rare earth supplementation does not impair meat quality. Additionally, no effects were noticed on carcass yield. According to EUROP, a classification system of slaughtered animals grading carcasses as to their lean meat contents, all carcasses of animals fed a rare earth containing diet were either graded as E (lean meat $>$ 55 %) or U (lean meat between 50 and 55 %), thus being among the best classes (Rambeck et al., 2004), (Miller, 2006).

Consistent with that, no significant effects on body composition and fish filet quality were observed after rare earths were supplemented to fish feed for several months (Tautenhahn, 2004), (Renard, 2005). Meanwhile, carcass quality of chickens was not shown to be affected either (Halle et al., 2004). Except for liver weight, which was slightly higher in control animals, no significant difference was observed between rare earth supplemented animals and the control regarding the weight of either muscle or organs (Halle et al., 2002a).

In conclusion, with respect to both oral toxicity and absorption, application of rare earths as feed additives to animals is considered to be safe. Furthermore, rare earths presented little tendency to accumulate in animal tissues, while additionally, carcass quality was not effected. Edibles from animals treated with rare earths are therefore safe, and no risk is to be expected for consumers.

12.2.3 Summary

The application of rare earth elements, mainly light ones, as feed additives to farming animals has been practised in China for decades. However, it was not until 1999 that growth promoting effects achieved thereby were recognized beyond China. Within the scope of increasing populations, animal production also needs to be enhanced by at least 2 % per year to meet the needs, whereas, to keep environmental loads as low as possible, natural resources have to be used efficiently. Yet, with the ban of all in-feed antibiotics throughout Europe, as of 2006, due to public concerns about both development and dissemination of multiresistant bacteria, powerful growth promoting agents vanished from the feed market. Thus, there is a strong demand for new, efficient, safe and inexpensive feed additives that may satisfy the needs provoked by these changes. Rare earth elements may therefore be a promising approach. However, housing, feeding and keeping conditions in China are of lower standard compared to European countries. Therefore, it was assumed, at first, that growth promotion by rare earths is not reproducible under highly optimized standards using high performance animals as it is the case in Europe or the United States. To the contrary of this expectation, pioneer studies on pigs were able to demonstrate increases in body weight gain of 5 - 19 % and improvements in feed conversion rate of 7 - 10 % due to dietary supplementation of inorganic rare earth compounds imported from China. Moreover, these improvements were even better than those reported for former in-feed antibiotics. Results obtained could not only be verified statistically but also reproduced in several other trials. Following Chinese reports on better performance enhancing effects achieved by using organic rare earth compounds instead of inorganic ones, the effectiveness of rare earth citrates was evaluated in proceeding experiments. Indeed, higher increases in body weight gain of up to 22.5 % could be obtained in pigs, whereas in poultry differences were even more obvious with best results being observed after rare earth ascorbates and citrates were applied. Soon afterwards, a temporary permission for the application of rare earth citrates, as feed additives for pig production, was granted in Switzerland, where, at present, rare earths can be purchased as either *Lancer*® or *Sanocer*® from the Swiss company *Zehentmayer*. Thereby, concentrations recommended range between 150 mg/kg and 200 mg/kg feed. However, concentrations may vary with the salt, to which rare earths are attached, as well as with the contents of individual rare earth elements presented in the mixture. Concentrations applied in several studies may therefore only be compared by calculating the total rare earth oxides. Furthermore, it is also assumed that optimum concentrations may vary within different animal species. Research performed so far beyond China could not only demonstrate significant ergo-tropic effects in pigs and poultry but also in rats, whereas, no effects were achieved in fresh water fish and controversial results were obtained so far in cattle. Yet, the mechanism behind these effects is still not well understood, even though several proposals have been made. Since rats responded to oral application of rare earths to a same extent as pigs regarding performance enhancement, they have been used as small animal models in further experiments, in order to provide additional information on optimum concentrations and compounds as well as on the mode of action.

In the course of safety assessments, low concentrations of rare earths were determined in several animal tissues. Especially in muscle, which is important for estimating food security, hardly any accumulation of rare earths was observed. Moreover, no correlation between rare earth contents in feed and animal tissue was found. Lanthanum concentrations in muscle ranged between 4.6 μg/kg and 8.3 μg/kg, whereas similar contents were also found in animals receiving a standard diet without supplementation. This is probably ascribed to the fact that rare earths occur ubiquitous, thus, both animals and humans take up rare earths through commercial feed. Regarding acceptable daily intake of rare earth oxides in the range of 0.1 mg/kg to 1.0 mg/kg body weight, the use of rare earth containing feed additives in animals will not pose any risk for consumers as to rare earth accumulation in animal products. Accordingly, no effects were observed on carcass quality of supplemented animals.

12.3 Possible Mode of Action of Rare Earths

Though rare earths have been shown to enhance animal performance under both Chinese and Western conditions, the underlying mechanism has not been clarified yet. Nevertheless, following biochemical and physiological properties of rare earths (Chapter 5) as well as information obtained in line with feeding experiments, several proposals have been made. Ou et al. (2000), for example, suggested four possible mechanisms, including enhanced enzyme activity, improved protein metabolism, suppression of bacterial growth and promoted secretion of digestive fluids in the stomach, so as to explain growth promoting effects of rare earths in animals, while, anti-inflammatory and immunostimulating actions have also been proposed (Flachowski, 2003), (Feldmann, 2003). Furthermore, effects on hormone activity as well as on cell proliferation have been considered as possible explanation for performance enhancing effects of rare earths (He et al., 2003a), (He et al., 2006b). However, it may also be possible that rare earths constitute essential elements as they are found ubiquitous, though, at present, evidence is lacking (Rambeck and Wehr, 2005).

As to the site of action, currently discussed mechanisms might be roughly divided into two categories. On the one hand, rare earths could exert their performance enhancing effects by local actions within the gastrointestinal tract. An assumption that is mainly supported by the fact that orally applied rare earths are only poorly absorbed. Yet, little amounts absorbed, on the other hand, may still be physiological available, thus, able to affect the intermediate metabolism in various manners. According to this subdivision, presently available information on the effects of rare earths in animals will be presented and discussed in this section, in order to possibly explain as to how rare earths can enhance animal performance. However, information on the mode of action is not only of scientific interest. Regarding their feasible registration as feed additives, rare earths have to be classified according to their mode of action as further discussed in Chapter 13.

12.3.1 Local Effect on the Gastrointestinal Tract

A number of reports showed that orally applied rare earths are only absorbed to a very small degree from the gastrointestinal tract (Section 12.2.2.2). Absorbed amounts in rats were reported to be less than 0.01 % (Durbin et al., 1956), (Evans, 1990) and absorption factors of 10^{-3} to 10^{-4} were determined in chickens (Fleckenstein et al., 2004). Accordingly, Hutchison and Albaaj (2005) stated that 99.36 % of the administered rare earth doses was recovered in feces of rats. This indicates that after oral application, the majority of rare earths accumulates within the chymus prior to excretion. On the background of poor gastrointestinal absorption, local effects stand to reason. Up to now, local effects discussed include both anti-bacterial and anti-inflammatory effects as well as improvements in nutrient uptake and digestibility.

12.3.1.1 Antimicrobial Effects

Following reports on antimicrobial properties of rare earths, it has been suggested that rare earths, similar to former in-feed antibiotics, may promote animal growth by influencing the development of bacterial species within the gastrointestinal tract selectively, hence, inhibiting undesired bacteria (Feldmann, 2003), (Flachowski, 2003), (Rambeck and Wehr, 2005). Rare earth elements could thereby maintain the micro-flora of the intestinal tract, which is also involved in digestion processes, and possibly also prevent any disease onsets. In Chinese fish farming, it was recorded that fish fed with rare earth supplemented feed demonstrated enhanced growth, while presenting increased resistance to pathogenics (Yeng, 1990), (Flachowski, 2003).

Earlier work already indicated that rare earths possess certain antibacterial properties (Burkes and McCloskey, 1947), (Wurm, 1951), (Muroma, 1958), (Evans, 1990), yet, effects seem to be dose-dependent. To inhibit bacterial growth, concentrations of 10^{-4} - 10^{-2} mol/l were necessary, while at lower concentrations of approximately 10^{-5} mol/l, rare earths were able to support bacterial growth (Muroma, 1958). However, antibacterial effects have also been demonstrated in more recent experiments. Cerium, for example, was able to inhibit the growth of several bacteria including E. coli, Bacillus pyocyaneus, Staphyloccous aureus, Leuconostoc and Streptococcus faecalis, when applied at concentrations ranging from 10^{-3} mol/l to 10^{-2} mol/l (Zhang et al., 2000b). In accordance with Zhang et al. (2000b), Ruming et al. (2002) also observed that cerium ions could influence the growth of bacteria dose-dependently. Hence at concentrations below 350 μg/ml, cerium stimulated the growth of E. coli, whereas at higher concentrations, at or above 400 μg/ml, growth was inhibited. Besides bacteria, rare earths were also shown to inhibit the formation and germination of fungal spores (Talburt and Johnson, 1967). Yet, multiple experiments demonstrated that bacteria, especially gram - negative ones (Peng et al., 2004), were more susceptible than yeast or fungi, while heavy rare earths tended to be more toxic than light ones (Muroma, 1958).

Different explanations for their antimicrobial actions have already been given. On the one hand, rare earths may cause bacterial flocculation by changing the structure and altering the surface charge of bacterial membranes (Sobek and Talbut, 1968), (Bentz et al., 1988). In the same manner, rare earths can promote cell aggregation and membrane fusion (Cassone and Garaci, 1974). Peng et al. (2004) showed that La^{3+} could change the structure of outer cell membrane of gram negative bacteria, such as E. coli, substantially, hence causing its damage. Gram negative bacteria usually have a peptidoglycan layer beneath the lipopolysaccharide making them less sensitive to lysozyme. Based upon substantial changes in the presence of lanthanum, cells became more susceptible to lysozymes. This explains why rare earths particularly inhibit the growth of gram negative bacteria as previously reported by Drossbach (1897), Muroma (1958). On the other hand, direct effects of rare earth on the bacteria metabolism in terms of inhibiting respiration processes (Brooks, 1921) or the phosphate - independent metabolism (Wurm, 1951) may be another possible explanation. In addition, Wenhua et al. (2003) demonstrated that at lower concentrations (0.5 - 30 μg/kg), La^{3+} could inhibit the absorbtion of external DNA by E. coli, thereby effectively decreasing its transformation. Finally, it is not known whether morphological or metabolic changes account for their effects. Ou et al. (2000) suggested that, due to their acid character, rare earth additives might lower the pH value in the digestive tract of piglets, thereby suppressing the growth of pathogenic bacteria.

Though anti-bacterial effects pose a reasonable explanation, Schuller et al. (2002), Böhme et al. (2002a), Kraatz et al. (2004) and Knebel (2004) have not been able to demonstrate significant antibacterial actions of rare earths in in-vivo studies on gut flora of poultry, piglets or in in-vitro studies on rumen microorganism.

Analysis of the intestinal micro-flora of chickens fed a rare earth containing diet revealed neither significant qualitative nor quantitative changes in the composition of individual microbial populations of the gastrointestinal tract (Schuller, 2001), (Schuller et al., 2002). Only little differences were observed as to the anaerobic total microbial count of ileum and caecum, whereas animals supplemented with rare earths presented a tendency towards lowest counts in the jejunum. Even though hardly any effects were noticed on the gastrointestinal micro-flora, results may be considered carefully as at the same time rare earths did not change any zootechnical parameters. Similarly, in the absence of performance enhancing effects, rare earths did not affect the composition of faecal bacterial populations in pigs, which was investigated in biomolecular studies using PCR-DGGE methods (Polymerase Chain Reaction Amplification (PCR) - Denaturing Gradient Gel Electrophoresis (DGGE)) (Kraatz et al., 2004).

Further experiments were conducted using RUSITEC (Rumen Simulation Technique), an artificial rumen system proven effective for evaluations of the microbial rumen metabolism, to investigate the impact of rare earth citrate on ruminal fermentation. Yet, ruminal fermentation could not be affected by rare earth citrates applied at 150 mg/kg, 750 mg/kg, 3750 mg/kg. Over the whole experimental period of ten days, no effects were observed on any of the parameters characterizing rumen-microflora, including pH values, NH_3 production, redox potential, fatty acid pattern or the amount of produced gas, whereas tetracycline, which was included as positive control, was shown to inhibit fermentation (Knebel, 2004), (Wehr et al., 2005b). Thus, as ruminal fermentation was unaffected by rare earths, it was concluded that, under RUSITEC conditions, ruminal microorganisms were probably not influenced. This further indicates that ergo-tropic effects demonstrated in animals may not be ascribed to influences on the gastrointestinal micro-flora. However, microbial conditions in monogastric animals, such as pigs, definitely differ from RUSITEC conditions, thus questioning the adoption of these results to all animal species. Indeed, a tendency in decreased contents of anaerobic bacteria ($1.7 \cdot 10^9$ in control, $60 \cdot 10^6$ at 50 mg, $17 \cdot 10^6$ at 100 mg, $92 \cdot 10^6$ at 200 mg) could be observed in the small intestines of pigs supplemented with rare earth citrates, while other microorganisms, including aerobic colony forming bacteria, enterobacteria and lactobacillus, seemed to be unaffected (Knebel, 2004), (Wehr et al., 2005b). These coincide with Schuller et al. (2002). Though only a few duodenal digesta samples, with four out of each experimental group, were analyzed for its microbial composition during this experiment, results indicate that rare earths may yet be able to affect the population of bacteria in small intestines. Therefore, further studies are recommended.

In addition, analysis of mainly directly taken small intestinal samples should also be performed in order to assess a possible impact of rare earths on microbial populations located closely to absorption sites, even though first biomolecular investigations did not reveal any differences to faecal microflora in pigs. Moreover, since antibacterial effects seem to be highly dose-dependent, it might also be of interest to determine the concentrations of rare earths in digesta samples after rare earth supplementation. Attention should also be paid to the chemical compound as variations of antimicrobial behavior have been reported for different rare earth compounds (Zhang et al., 2000b). Minimum growth-inhibiting concentrations of $1 \cdot 10^{-3}$ mol/l for E. coli and B. pyocyaneus, $2 \cdot 10^{-3}$ mol/l for St. aureus and $1 \cdot 10^{-2}$ mol/l for Leuconostoc and Streptococcus faecalis, respectively, and minimum bactericidal concentrations of $2 \cdot 10^{-3}$ and $1 \cdot 10^{-2}$ mol/l for B. pyocyaneus, E. coli and Leuconostoc were reported for a cerium-humic acid complex. Surprisingly, bacterial growth of all species was shown to be promoted when a cerium-citrate complex was applied instead. This indicates that effects of rare earths on bacterial growth vary with the chemical compound used.

Nevertheless, other authors suggested that the combination of antibacterial effects with anti-inflammatory properties, as observed for rare earths, may account for their performance enhancing effects of rare earths on animals (Feldmann, 2003), (Flachowski, 2003). Basile et al. (1984) described that lanthanide salts could obviously inhibit histamine and serotonin induced changes in vascular permeability after intraperitoneal application, yet no significant effects were observed when orally applied.

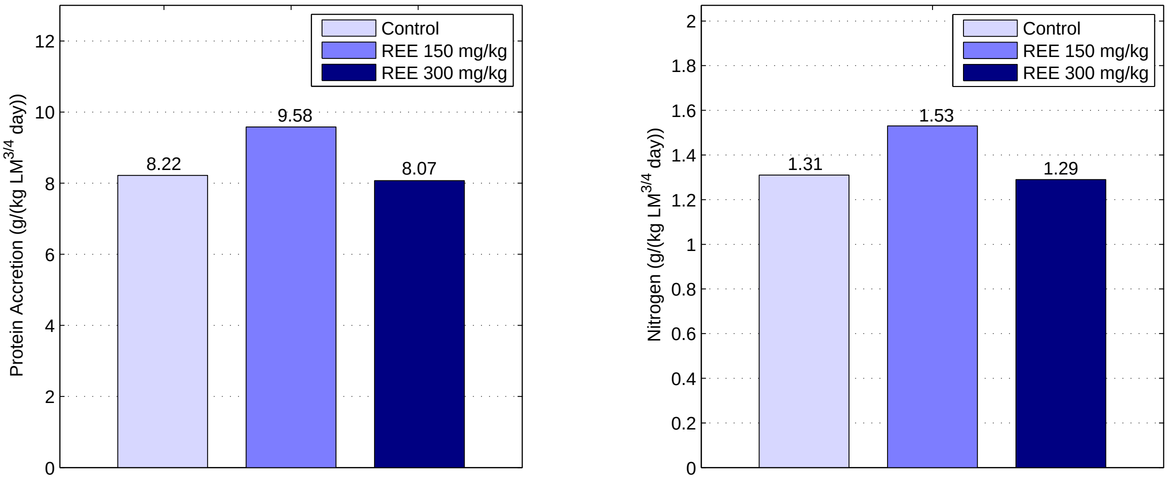
Furthermore, besides influencing bacterial growth, it was also reported that rare earths may exert anti-viral effects (Bjorkman and Horsfall, 1948), (Sedmak et al., 1986), (Liu et al., 1998). These effects have been attributed to either enhanced interferon activities (Sedmak et al., 1986) or direct anti-viral properties (Liu et al., 1998). This might also contribute to enhanced growth due to decreased cases of illness, yet, further research on this is required.

12.3.1.2 Improvements in Digestibility and Utilization of Nutrients

The mechanism underlying performance enhancing effects may also be related to improvements in nutrient digestibility and availability (Azer, 2003), (Bayerischer Rundfunk, 2003). A Chinese report demonstrated that rare earths were capable of improving the digestibility of both total energy and protein in pigs, thereby enhancing feed utilization (Ming et al., 1995). Accordingly, Hu et al. (1999) observed significant better apparent digestibilities of energy, crude protein as well as total essential and non-essential amino acids in pigs whose diet was supplemented with rare earth elements. Several other Chinese scientists also attributed performance enhancing effects of rare earths to improved digestibility and utilization of nutrients (Li et al., 1992a), (Cheng et al., 1994), (Zhu et al., 1994), (Lu and Yang, 1996), (Xu et al., 1998). At the same time, a trend towards increased utilization of dietary nutrients (total energy, crude protein, crude fat) in animals treated with a rare earth supplemented diet ($p > 0.05$) was demonstrated in another digestive and metabolic trial (Xie and Wang, 1998).

Better utilization of nutrients was also suggested after feeding trials were performed on pigs and quails under Western conditions, in which higher body weight gain was observed along with reduced feed consumption (Flachowski, 2003). Yet, no differences in zinc absorption due to rare earth supplementation were noticed between rare earth supplemented pigs and the control group indicating that rare earths may not influence the absorption of other trace elements either (Knebel, 2004).

However, investigations on the effects of rare earths on energy-, carbohydrate- and nitrogen-balance as well as the digestibility of nutrients in piglets using respiration chambers (Prause et al., 2004) revealed that, along with higher nitrogen uptake (14 % ($p = 0.054$)), animals receiving rare earth citrates at 150 mg/kg feed put on more protein (17 % ($p = 0.104$)), compared to control animals (Table D.1 and Figure 12.15), whereas, supplementation of rare earths at higher concentrations (300 mg/kg feed) did not show any effects (Prause et al., 2005a), (Prause et al., 2005c). Enhanced fat accretion was also observed. Together with increased protein accretion, this might be ascribed to enhanced feed intake, while increased nitrogen intake and utilization may account for the fact that pigs supplemented with rare earths put on more protein (Kyriazakis and Emmans, 1992), (Bikker et al., 1995), (Tome and Bos, 2000). Though not significant, Prause et al. (2005a) also noticed increases in energy balance, carbonate retention and digestibility of nutrients (1 - 2 %) in animals supplemented with low dose rare earths, while again no effect occurred at 300 mg/kg feed. All in all, a clear tendency towards improved nutrient digestibility, especially to the protein balance, could be revealed in this experiment. Decreases in feed conversion demonstrated at low dose (150 mg/kg) application of rare earths, may therefore be attributed to improved digestibility of nutrients.



(a) Protein Accretion

(b) Nitrogen Balance

Figure 12.15: Effects of rare earth (RE) citrate on protein accretion and nitrogen balance of pigs (Prause et al., 2005c).

On this basis, it was suggested that rare earths may influence the permeability of intestines, thereby, enhancing the absorption of different nutrients (Prause et al., 2004). But rare earths may also form complexes with proteins which in turn may enhance their uptake or metabolism of protein. In addition, Ou et al. (2000) proposed that rare earths can promote the secretion of digestive fluids in animal stomachs. Indeed, lanthanum was shown to increase gastric acid secretion dose-dependently in in-vitro studies performed on isolated mice stomachs (Xu et al., 2004). The mechanism underlying was thought to involve either the release of gastrin, histamine or the activation of their receptors. Furthermore, Chinese scientists suggested that rare earths may not enhance the utilization of protein or other nutrients, such as carbohydrates, by local effects but by influencing the activity of certain hormones (Xie et al., 1991), (Yang et al., 1992a), (Xie et al., 1995), whereas Prause et al. (2004) proposed that enhancing the activities of certain enzymes involved in the digestive tract or in nutrient metabolism may also account for improved digestibility. However, this will be further considered in line with effects on the intermediate metabolism.

Blood samples taken from rats, whose diet was supplemented with rare earths for 16 days, revealed increases in both creatine and urea concentrations, which may also indicate an impact on protein metabolism through the intermediate metabolism (He et al., 2003a) (Table D.7). Though, at the same time neither total protein nor albumin were affected and no influence on any of these parameters was observed in other feeding trials performed on pigs (He et al., 2001), (Borger, 2003) (Table D.4).

Protein to energy ratios in animal diets, especially in fish, are generally considered to play a major role in animal nutrition in order to achieve optimum growth (Tautenhahn, 2004). Since protein constitutes the most expensive source of energy in feed, commercial feed production often keeps protein levels down to minimum levels required to maintain optimum growth and feed conversion (Pillay, 1990). Thus, if rare earths are able to improve the protein balance as shown by Prause et al. (2005a), not only performance might be improved but also protein contents in diets, hence, making feed cheaper. In intensive aquaculture practised in Europe, protein utilization and digestibility are already highly optimized using high quality feed and fast growing strains. This might therefore be a possible explanation for the absence of performance enhancing effects noticed in fish feeding experiments.

In contrast to improvements in digestibility reported by Prause et al. (2005a), Böhme et al. (2002a) did not observe any significant impact of different rare earth compounds (rare earth nitrates, rare earth citrates, rare earth ascorbates and lanthanum chloride applied at 100 mg/kg feed as the sum of lanthanum and cerium) on the digestibility of crude nutrients in nutritional balance tests performed on 40 pigs. At most, a tendency of better crude fibre utilization was observed in rare earth ascorbate supplemented animals, yet this was still below 1 %. However, rare earths did not present any performance enhancing effects in this trial. Consequently, with respect to the mode of action, results may have to be interpreted carefully.

Nevertheless, effects of rare earths might also be produced by influencing the intestinal motility, as actions on smooth muscle of both stomach and intestine have been described. Even though mainly inhibitory effects were observed, tone can be temporary increased, too (Evans, 1990), (Weiss and Goodman, 1969), (Weiss, 1974), (Goodman and Weiss, 1971), (Triggle and Triggle, 1976). This in turn may contribute to enhance digestibility or increased nutrient intake by changing the passage rate through the digestive system. Additionally, gastrointestinal motility may also be controlled by the vegetative nervous system. Though transport of rare earths to nervous tissues is supposed to be slow (Evans, 1990), transmission of nervous impulses was shown to be affected by rare earths as well. According to van Breemen and de Weer (1970), lanthanum could decrease the efflux rate of calcium in giant axons, which was previously injected with calcium by 87 %. In the same way, lanthanum inhibited calcium uptake in rabbit vagus nerves (Kalix, 1971). On this basis, gastrointestinal motility, nutrient absorption and secretion of digestive juices might be influenced by rare earths via the nervous system.

Further authors suggested that performance enhancing effects might be ascribed to the modification of phosphorous compounds by rare earths, thereby, allowing better utilization of these compounds (Fleckenstein et al., 2004). Accordingly, phosphate binding properties of rare earths have been reported in several studies (Evans, 1990), (Diatloff et al., 1995a), (Hutchison and Albaaj, 2005). Furthermore, rare earths were shown to influence the phosphate metabolism in bacteria by the formation of insoluble phosphate rare earth compounds (Wurm, 1951). Yet, no differences due to rare earth application could be observed in serum phosphate concentrations of either pigs (Borger, 2003) (Table D.4) or rats (He et al., 2003a).

Due to anti-oxidative effects, rare earths may also be able to protect fatty acids, such as omega-3 fatty acids, present in the diet from oxidization. Rare earths could thereby preserve nutrients within the feed or, moreover, enhance their uptake. Anti-oxidative properties have been widely reported for rare earth elements. Dose and species dependent, rare earths were shown to either inhibit or promote ROS-mediated (reactive oxygen species) processes, whereas inhibition was described for light rare earths with increasing concentrations. These effects have been attributed to hydroperoxides binding, thus inhibiting lipid peroxidation and the oxidation of membrane proteins, or to magnetic interaction with free radicals (Shimada et al., 1996), (Wang et al., 2003b).

12.3.2 Effects on the Intermediate Metabolism

Various studies demonstrated that only a very small amount of orally applied rare earths is absorbed within the gastrointestinal tract (Durbin et al., 1956), (Eisele et al., 1980), (He and Rambeck, 2000), (Fiddler et al., 2003a). Yet, a feeding experiment performed on rats revealed that, besides ergo-tropic effects in terms of increased body weight gain and improved feed conversion rate, rare earths were also able to cause some deviations in biochemical blood parameters (He et al., 2003a). It was therefore suggested that despite the fact that only a tiny amount is bioavailable, rare earths may still be capable of affecting physiological processes within the animal body. This theory has been supported by several authors (Xie et al., 1995), (He and Rambeck, 2000), (He et al., 2001), who reported changes in hormone and enzyme activities as well as in other blood parameters after rare earth supplementation. Thus, rare earths may affect the intermediate metabolism in many different ways including hormone levels, enzyme activities, protein or lipid metabolism. In earlier studies, it was claimed that cerium might be an effective stimulant of the metabolism increasing appetite and body weight in humans after low dose i.v. injection (Haese, 1956). Furthermore, amounts absorbed may also influence other cellular functions, such as cell proliferation or additionally support the immune system.

12.3.2.1 Interaction with Calcium

A wide range of physiological and biochemical processes in both human and animal bodies has already been shown to be affected by rare earth elements (Chapter 5), whereas most of these processes are known to be Ca^{2+} - depending. To that effect, several pharmacological or biochemical properties of rare earths, such as inhibiting coagulation (Jakupec et al., 2005), muscle contraction (Triggle and Triggle, 1976) and transmission of nervous impulses (Vaccari et al., 1999) or influencing hormonal responses (Enyeart et al., 2002) or the release of histamine from mastcells (Beaven et al., 1984), are ascribed to their high resemblance to calcium ions (Table 5.1).

Rare earths not only present a marked similarity in both size and bonding but also in coordination geometry and donor atom preference, which allows them to replace Ca^{2+} specifically in various physiological processes. This substitution, even though occurring isomorphously, does not necessarily lead to an inhibition of physiological processes such as enzyme activities (Evans, 1990), (Jakupec et al., 2005). However, several calcium channels and in addition the functions triggered were reported to be inhibited by rare earths, which is ascribed to the fact that, compared to Ca^{2+}, rare earth elements possess a higher charge to volume ratio giving them a greater affinity for Ca^{2+} binding sites (Evans, 1990), (Horrocks and Sudnick, 1979), (McCusker and Clemmons, 1997). Interactions of rare earth elements with cellular and subcellular processes in animal systems as to their calcium substitution, have been reviewed before by Brown et al. (1990). Processes involved, among others, include cell communication through junctional membranes, actinomyosin contraction, activation of phosphorylase kinase in muscle, hormone-cell interactions, determination of cellular permeability and stabilization of cellular membranes (Mikkelson, 1976). Furthermore, calcium can influence the transport of several monovalent ions. It was also assumed that both calcium and calcium-like substances, that is rare earth elements, act like gates, occluders or competitors for sodium and potassium channels.

12.3.2.2 Influence on Certain Cellular Functions

Hence, based upon their high resemblance to calcium ions, rare earths can affect a multitude of cellular functions (Weiss, 1974), (Nayler, 1975), (Hanoika et al., 1994), (Jakupec et al., 2005), which may possibly account for their performance enhancing effects observed in animals.

However, related to this is the question whether or not rare earths can pass through the plasma membrane of animals. Results published so far are conflicting. There are several authors suggesting that rare earths, especially lanthanum, may influence the cellular metabolism by passing through the membrane (Brown et al., 1990). In contrast to that, direct and indirect evidence has been given that rare earth ions can hardly penetrate the cellular membrane (Langer and Frank, 1972), (Szasz et al., 1978), (Flatt et al., 1980). Yet, Powis et al. (1994) found out that rare earths could be transported by sodium - calcium channels, hence, triggering hormone releases.

Though cellular entry is still debated, rare earths were shown to affect cell proliferation. Cell injury and proliferation are closely related and effects of rare earths, therefore, depend on the concentration applied. Thus, low dose cerium was demonstrated to promote growth of cardiac fibroblasts in rats (Preeta and Nair, 1999). In the same manner, Gd^{3+} enhanced cell proliferation of hepatocytes (Rai et al., 1997), (Ishiyama et al., 1995), while low dose Ce^{3+} was also shown to enhance cell growth and change the cell cycle of primary cultured hepatocytes (Shen et al., 1999). In contrast to that, rare earths were also reported to hamper cell growth by the inhibition of spindle fibre orientations during cell division (Brown et al., 1990). Yet, cell culture experiments on preadipocytes (3T3-L1 cells) revealed that rare earths can stimulate the proliferation of these cells (He et al., 2003b), (He et al., 2006b). Additionally, they were also able to decrease the concentration and composition of monounsaturated fatty acids in differentiating adipocytes. This indicates that rare earths may have an impact on adipogenesis and lipogenesis rate in adipose tissue.

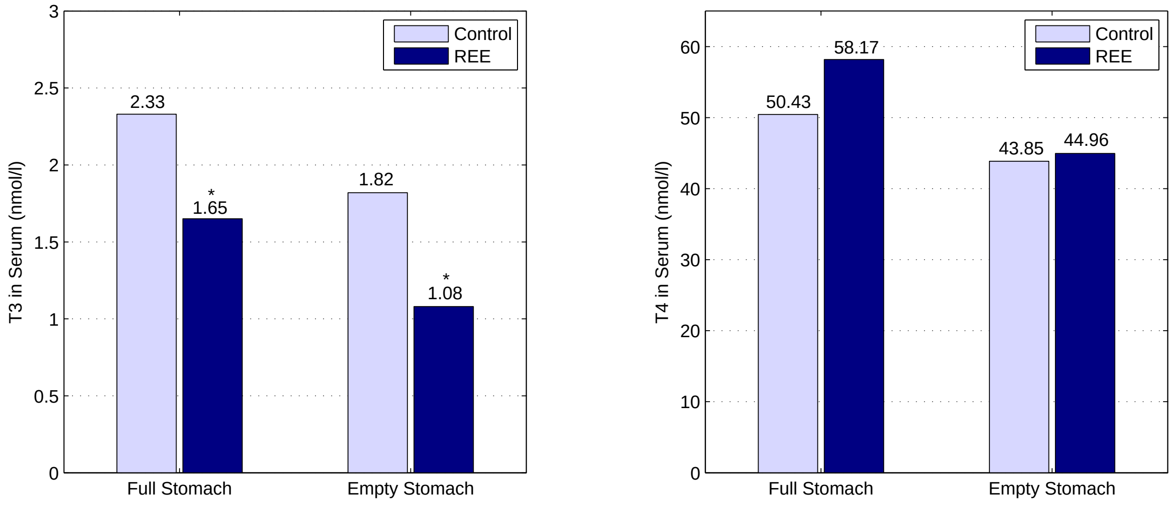
It is generally assumed that rare earths affect cell metabolism by either inhibiting or replacing calcium (Fernando and Barritt, 1995). However, the mechanisms underlying cell proliferation of rare earths are not yet understood. It has been suggested that these effects may also be related to increased DNA, RNA and protein synthesis (Wang et al., 2003b), since Smith and Smith (1984) demonstrated that lanthanum chloride could promote DNA synthesis and stimulate embryogenesis in cultured fibroblasts (Swiss 3T3 and 3T6 cells). In addition, cellular functions may be influenced by rare earths acting as enzymes themselves (Bamann, 1924), (Eichhorn and Butzow, 1965), (Yajima et al., 1994), (Franklin, 2001) since rare earths were shown to induce the hydrolysis of phosphatidyl-inositol, a trigger substance in signal transduction pathways (Wang et al., 2003b). Furthermore, Eichhorn and Butzow (1965) described that rare earths possess the ability to depolymerize RNA molecules and nucleotides, whereas, under physiological conditions, rare earths were capable of forming adenosine 3',5'- cyclic monophosphate from adenosine triphosphate (Yajima et al., 1994). On this basis, rare earths are likely to possess a certain phosphatase activity as well as a catalytic potential. Accordingly, Franklin (2001) reported that rare earth ions are capable catalysts for hydrolytic splitting of phosphate ester bonds including those of DNA. Though the biological relevance of these actions is still unclear, rare earths may have a high impact on the total metabolism influencing physiologically important phosphate compounds (Bamann et al., 1954), such as RNA. Especially cerium was expected to affect the carbohydrate metabolism, as it was shown that cerium may break down meta-, pyro- and poly-phosphates into ortho-phosphates (Haese, 1956).

12.3.2.3 Influence on Hormones and Enzymes

Notwithstanding cellular functions, metabolism may also be modulated by affecting the activity of certain hormones and enzymes. There is a great number of G protein coupled hormone receptors known to be calcium dependent, hence, susceptible to rare earth interactions. Inhibition of hormone binding to ACTH receptors has already been demonstrated for rare earths (Enyeart et al., 2002). The marked reduction in receptor affinity for ACTH was caused by competitively antagonizing calcium from its specific site, thus preventing ACTH binding, while at the same time accelerating its dissociation from the receptor. Receptor binding of several other hormones may therefore also be inhibited. Earlier studies already indicated that rare earths may affect the activity of hormones or enzymes based upon their high resemblance to calcium ions (Hanoika et al., 1994), (Nayler, 1975), (Takada et al., 1999). Accordingly, lanthanum chloride was shown to increase both the basal and TSH induced release of T_4 in a chicken in vitro system (Lam et al., 1986), whereas, Segal and Ingbar (1984) demonstrated that at 25 μmol lanthanum produced a rapid four to six-fold increase in calcium accumulation in rat thymocytes. It was suggested that this might be the result of potentiating the response of these cells to T_3 (Segal, 1986). Hence, interactions with hormone levels display a possible explanation for growth performance enhancing effects of rare earths, as several hormones, especially growth hormone but also thyroid hormones, are known to be involved in the regulation of body growth and metabolism including protein, fat and carbohydrate metabolism (Bayrhuber and Kull, 1989). This is consistent with several Chinese reports (Xie et al., 1991), (Yang et al., 1992a), (Xie et al., 1995) proposing changes in hormone activities as mechanism underlying performance enhancement of rare earths.

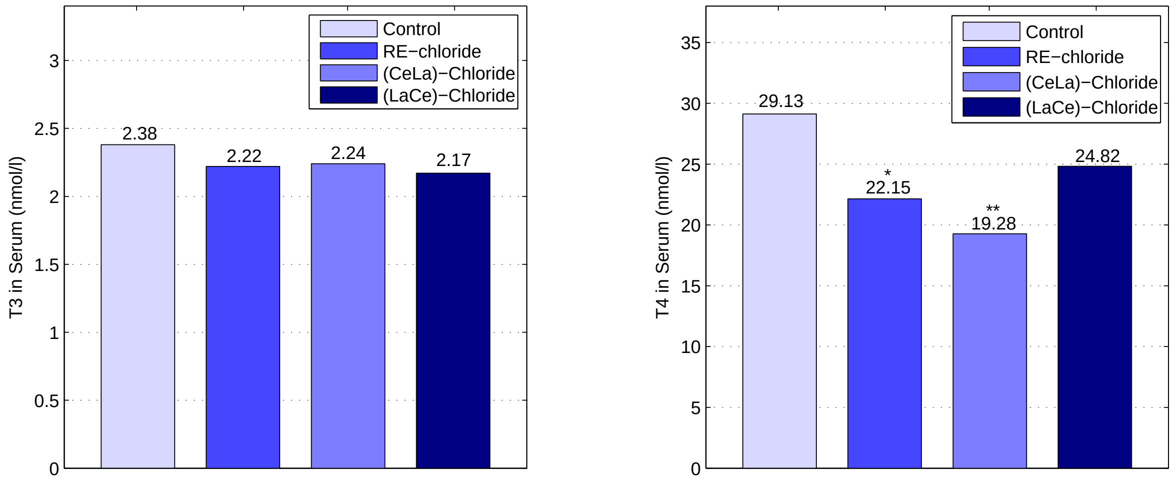
At present, effects are not fully investigated and both increases and decreases in hormone activities, especially thyroid hormones and growth hormone (Xu et al., 1999), (Wang and Xu, 2003), (He et al., 2001), (He et al., 2003a), (Borger, 2003), (Förster et al., 2006), were reported in several feeding trials. However, it has to be considered that results may only be compared to a limited extent, as concentrations of thyroid hormones may be influenced by a variety of factors, such as the relation between feeding and time at which blood samples are taken. According to He et al. (2001), significantly lower T_3 values ($p < 0.01$) were observed in pigs previously treated with rare earths. Values of 1.65 and 1.08 nmol/l, respectively, were determined at the end of growing and fattening, whereas T_3 concentrations in the control group were 2.33 and 1.82 nmol/l, respectively (Table D.2 and Figure 12.16). Though not significant, decreased serum T_3 concentrations of 6.4 %, 5.9 % and 9 %, respectively, were noticed in pigs supplemented with 300 mg/kg, 100 mg/kg and 200 mg/kg rare earths, as shown in Table D.3 and Figure 12.17 (Eisele, 2003). Decreases in T_4 concentrations of up to 34 % ($p < 0.01$) occurred in animals whose diet was supplemented with rare earths at 100 mg/kg, followed by 24 % ($p < 0.05$) at 300 mg/kg rare earths. Even though this is not in line with previous studies, which reported higher T_4 concentrations in supplemented animals (He et al., 2001), (Schuller et al., 2002), decreased T_4 concentrations were also reported after rare earth application to broilers in Chinese literature (Xie et al., 1995).

Blood samples taken after the first and the last week of a feeding trial performed recently on piglets revealed increases in both T_3 and T_4 concentrations due to rare earth supplementation, as can be seen in Table D.5 (Förster et al., 2006). Elevated triiodothyronine (T_3) concentrations were



(a) T_3 **(b)** T_4

Figure 12.16: Effects of rare earth (RE) chlorides on T_3 (in nmol/l) and T_4 (in nmol/l) of pigs; values with an asterisk ($*$) differ significantly $p < 0.05$ (He et al., 2001).



(a) T_3 **(b)** T_4

Figure 12.17: Effects of rare earth (RE) chlorides on T_3 (in nmol/l) and T_4 (in nmol/l) of pigs (Eisele, 2003).

also found in chickens in a Chinese feeding trial. In addition, increased growth hormone concentrations were observed (Xie et al., 1995). The same was reported in another feeding trial on chickens (Xie and Wang, 1998). Significantly increased growth hormone (GH) levels of 88.8 % were obtained in pigs whose feed was supplemented with rare earths ($p < 0.05$) (Xu et al., 1999). Along with that, concentrations of both thyroid hormones (T_3, T_4) were also increased significantly by 36.7 % and 28.9 % ($p < 0.05$), respectively. On this basis, it was assumed that supplementation of rare earths to pigs stimulates both synthesis and secretion of growth hormone and thyroid hormones, thereby, enhancing the assimilation of nutrients and consequently animal growth. This was supported by Wang and Xu (2003), who also observed significantly elevated serum levels of growth hormone after rare earth application, while, at the same time, performance was promoted. The same was reported in a study recently performed on pigs (Liu and Hasenstein, 2005) (Table D.6).

Considering the results of previously described studies, it could be demonstrated that rare earths are capable of changing the activity of thyroid hormones as well as growth hormone. However, the impact of rare earths is not completely investigated. Yet, as it is known that thyroid hormones are involved in body growth, nitrogen and lipid metabolism, alterations in their balance affects energy turnover and body weight (Rosenbaum et al., 2000), (He et al., 2001), (Wiesner and Ribbeck, 1991). Thyroxin, for example, may accelerate oxidative processes in all body cells, thereby enhancing the basal metabolism (Bayrhuber and Kull, 1989). Physiological T_4 concentrations of 45.6 ± 2.4 nmol/l, with blood taken 16 hours after feeding, are described in literature for pigs with a body weight of 60 kg (Rogdakis et al., 1979), whereas a similar range of 40 - 55 nmol/l for T_4 was also reported more recently (Kraft and Dürr, 1997). Concentrations of T_4 are generally higher than that of T_3, as T_4 accounts for most of the thyroid hormone secreted by the thyroid gland. However, after being secreted into the circulation, more than 99 % of T_4 are bound to plasma proteins, whereas the minor part is unbound, thus, biologically active and capable of entering cells throughout the body (Nelson, 2003). Within the cell, T_4 may be deiodinated to form T_3 depending on the metabolic demands of the tissue at that time. Intracellular T_3, which has a much higher affinity for receptor binding, presents a greater biological activity and is believed to be the primary hormone that induces physiological effects. Proper concentrations of T_3 are necessary to preserve an optimum basal metabolic rate economically efficient for animal growth and fattening (Rosenbaum et al., 2000), (He et al., 2001).

Based on previously gained information, promoting the activity of thyroid hormones as well as that of growth hormone supports the theory that rare earth can affect the intermediate metabolism. Improvements in digestibility, utilization and metabolism of nutrients may thereby be achieved, possibly accounting for performance enhancing effects.

Yet other hormones such as insulin and sex hormones may also be influenced by rare earths. Hence, by competitively substituting calcium from its site, rare earths were able to increase insulin binding to its receptors (Williams and Turtle, 1984), (Enyeart et al., 2002). Though interactions between rare earths and calcium specific or non-specific sites on proteins, including ion channels, enzymes and receptors, are generally inhibitory, insulin receptors seem to pose an exception. Thus, rare earths may also affect the intermediate metabolism by influencing the carbohydrate metabolism via insulin. This might be supported by significantly decreased serum glucose levels, observed in rats whose diet was supplemented with rare earths (He et al., 2003a). Earlier work already described decreased glucose concentrations due to rare earth application (Arvela and Karki, 1971). Conversely, Xu et al. (1999) found increased glucose concentrations, whereas glucose levels remained unchanged in other feeding trials performed on pigs (Ming et al., 1995), (He et al., 2001), (Borger, 2003).

With respect to sex hormones, it has been reported before that 1 mM $LaCl_3$ could significantly suppress the stimulation of progesterone by luteotropin in isolated ovarian cells, as calcium ions may modulate the biosynthesis of steroid hormones (Veldhuis and Klase, 1982). Thus, the impact of rare earths on sex hormones may explain why Kessler (2004) found significant performance enhancing effects to be more pronounced in female fattening pigs compared to barrows. However, in addition to suppressing the stimulatory actions of luteotropin, other hormones such as prostaglandin E_2 and L-adrenaline, which are believed to act via cyclic AMP, were also impeded under calcium deficient conditions (Veldhuis and Klase, 1982). According to Wang et al. (2003b), rare earths can also influence cAMP, thus the cell signaling system and thereby further hormone responses. In the same manner, lanthanum could inhibit the ACTH-stimulated cAMP formation, thereby hampering steroidogenesis in isolated adrenal cortex cells (Haksar et al., 1976). By substituting calcium at superficial binding sites on the cell membrane, lanthanum was suggested to affect the regulation of adenylate cyclase by ACTH. Influences of rare earths on adenylate cyclase were also reported by Nathanson et al. (1976).

Changes in enzyme activities have not only been reported on adenylate cyclase (Nathanson et al., 1976) or Na^+ - K^+ ATPase (David and Karlish, 1991) in biochemical studies but also in blood samples taken during feeding experiments. Especially liver enzymes were affected, which may indicate that rare earths have an impact on liver. While Ming et al. (1995) noticed increased alanine transaminase (ALT) concentrations and decreased aspartate transaminase (AST) and alkaline phosphatase (AP) levels in pigs, rare earths increased both ALT ($p < 0.05$) and AP during a rat feeding trial (He et al., 2003a) (Table D.7). Recurrently, increased liver enzyme activities were also observed in pigs (Borger, 2003) and mice (Kawagoe et al., 2005) after oral application of rare earths. Similar results have already been presented in earlier literature (Salas et al., 1976), though Evans (1990) only reported increased ALT and AST after injection. Nevertheless, there are also feeding trials in which no significant influence on AST, ALT or AP occurred after dietary rare earth supplementation (He et al., 2001). Additionally, enzymes involved in the digestive system were also shown to be affected by rare earth application. It is known that the conversion of trypsinogen into its active form trypsin is catalyzed by calcium, whereas at the same time, calcium also prevented the autodigestion of trypsin (Buck et al., 1962). Thus, by replacing calcium rare earths were able to accelerate the autocatalytic activation of trypsinogen. Though rare earth concentrations needed were 100 times lower, their outcome was more effectual than that of calcium (Evans, 1990), (Darnall and Birnbaum, 1970), whereas the inverse was observed at high concentrations (Gomez et al., 1974).

In a similar way, rare earths can also affect several other enzymes, which are important as to digestion and utilization of nutrients, such as α - amylase, enolase and phospholipase (Smolka et al., 1971), (Brewer et al., 1981), (Evans, 1990). Furthermore, Hershberg et al. (1976) demonstrated that gadolinium could replace calcium competitively from porcine pancreatic phospholipase A2. Similarly, cerium was shown to enhance the activity of α - amylase in porcine pancreas when applied at low concentrations of 0.5 - 10 μmol/l (Gomez et al., 1974), whereas, decreases in its activity occurred at high concentrations ($>$ 10 μmol/l) (Wang et al., 2000b), (Wang et al., 2002). Nevertheless, changes in enzymatic activity have not only been observed in biochemical studies. Improvements in amylase activity of 10 % was also described in carp fries; additionally, rare earths were able to enhance the activities of lipase, proteinase and catalase in liver and pancreas of fish (Shao et al., 1999), (Wang et al., 1999). Similar results were obtained in chickens (Xie and Wang, 1998). To that effect, it may be assumed that rare earths can improve animal performance by influencing the activity of enzymes involved in either the digestive system, such as proteinase and α - amylase, or the nutrient metabolism as previously mentioned.

Superoxide dismutase (SOD) constitutes another enzyme shown to be affected by rare earths (Wang et al., 1999), (Xie and Wang, 1998). It catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide and therefore plays an important role of the antioxidant defense in nearly all cells exposed to oxygen. As to anti-oxidative properties, effects of rare earths on reactive oxygen species (ROS) have already been described in Chapter 5. Yet, anti-oxidative defense is also an important tool of the immune system.

12.3.2.4 Immune System Stimulating Abilities

Apart from influencing the immune system indirectly by presenting anti-oxidative properties, other immunomodulating abilities have also been ascribed to rare earths (Ni, 1995), (Li et al., 1998b), (He et al., 2003b). Accordingly, it was reported that rare earths can stimulate the immune system (Ni, 1995) and the histamine secretion of mast cells (Foreman and Mongar, 1973) dose-dependently (Chapter 5). Lazar et al. (1985) described increased survival rates from anaphylactic death in mice due to the application of $GdCl_3$, whereas, the transformation of splenic lymphocytes was stimulated in mice after lanthanum nitrate was orally applied at low concentrations (Wang et al., 2003b). Significant increases in the phagocytic function of polymorphonuclear mice leucocytes were observed two days after rare earth citrates were applied intra peritoneal at 0.1 mg per kg body weight (Chen et al., 1995a). Based on these results, it was suggested that oral intake of less or slightly more may strengthen the immune system. Positive effects on the immune system due to rare earth application have already been considered as possible mode of action explaining performance enhancing effects in animals (Feldmann, 2003), and recent investigations on cell lines demonstrated dose-dependent effects of lanthanum and cerium on the production of blood cells within the bone marrow (Flachowski, 2003), as to synthesis and reduction of white blood cells. Thus, rare earths may thereby affect the immune system. However, as might be expected due to immune system activation, no difference in thymus or spleen weight was observed between rats receiving a rare earth-containing diet and control animals (Table D.7) (He et al., 2003a).

12.3.2.5 Essential Element

Despite their indisputable effects on calcium depending processes as well as on several cellular functions, rare earths have no known biological function in this respect. However, even though there are no evidences at present, it might also be possible that rare earths are essential trace elements for humans and animals. This has been hypothesized as rare earths occur ubiquitous in soils and plants (Wyttenbach et al., 1998b), (Krafka, 1999), commercial feed and in tissues of humans and animals (Evans, 1990), (Eisele, 2003), (Borger, 2003), (Kraatz et al., 2004).

12.3.2.6 Summary

Numerous experiments demonstrated that rare earths are capable of enhancing animal performance. Nevertheless, information on the mode of action is still patchy, though several proposals have been made as listed beneath.

- antibacterial properties
- anti-oxidative properties
- improved digestibility and utilization of nutrients
- influences on hormone and enzyme activities
- enhanced cell proliferation

- stimulation of the immune system
- possible essential elements

According to the site of action, effects may be divided into local effects within the gastrointestinal tract or effects on the intermediate metabolism. Within the scope of local effects, antibacterial properties of rare earth elements have been closely focused. It was assumed that rare earths may promote the microbial balance within the gastrointestinal tract by suppressing growth of undesired bacteria. Even though rare earths were multiply reported to affect bacterial growth dose-dependently in culture experiments, analyzing the microbial composition of the gastrointestinal tract of either chickens or pigs did not reveal any significant differences due to rare earth application. Consistently, no effects of rare earths were achieved on rumen fermentation, thus on rumen microorganism, using RUSITEC, an artificial rumen.

Furthermore, it was suggested that rare earths might exert their performance enhancing effects by improving digestibility and utilization of nutrients. Various Chinese feeding trials described improved digestibility due to dietary rare earth supplementation. Yet, no effects were obtained in nutritional balance tests performed on pigs. In contrast, a tendency towards improved digestibility, especially with respect to protein balance, was reported in another study, which applied respiration chambers, along with decreased feed conversion rate. Increased permeability of intestinal membranes, enhanced secretion of digestive fluids and gastrointestinal motility following rare earth application have further been considered to explain enhanced digestibility. Additionally, it was suggested that the ability of rare earths to bind to phosphorus compounds may improve the uptake or utilization of these complexes. Anti-oxidative properties ascribed to rare earths may also contribute to performance enhancing effects by either preserving nutrients in the diet or promoting their uptake.

However, as to their great resemblance with calcium ions, performance enhancing effects may also be the consequence of rare earth impact on several cellular functions as well as hormone and enzyme activities. Accordingly, enhanced cell proliferation due to rare earth application could be demonstrated for several cells including fibroblasts, hepatocytes and adipocytes. In addition, rare earths were shown to increase the concentration of fatty acids differentiating in adipocytes, indicating an impact on the lipid metabolism. Based upon higher creatinine and urea levels determined in blood taken from rats after rare earth supplementation, it was also proposed that rare earths may affect the protein metabolism. However at the same time, neither albumin nor total protein concentrations were affected.

Interactions with either calcium or hormone receptors account for influences on both hormone and enzyme activities. Furthermore, rare earths have been shown to affect the signal transmitting system, which is also involved in several hormone responses. Thus, it was shown that serum concentrations of growth hormone, thyroid hormones as well as α - amylase could be changed by rare earths. As these hormones are highly involved in growth regulating processes, rare earths may exert their performance enhancing effects by influencing their activities. Increasing α - amylase levels may lead to better digestibility of carbohydrates. In addition, growth promoting effects of rare earths may also be attributed to immuno-modulating activities. It is also possible that a combination of all effects describe above accounts for growth enhancing effects or that rare earths are not yet discovered essential elements. Finally, the mechanism underlying performance enhancing effects of rare earths on animals has not yet been verified and further research is required.

CHAPTER 13

DISCUSSION, PERSPECTIVES AND CONCLUSION

IT was the aim of this study to assess how rare earths may be adopted in animal production as efficient and safe feed additives. This concluding discussion will, therefore, attempt to sum up the results obtained in Western feeding trials, to put them in perspective and point out the needs for further research.

In China, rare earth elements have already been used for decades in agriculture as both fertilizers and feed additives, mainly containing lanthanum, cerium, praseodymium and neodymium. Though growth promotion has been reported for nearly all categories of farming animals in China, effects have been most pronounced in pigs and poultry (Xiong, 1995). According to He and Xia (1998a), body weight gain increased by 5 - 23 % in piglets (7 kg) supplemented with rare earth elements, while similar results in terms of increased body weight gain by 11 - 20 % and improved feed conversion rate of 5 - 9 % were demonstrated in piglets in line with other experiments (Li et al., 1992a), (Zhu et al., 1994). Additionally, improvements were also noticed in growing pigs (Wan et al., 1997), (Hu et al., 1999). Wang and Xu (2003) observed increased body weight gain of 13 % and decreased feed conversion rate of 7 % in pigs, while recently performed studies showed similar results (Liu, 2005). Increases in body weight gain of 8 - 23 % along with decreased feed conversion of 8 - 16 % have also been reported in chickens (Zhang and Shao, 1995), (Yang et al., 2005). However, it is generally agreed that in order to adopt rare earths as feed additives in Europe, studies have to be conducted under high standardized conditions as to reflect those prevailing in Europe.

Nevertheless, feeding experiments performed under Western conditions to this day were able to show that dietary supplementation of rare earths had positive effects on both animal growth and feed conversion of pigs and poultry kept and fed under Western conditions. Improvements in body weight gain and feed conversion rate of 5 - 19 % and 7 - 10 % were noticed in pigs (He and Rambeck, 2000), (Kessler, 2004). Accordingly, increased body weight gain of 12 - 19 % and improved feed conversion of 3 - 11 % were also described in other trials (He et al., 2001), (Borger, 2003). Yet, performance enhancing effects were not only achieved under experimental conditions but also under field conditions (Eisele, 2003). In chickens, increased final body weight by up to 7 % was observed (Halle et al., 2002a), while recently performed studies showed increased body weight gain of more than 5 % (He et al., 2006a). In accordance with Chinese reports, best results were also achieved in pigs, followed by poultry in Western feeding trials.

However, positive results could not always or only partly be demonstrated in other feeding trials (Schuller et al., 2002), (Kraatz et al., 2004). This may, on the one hand, be ascribed to the fact that according to Chinese literature rare earths may only exert performance enhancing effects when applied at a certain amount. On the other hand, it may be related to the chemical compound applied. Furthermore, in case of Kraatz et al. (2004), it has been assumed that unusually high protein contents presented in the diet, may have hampered the effects of rare earths.

As to aquaculture, no effects of rare earths could be obtained in carps, rainbow trouts or nil tilapia (Renard, 2005), (Tautenhahn, 2004). In contrast, Chinese literature reported increased yield of 16 - 23 % in different fish species (Tang et al., 1998d). As the effects of performance enhancing substances strongly depend on keeping and feeding conditions (Wenk, 2004b), it might be assumed that European aquaculture proficiency levels are already highly standardized using high quality feed and fast growing strains, therefore hardly allowing any further growth promotion. Furthermore controversial results as to performance enhancing effects of rare earths have so far been described for ruminants (Miller, 2006), (Meyer et al., 2006). Yet, two studies performed may not allow any definite statement and further studies are tended. Notwithstanding, ergo-tropic effects of rare earths demonstrated in rats coincide with those observed in pigs. As a consequence, rats are used as a small animal model in future experiments as to provide additional information on the effects of rare earths and the underlying mechanism.

Based on results obtained to this day from Western feeding experiments, it might be concluded that the outcome of dietary rare earth application varies with the animal species. Yet, concentration and type of rare earths applied as well as the composition of individual rare earth elements have also been shown to be important factors influencing performance enhancing effects of rare earths on animals, as already assumed by He et al. (2003a).

Hence, dose-dependent effects could be observed. According to Knebel (2004), only little performance enhancing effects were achieved when rare earth citrates were applied at 50 mg/kg feed, whereas with increasing concentrations from 100 mg/kg feed to 200 mg/kg feed, effects became more obvious, including improvements of body weight gain of 8.6 to 22.5 % and feed conversion of 5.5 %. Similarly, Prause et al. (2005c) reported significantly improved feed conversion of 9 % after rare earth citrates were applied at 150 mg/kg feed, whereas no effects were noticed at 300 mg/kg feed. In another study it was demonstrated that concentrations exceeding 200 mg/kg feed could even cause adverse effects, though performance enhancement was achieved at 100 mg/kg feed (Förster et al., 2006). These results coincide with the general observation of hormesis effects in rare earths. Thus, along with increasing concentrations effects may vanish or even turn to the opposite, though being obvious at low concentrations (Tripp, 2005), (Wang et al., 2003b). Dose-dependent effects as described in European feeding trials also correspond to Chinese literature which reported the necessity of accurate concentrations in order to promote animal growth (He and Rambeck, 2000). Furthermore, dose-dependency has also been described for the majority of biochemical and pharmacological properties of rare earths including antibacterial effects (Zhang et al., 2000b), immunomodulating properties (Wang et al., 2003b) and effects on cell proliferation (Greisberg et al., 2001).

However, not only the concentration but also the chemical compound, especially the anion bound to rare earths, seems to affect their performance enhancing effects. In China, different effects were described depending on the rare earth source applied (He and Rambeck, 2000) and several Chinese scientists concluded that the effects vary with the rare earth species used (Xie et al., 1991), (Lu et al., 2000). Currently, organic rare earth compounds are mainly used as feed additives in China (Xiong, 1995). In line with Chinese reports (Chen, 1997), slightly better growth promoting effects were observed in both pigs (Knebel, 2004) and poultry (Halle et al., 2002a) due to the application of organic instead of inorganic rare earth compounds. At a concentration of 62 mg/kg TREO, body weight gain was increased by up to 22.6 % when organic rare earth compounds (citrates) were applied to the feed of piglets, whereas similar concentrations of rare earth chlorides (66.5 mg/kg) improved body weight gain by 19 % (He et al., 2001). In broilers, first experiments performed applying rare earth chlorides could not observe any improvements as to fattening performance (Schuller, 2001), whereas, increased rearing performance of 3 - 7 % was achieved using rare earth ascorbate in a similar subsequent trial (Halle et al., 2002a). Accordingly, better effects of organic rare earth compounds compared to inorganic ones were also obtained in broilers in a recently performed feeding experiment (He et al., 2006a).

Differences in performance enhancing effects of rare earths as to the anion may be attributed to variations in both absorption and bioavailability of chemical compounds. It has been suggested that water soluble rare earth compounds, such as chlorides, may be almost completely hydrated within the digestive tract, therefore absorbed to a lesser extent (Ji et al., 1985b), whereas organic compounds may present higher absorption rates. Variations in bioavailability as to their chemical form have already been described in literature for several other elements including zinc and copper (Ammerman et al., 1995), (Matsui et al., 1996). Yet, there is no consistency as to whether organic compounds are more available. Nevertheless, it is assumed that both the strength of bonding as well as physiological pH conditions highly affect bioavailability (Cao et al., 2000a).

Ionic compounds are expected to dissociate completely under acidic conditions (Möller, 1963), whereas for rare earth complexes dissociation is less likely to occur, therefore complicating both gastrointestinal absorption and interaction with biological ligands. Stability constants have been shown to vary among different organic acid rare earth complexes, usually increasing with the number of carboxyl groups (Evans, 1990). Nevertheless, dissociation may not only depend on the stability. Though providing higher stability compared to competing biological ligands, citrate, a tricarboxylic acid, generally presents a lower affinity for rare earth ions, thus gives them up more easily. Furthermore, under acidic conditions, such as those prevailing in the stomach of animals ranging from 0.5 to 2.5 (Leach and Patton, 1997), it is considered unlikely that organic rare earth compounds remain chelated (Guo et al., 2001). Most metal chelates involving amino acids or proteins are reported to dissociated at a pH of either less than 3 or greater than 9 (Cao et al., 2000a). Therefore, they would present a similar behavior as inorganic compounds after reaching animal stomachs. Hence, a definite statement on whether organic rare earth compounds are more available is not to be made.

However, association and chemical properties of different rare earth complexes have also been reported to be important factors as to antimicrobial actions (Zhang et al., 2000b). It could be observed that while cerium-humic acid complexes strongly inhibited the growth of several bacteria, cerium-citrate complexes, on the contrary, did not inhibit but promote bacterial growth. This indicates that the type of chemical compound has a great impact on both magnitude and direction of pharmacological effects, hence may be also on performance enhancing effects.

Another factor possibly affecting the efficacy of rare earths as to growth promotion may be the percentage of individual rare earth elements presented within the compound applied. Performance enhancing effects have been shown to be more obvious when a mixture of rare earth elements was applied instead of pure lanthanum chloride (99.7 %). At a concentration of 150 mg/kg feed, rare earth chlorides (La, Ce, Pr, Nd) improved both body weight gain and feed conversion rate in pigs by 5 % and 7 %, respectively, whereas, improvements of 2 % and 5 % were achieved when pure lanthanum chloride was applied at the same concentration (Rambeck et al., 1999a). In a similar manner, He et al. (2003a) observed increases in body weight gain of 7 % along with decreases in feed conversion of 11 % after a mixture of rare earth chlorides was supplemented to the feed of rats. Though sole lanthanum chloride application could also enhance performance, body weight gain and feed conversion were improved to a lesser extent. Thus, as to performance enhancing effects, there must be differences between individual rare earth elements. This may result from variations in chemical and biochemical structures which in turn might affect their efficacy. Even though rare earths are considered as a chemical homologous group, differences have been reported as to electronic configuration or the oxidation state. In contrast to Ce^{3+}, La^{3+} does not possess any unpaired f-electron (Evans, 1990). Furthermore, while lanthanides generally favor trivalent oxidation states, cerium may also occur as Ce^{4+} (Cotton et al., 1999). In plants, it has already been reported that Ce^{4+} is less available than Ce^{3+} (Wei et al., 2001). It might therefore be assumed that the same applies to animals.

In addition, as for growth promoting substances in general, environmental conditions and nutritional levels also seem to interfere with performance enhancing effects of rare earth feed additives.

Nevertheless, disregarding the chemical compound, in pigs best effects have been obtained when rare earths were applied at 200 to 300 mg/kg feed (He et al., 2001), (Knebel, 2004). This slightly higher than concentrations recommended in Chinese animal husbandry (100 - 200 mg per kg feed) (Böhme et al., 2002a). Factoring the chemical compound into the calculation, concentrations may have to be converted to a uniform dimension. The amount of total rare earth oxides (TREO) is considered as reliable basis in order to compare rare earth concentrations used in different experiments (Richter, 2006). Thus, the sum of individual rare earth oxides determined in a sample allows a comparison of rare earths applied as to concentration and compound, yet not as to the composition in percent of individual rare earth elements, since the content of total rare earth oxides of 44.3 % may be composed of 44.3 % lanthanum oxide or of 10 % cerium oxide and 34.3 % lanthanum oxide and so on.

Nevertheless, comparing Western feeding trials on this basis, positive effects in pigs and rats were observed at concentrations of 65 to 132 mg/kg feed total rare earth oxides (TREO) (Knebel, 2004), (He et al., 2001), (Kessler, 2004), (He et al., 2003a), whereas lower concentrations of 20 mg/kg to 30 mg/kg feed total rare earth oxides (TREO) were needed in poultry (Halle et al., 2002a), (He et al., 2006a). This indicates that the amount required varies with the animal species. Though less pronounced, performance enhancing effects could still be achieved in pigs, when rare earths were applied at lower concentrations (33 mg/kg to 32 mg/kg feed TREO) (Rambeck et al., 1999a), (Förster et al., 2006). In contrast, Böhme et al. (2002a) did no observe any effects at concentrations ranging from 31 mg/kg to 46 mg/kg feed total rare earth oxides. Poorer results were obtained in other feeding experiments at concentrations exceeding 132 mg/kg feed TREO (Eisele, 2003), while Förster et al. (2006) did not observe any ergotropic effects at 64 mg/kg feed TREO. Just as little, Prause et al. (2005c) noticed any effects when rare earths were applied at 96 mg/kg feed TREO. In contrast, slightly increased body weight gain of 3.6 % was achieved at the same concentration by Miller (2006). Inconsistencies as to strict dose-effect relationships may yet be ascribed to interferences among the percentage concentrations of individual rare earth elements or to differences in experimental course and design. Expecting effective concentrations to be below 30 mg/kg feed TREO in poultry, might explain, why Schuller (2001) did not observe any effects in broiler applying concentrations of more than 66 mg/kg feed TREO.

Even though performance enhancing effects of rare earths on animals kept, housed and fed under Western conditions could be demonstrated in both experimental and field trials, results should be further confirmed in experiments using a higher number of animals. Moreover, within the scope of feeding trials performed, several questions have been revealed as to optimized rare earth application to animals (dosage and mixture) and their mode of action, hence implicating the need for further research as summarized beneath.

- Feeding trials on a higher number of animals
- Relationship between application dose and effect
- Determination of optimum concentrations
- Impact of individual rare earth elements on growth promoting effects of rare earths
- Impact of the chemical compound on the effects of rare earths on animals
- Effects of rare earths on the microbial composition within the gastrointestinal tract of different animal species
- Effects of rare earths on the micro-flora according to different sections of the gastrointestinal tract
- Extent to which rare earths may affect animal metabolism (liver, thyroid etc.)
- Effects of rare earths on cell proliferation
- Identification of possible explanations for the mode of action
- Environmental behavior of rare earths

Though research performed so far showed that concentration, type of chemical compound as well as the percentage of rare earth elements within the compound seem to interfere with performance enhancing effects of rare earths on animals, more detailed information on this is necessary. A dose-dependency of performance enhancing effects of rare earths has been described both in Chinese and Western feeding trials. However, a proper dose-effect relationship has not yet been established. Future studies should therefore be designed to whether a proper dose-response relation may be determined at all. If so, optimum concentrations or concentration ranges may also be defined.

Furthermore, Chinese scientists reported better performance enhancing effects of organic rare earth compounds compared to inorganic ones and as a results rare earth products commercially available in China at present mainly contain organic sources. Though better effects were also obtained in Western feeding studies, further experiments should aim at investigating which anion (chloride, nitrate, citrate, acetate, amino acids etc.) may provide the best results. Along with the type of chemical compound, it may also be of interest to assess the impact of different oxidation states of rare earth metals on their performance enhancing effects.

Improvements also seem to depend on the composition of individual rare earth compounds within the rare earth product applied. Some studies reported better effects when a mixture containing lanthanum, cerium, neodymium and praseodymium was applied than sole lanthanum chloride. Nevertheless, further research may reveal if the same performance enhancing effects can also be achieved using single rare earth elements, such as lanthanum or cerium, which were dominating in rare earth mixtures. Based upon comprehensive authorization procedures, registration of rare earths as feed additives may be facilitated if only one definite single rare earth compound, such as lanthanum carbonate or lanthanum citrate, instead of a rare earth mixture has to be accepted.

As to the mode of action, it is still unclear how rare earths exert their performance enhancing effects. Several approaches have already been made including anti-bacterial, immuno-modulating, anti-inflammatory and anti-oxidative effects, enhanced enzyme or hormone activities as well as effects on digestibility and utilization of nutrients or cellular functions.

There are a few studies reporting no effects of rare earths on the gastrointestinal flora of animals. However, based on the comparatively low number of investigations, studies should be repeated in order to verify whether or not rare earths may influence the microbial composition within the gastrointestinal tract. Additionally, it has to be considered that changes may only occur in different sections of the gastrointestinal tract, whereas, analysis of mainly directly taken small intestinal samples may help to assess a possible impact of rare earths on microbial populations located closely to absorption sites. As research describes antibacterial effects to be highly dose-dependent it might also be of interest to determine exact concentrations of rare earths within the gastrointestinal tract, thus the chymus.

Additional nutritional trials particularly focusing on protein and nitrogen balance are also recommended, as improvements in digestibility were reported by Prause et al. (2005c). Moreover, within the scope of studying the mode of action, investigations should also be focused on the extent to which and the mechanism how rare earths may affect animal metabolism (liver, thyroid etc.).

As performance enhancing effects achieved in rats were comparable to those in pigs, rats may serve as a reliable small animal model for further research. In addition, chickens and quails may also provide animal models suitable for studying the effects of rare earths.

Presently, research on rare earth elements is in full swing and additional investigations are already planned at the University of Munich and at other institutes to narrow down the mode of action, as well as to determine optimum concentrations and the effect of chemical compounds in rat feeding experiments. Currently performed and future investigations are listed as follows.

- Effects of different rare earth compounds on animal growth and animal metabolism (blood analysis) (rat feeding experiment)
- Effects of rare earths on performance of dairy cows
- Effects of different cerium compounds on animal performance (rat feeding experiment)
- Studies performed on pigs and veal cattle are scheduled to be repeated [FAL Brunswick]
- a project promoted by the DFG (Deutsche Forschungsgesellschaft - German Research Foundation) is prearranged to investigate the mode of action (Cooperation of University of Munich and FAL Brunswick)

- Additional feeding trials applying rare earth citrates to a higher number of pigs are also intended

Though it is assumed that long-term application of rare earths will not seriously affect the environment, further studies should be conducted. Future projects are already under way as described in Chapter 7.

As to the registration of rare earth elements as feed additives within the European Community, some general information may also be of interest. In order to assure food safety, a new law has been enacted in Germany on the 1. September 2005, combining both animal feed and food legislation in one lot (Bundesgesetz, 2005). Hence, animal feed has been recognized as the first element within the food production chain and consequently been included (Bundesministerium für Verbraucherschutz, 2005). At EC level, a new EC regulation governing the use of feed additives in animal nutrition has already been passed in 2003 [EC regulation No 1831/2003]. Accordingly, in order to be registered, feed additives must not have any detrimental effects on either the state of health of humans and animals or the environment.

A detailed report on the safety of rare earth application to animals and humans as well as on the environmental impact is given in Chapter 6, Chapter 7 and Chapter 12. It can be concluded that with respect to low rare earth concentrations of 200 mg/kg feed no severe effects are to be expected on the environment. Amounts of rare earths applied to soil following fertilization with liquid manure are definitely much smaller than those already present (Tyler, 2004). Quite the contrary, rare earth application may reduce environmental loads, since as a consequence of better nutrient utilization less feces is produced. In addition, oral toxicity of rare earths comparable to table salt and oral LD_{50} values beyond 1 g per kg body weight (Wald, 1990), (Richter, 2003) indicate the safe use of rare earth feed additives in animals. This could also be confirmed in numerous feeding experiments (He et al., 2001), (Knebel, 2004), (Fleckenstein et al., 2004), (Miller, 2006) during which harmful effects on animal health were not observed at all.

Furthermore, in consequence of poor gastrointestinal absorption, very low accumulation has been detected in animal tissues (He et al., 2001), (Böhme et al., 2002a), (Eisele, 2003), whereas rare earth concentrations were in a similar range as in control animals. This can be attributed to the fact that rare earths occur ubiquitous, consequently they are also found in commercial diets (Krafka, 1999). As a result, tissue contents of rare earths between μg/kg and mg/kg body weight could be determined in both animals and humans receiving a normal diet (Evans, 1990). A comparison between the possible daily intake of 2.10 - 2.50 mg/person/d (Su et al., 1993) and the acceptable daily intake (ADI) of 12 - 120 mg rare earth nitrates per person and day (Song et al., 2005), implicates that no risk for consumers is to be expected due to the use of rare earth feed additives in animal production. On this basis, rare earths already meet main conditions as to environmental, animal and human safety.

Within the EC regulation No 1831/2003, generic terms, such as growth promoter, performance enhancer or ergo-tropic substances, have been completely excluded. Being authorized implies that feed additives have to influence one of the following aspects positively: feed consistence, composition of animal foodstuffs, color of ornamental fish and birds, ecological consequences of animal production or animal production including performance and well-being of animals. Thus, according to their effect, feed additives are now categorized into five groups comprising technological (preservative, antioxidants, stabilizers etc.), sensory (dyestuffs and favors), nutritional (vitamins, trace elements, amino acids, urea and its derivatives) and zootechnical (promoters of digestibility, stabilizers of the gastrointestinal micro-flora, substances favorable to the environment and miscellaneous zootechnical substances) additives or coccidiostats and histomonostats (Busch, 2005). Consequently, in order to be registered as feed additives, rare earths have to be arranged into one of these groups. However, the mechanism underlying performance enhancing effects of rare earths is still not completely understood, though several proposals have been made (Section 12.3).

Nevertheless, within the scope of presenting characteristics of trace elements, rare earths would have to be classified as nutritional additives. The fact that rare earths occur ubiquitous in soil, plants (Krafka, 1999), but also in human and animal tissues (Evans, 1990), (Eisele, 2003), has lead to the assumption that rare earths might be essential trace elements for animals and humans. However, to this day, evidence has not been supplied. Notwithstanding, due to their similarity to calcium ions, rare earth have been shown to affect several biological processes within the body, thereby influencing the intermediate metabolism in various manners. Hence, rare earths were able to affect several enzymatic activities, including those of enzymes involved in the gastrointestinal tract (Brewer et al., 1981), (Wang et al., 2002). Additionally, hormones considered important as to body metabolism, such as thyroid hormones (He et al., 2003a), (He et al., 2001), (Förster et al., 2006), growth hormone (Wang and Xu, 2003), (Liu and Hasenstein, 2005) and insulin (Enyeart et al., 2002) have been shown to be affected by oral rare earth application. Yet, despite their indisputable effects on numerous calcium depending processes, there is no biological function of rare earths in this respect.

However, if rare earths enhance nutrient digestibility or stabilize the gastrointestinal flora, they would be registered as zootechnical additive. It has been suggested that improved digestibility of nutrients may account for performance enhancing effects of rare earths and, consistently, several Chinese scientists were able to demonstrate enhanced digestibility and utilization of nutrients after feeding rare earths to animals (Cheng et al., 1994), (Lu and Yang, 1996), (Xu et al., 1998). This was further supported by the findings of increased body weight gain along with decreased feed conversion rate, as reported in European studies. Yet, results obtained in nutritional experiments were controversial. On the one hand, Prause et al. (2004) was able to demonstrate improved nutrient digestibility within the scope of investigating the energy-, carbohydrate- and nitrogen- balance and the digestibility of nutrients in piglets using respiration chambers. Böhme et al. (2002a), on the other hand, did not observe any effects in nutritional balance tests performed on pigs. Fleckenstein et al. (2004) suggested that rare earths may enhance the utilization of phosphorous compounds based upon phosphate binding abilities. Nevertheless, up to now, no definite statement can be made as to whether or not rare earths are capable of enhancing digestibility or utilization of nutrients.

Stabilization of intestinal micro-flora has also been assumed to possibly explain growth promotion due to rare earth application, as dose-dependent effects on bacteria were multiply described in literature (Muroma, 1958), (Zhang et al., 2000b), (Ruming et al., 2002). Though there was a tendency towards decreased anaerobic bacteria populations, investigations performed in line with feeding trials have not yet been able to demonstrate significant effects of rare earths on the microbial composition within the gastrointestinal tract of pigs, poultry or within the rumen of cattle (Schuller, 2001), (Knebel, 2004). Furthermore, significant changes have neither been observed in the composition of faecal bacterial populations in biochemical studies (Kraatz et al., 2004). With respect to anti-oxidative properties, rare earths could also be registered as technical additives.

Following the EC regulation No 1831/2003, a new European Food Safety Authority (EFSA) has been released as of 2004, which implicates that only feed additives passing a comprehensive procedure may be allowed on the European market. Consequently, high costs are involved in the registration of feed additives as pointed out recently by Pape (2004). Hence, in order to be registered as feed additive, rare earths need to overcome several bureaucratic wattles. Nevertheless, a temporary permission for the use of rare earths as feed additives in pigs has been granted in Switzerland, in 2003 (Rambeck and Wehr, 2004). Currently, rare earth containing feed additives may be purchased as *Lancer*® from the Swiss company *Zehentmayer* (Zehentmayer, 2006), whereas recommended concentrations range from 150 mg/kg to 300 mg/kg feed. Following the temporary authorization of rare earth containing feed additives in Switzerland, the focus is now on getting this permission of rare earth application to farming animals extended to all the countries in the European Union.

In conclusion, it could be demonstrated that rare earths can enhance performance of pigs and poultry housed and fed under Western conditions. These results coincide with Chinese literature, which reports the successful use of rare earths as feed additive in animal husbandry in China. Along with performance enhancing effects, rare earths also presented very low oral toxicity, even in long-term feeding trials. Additionally, hardly any accumulation was noticed in animal tissues. On this basis, rare earth application as feed additives is considered to be safe for both animals and humans. Supplementary costs following rare earth application amount up to only five to ten US$/kg for rare earths plus transportation costs, while according to current recommendations only approximately 250 mg rare earths would have to be supplemented to one kg feed. Therefore, rare earths might be of interest as effective, safe and inexpensive feed additive in animal production, especially in pig and poultry production. Furthermore, on the background of recent public debates on food safety and development of resistance bacteria following the application of in-feed antibiotics, originating from natural resources, rare earths might also meet public opinion.

APPENDIX A

MEDICINE

	Control	RE 50 mg/kg	RE 100 mg/kg	RE 200 mg/kg
n	7	7	7	7
Calcium	341.47 ± 6.61	330.31^{*} ± 6.07	330.25^{*} ± 6.58	347.35 ± 6.26
Phosphorous	178.48 ± 3.06	180.92 ± 1.24	177.04 ± 6.56	179.47 ± 1.69
Ca/P	1.91 ± 0.04	1.83^{*} ± 0.03	1.87^{*} ± 0.06	1.94 ± 0.05

Table A.1: Effects of rare earth (RE) citrates on calcium phosphorous ratio of piglets; values with an asterisk ($*$) differ significantly $p < 0.05$; n: number of animals per group (Knebel, 2004).

	Control (SHAM)	Control (OVX)	La carbonate	La carbonate + Vit D	La mixture	La mixture + Vit D
PD (AUC)	$130.9^{*} \pm 32.1$	192.4 ± 14.7	162.9 ± 52.3	$140.5^{*} \pm 26.5$	$150.3^{*} \pm 31.3$	$131.7^{*} \pm 22.1$
OC (AUC)	643 ± 131.6	770.0 ± 235.1	888.6 ± 196.1	1014.7 ± 274.9	989.5 ± 269.4	858.7 ± 168.6
Ca (mg/g ash)	$430.7^{*} \pm 28.8$	361.2 ± 41.1	$425.2^{*} \pm 25.8$	$429.8^{*} \pm 17.6$	$432.8^{*} \pm 15.6$	$430.9^{*} \pm 20.4$

Table A.2: Effects of dietary supplementation of a mixture of lanthanum (La) salts or lanthanum carbonate with and without Vitamin D on bone turnover (pyridinoline (PD in AUC) and osteocalcin (OC in AUC) as well as on bone (tibia) mineral content (calcium Ca in mg/g ash) in ovariectomized rats; mean values ± standard deviation; values with an asterisk ($*$) differ significantly $p < 0.05$ from the OVX control; calculated as an area under the curve (AUC) for all determined values (Wehr et al., 2006).

APPENDIX B

RESULTS OF FEEDING TRIALS

n	Control 24	75 mg La 12	150 mg La 12	75 mg RE 12	150 mg RE 12
initial BW (kg)	7.33 ± 1.54	7.32 ± 1.18	7.33 ± 1.22	7.33 ± 1.29	7.33 ± 1.16
end BW (kg)	17.27 ± 3.83	17.53 ± 2.53	17.27 ± 2.90	17.54 ± 3.18	17.80 ± 3.08
Results during the first two weeks					
FI (g/pig/day)	285 ± 31	284 ± 28	292 ± 24	287 ± 33	292 ± 26
BWG (g/day)	165 ± 72	178 ± 52	175 ± 46	190 ± 43	193 ± 45
FCR (kg/kg)	1.84 ± 0.50	1.63 ± 0.29	1.68 ± 0.16	1.55 ± 0.24	1.54 ± 0.17
Improvements compared to the control					
FI (%)		0	+ 2	+ 1	+ 2
BWG (%)		+ 8	+ 6	+ 15	+ 17
FCR (%)		+ 11	+ 9	+ 16	+ 16
Results during the last three weeks					
FI (g/pig/day)	758 ± 112	742 ± 83	729 ± 75	743 ± 83	736 ± 82
BWG (g/day)	360 ± 88	368 ± 62	356 ± 79	360 ± 93	370 ± 78
FCR (kg/kg)	2.14 ± 0.25	2.03 ± 0.14	2.07 ± 0.20	2.10 ± 0.21	2.01 ± 0.17
Improvements compared to the control					
FI (%)		- 2	- 4	- 2	- 3
BWG (%)		+ 2	- 1	0	+ 3
FCR (%)		+ 5	+ 3	+ 2	+ 6
Results over the whole experimental period					
FI (g/pig/day)	569 ± 77	559 ± 61	554 ± 53	561 ± 61	559 ± 58
BWG (g/day)	285 ± 70.3	292 ± 52.0	284 ± 55.7	292 ± 66.3	299 ± 60.0
FCR (kg/kg)	2.02 ± 0.21	1.93 ± 0.11	1.97 ± 0.14	1.95 ± 0.16	1.89 ± 0.16
Improvements compared to the control					
FI (%)		- 2	- 3	- 1	-2
BWG (%)		+ 2	0	+ 2	+ 5
FCR (%)		+ 5	+ 3	+ 4	+ 7

Table B.1: Effects of dietary supplementation of rare earth (RE) chlorides and lanthanum (La) chloride at different concentrations on feed intake (g/g) daily body weight gain (BWG in g per day) and feed conversion rate (FCR in kg/kg) of piglets; mean values ± standard deviation; there was no significant difference among the experimental groups; n = number of animals in each experimental group (Rambeck et al., 1999a).

	Control	RE 300 mg	p-value
n	7	7	
intial BW (kg)	17.7 ± 1.9	17.4 ± 2.6	
end BW (kg)	53.2 ± 6.2	59.6 ± 5.2	
During the first two week of the experiment			
BWG (g/day)	305 ± 40	381 ± 33	< 0.01
FI (g/day)	794 ± 34	769 ± 72	> 0.05
FCR (kg/kg)	2.64 ± 0.35	2.09 ± 0.21	< 0.01
improvements BWG (%)		+ 25	
improvements FI (%)		- 3	
improvements FCR (%)		+ 21	
During the last three weeks of the experiment			
BWG (g/day)	745 ± 117	879 ± 91	< 0.05
FI (g/day)	1738 ± 185	1878 ± 169	> 0.05
FCR (kg/kg)	2.35 ± 0.13	2.14 ± 0.08	< 0.01
improvements BWG (%)		+ 18	
improvements FI (%)		+ 8	
improvements FCR (%)		+ 9	
Over the whole experimental period			
BWG (g/day)	635 ± 91	755 ± 68	< 0.05
FI (g/day)	1502 ± 142	1606 ± 130	> 0.05
FCR (kg/kg)	2.38 ± 0.12	2.13 ± 0.08	< 0.01
improvements BWG (%)		+ 19	
improvements FI (%)		+ 7	
improvements FCR (%)		+ 10	

Table B.2: Effects of rare earth (RE) chlorides on body weight (BW in kg), daily body weight gain (BWG in g), daily feed intake (FI in g) and feed conversion rate (FCR in kg/kg) in pigs; mean values ± standard deviation; p-value: significance; n: number of animals per experimental group (He and Rambeck, 2000).

	Control	RE 300 mg	p-value
n	7	7	
Growing period			
initial BW (kg)	17.7 ± 1.9	17.4 ± 2.6	NA
end BW (kg)	53.2 ± 6.2	59.6 ± 5.2	> 0.05
BWG (g/day)	635 ± 92	755 ± 68	< 0.05
FI (g/day)	1502 ± 142	1606 ± 130	> 0.05
FCR (kg/kg)	2.38 ± 0.12	2.13 ± 0.08	< 0.01
improvements BWG (%)		19	
improvements FI (%)		7	
improvements FCR (%)		11	
Fattening period			
initial BW (kg)	53.2 ± 6.2	59.6 ± 5.2	NA
end BW (kg)	76.8 ± 9.6	86.0 ± 7.0	> 0.05
BWG (g/day)	842 ± 139	941 ± 143	> 0.05
FI (g/day)	2222 ± 277	2462 ± 227	> 0.05
FCR (kg/kg)	2.71 ± 0.19	2.63 ± 0.17	> 0.05
improvements BWG (%)		12	
improvements FI (%)		11	
improvements FCR (%)		3	

Table B.3: Effects of rare earth (RE) chlorides on body weight (BW in kg), daily body weight gain (BWG in g), daily feed intake (FI in g) and feed conversion rate (FCR in kg/kg) in pigs; mean values ± standard deviation; p-value: significance; NA: not available; n: number of animals per experimental group (He et al., 2001).

	Control	RE 300 mg/kg
n	8	8
Body weight (kg)		
initial BW	17.7 ± 1.7	17.4 ± 2.4
BW after 8 weeks	53.2 ± 5.7	59.6 ± 4.8
final BW 12 weeks	76.0 ± 8.6	86.0 ± 6.4
Improvement (%)		13
Daily feed intake (g/d)		
1. - 2. week	794 ± 32	791 ± 33
3. - 4. week	1409 ± 137	1497 ± 120
5. - 6. week	1766 ± 175	1896 ± 180
7. - 8. week	2042 ± 261	2240 ± 219
9. - 10. week	1917 ± 267	2223 ± 190
11.- 12. week	2565 ± 288	2696 ± 274
Feed conversion (kg/kg)		
1. - 2. week	2.64 ± 0.32	2.09 ± 0.19
3. - 4. week	2.14 ± 0.13	2.12 ± 0.14
5. - 6. week	2.30 ± 0.17	2.11 ± 0.16
7. - 8. week	2.59 ± 0.20	2.19 ± 0.05
9. - 10. week	2.77 ± 0.20	2.52 ± 1.05
11.- 12. week	2.68 ± 0.27	2.48 ± 0.24

Table B.4: Effects of rare earth elements (REE) on body weight gain (BWG in g/animal/d) and feed conversion (kg/kg) of piglets; mean value ± standard deviation; n: number of animals per group (Borger, 2003).

	Control	RE 300 mg/kg RE chlorides	LaCe I 100 mg/kg $LaCl_3$ 200 mg/kg $CeCl_3$	LaCe II 200 mg/kg $LaCl_3$ 100 mg/kg $CeCl_3$
n	12	12	12	12
		Body weight (kg)		
initial BW	15.4 ± 1.8	15.3 ± 1.5	15.4 ± 1.8	15.6 ± 2.0
BW day 42	39.3 ± 3.0	38.6 ± 2.9	39.2 ± 3.1	39.4 ± 3.9
BW day 83	73.6 ± 8.5	75.9 ± 7.6	76.7 ± 7.4	76.1 ± 7.5
		Daily feed intake (g/d)		
1. - 2. week	596 ± 0	585 ± 33	596 ± 0	595 ± 6
3. - 4. week	1129 ± 11	1124 ± 21	1118 ± 39	1111 ± 66
5. - 6. week	1553 ± 144	1559 ± 114	1564 ± 115	1573 ± 137
7. - 8. week	1736 ± 275	1796 ± 263	1815 ± 246	1790 ± 264
9. - 10. week	1939 ± 363	2042 ± 405	2032 ± 296	1983 ± 360
11.- 12. week	2203 ± 401	2379 ± 393	2332 ± 319	2342 ± 330
1.- 12. week	1529 ± 184	1583 ± 181	1579 ± 148	1568 ± 170
		Daily body weight gain (g/d)		
1. - 2. week	324.4 ± 53.9	306.9 ± 17.5	311.5 ± 58.5	304.1 ± 42.8
3. - 4. week	641.7 ± 45.3	641.7 ± 50.2	626.8 ± 51.7	614.3 ± 87.3
5. - 6. week	767.3 ± 114.2	736.3 ± 120.4	781.0 ± 126.2	807.1 ± 109.2
7. - 8. week	796.4 ± 152.9	843.5 ± 157.0	845.2 ± 125.4	808.3 ± 158.4
9. - 10. week	884.5 ± 182.3	922.6 ± 161.1	942.9 ± 132.6	936.9 ± 106.9
11.- 12. week	830.1 ± 226.2	964.7 ± 139.0	957.1 ± 128.5	945.5 ± 131.5
1.- 12. week	710.6 ± 94.5	738.7 ± 83.0	746.7 ± 79.7	738.8 ± 70.9
		Feed conversion (kg/kg)		
1. - 2. week	1.89 ± 0.33	1.90 ± 0.14	1.98 ± 0.39	1.99 ± 0.30
3. - 4. week	1.77 ± 0.12	1.76 ± 0.12	1.79 ± 0.11	1.84 ± 0.24
5. - 6. week	2.04 ± 0.16	2.15 ± 0.29	2.03 ± 0.23	1.96 ± 0.15
7. - 8. week	2.20 ± 0.17	2.15 ± 0.14	2.15 ± 0.14	2.23 ± 0.16
9. - 10. week	2.21 ± 0.21	2.21 ± 0.17	2.16 ± 0.17	2.11 ± 0.22
11.- 12. week	2.84 ± 1.02	2.49 ± 0.42	2.45 ± 0.26	2.50 ± 0.35
1.- 12. week	2.16 ± 0.09	2.15 ± 0.11	2.12 ± 0.08	2.12 ± 0.10
		Performance parameters over the whole fattening period[a]		
BW end (kg)	91.2 ± 8.9	95.4 ± 9.2	94.4 ± 8.1	95.1 ± 9.5
FI (g/d)	1704 ± 216	1789 ± 212	1752 ± 176	1768 ± 195
BWG (g/d)	673.1 ± 84.7	704.7 ± 81.1	686.7 ± 64.6	707.3 ± 67.6
FCR (kg/kg)	2.53 ± 0.11	2.54 ± 0.14	2.52 ± 0.13	2.52 ± 0.14

Table B.5: Effects of rare earth elements (REE) on feed intake (FI in g/animal/day), body weight gain (BWG in g/animal/d) and feed conversion (kg/kg) of piglets, second trial; mean value ± standard deviation; [a] including the period in which only complete diets without rare earths supplementation were fed (Eisele, 2003).

	Control	RE A	RE B
n	12	12	12
Feed Intake (g/animal/d)			
1. – 3. week	443 ± 18	433 ± 81	447 ± 12
4. week	1326 ± 74	1280 ± 320	1409 ± 54
5. week	1972 ± 186	1880 ± 446	2105 ± 107
6. week	2190 ± 294	2017 ± 553	2265 ± 285
7. week	2550 ± 242	2175 ± 636	2615 ± 313
8. week	2979 ± 319	2588 ± 680	3086 ± 296
9. week	3306 ± 349	3026 ± 765	3445 ± 316
10. week	3568 ± 391	3324 ± 750	3777 ± 312
1. – 6. week	1698 ± 130	1557 ± 395	1768 ± 133
1. – 10. week	3284 ± 333	2980 ± 724	3436 ± 292
Body weight (kg)			
initial BW	8.3 ± 0.7	8.3 ± 0.7	8.3 ± 0.7
BW day 68	40.0 ± 3.7	37.5 ± 7.9	40.3 ± 3.7
Body weight gain (g/animal/d)			
1. – 3. week	190 ± 59	227 ± 40	216 ± 54
1. – 6. week	852 ± 96	867 ± 55	877 ± 65
1. – 10. week	3284 ± 333	2980 ± 724	3436 ± 292
Compared to the control (%)		- 4.3	- 2.6
Feed conversion (kg/kg)			
1. – 3. week	2.53 ± 0.81	2.10 ± 0.35	2.21 ± 0.73
1. – 6. week	2.08 ± 0.22	1.99 ± 0.09	2.06 ± 0.15
1. – 10. week	2.30 ± 0.15	2.20 ± 0.08	2.24 ± 0.12
Compared to the control (%)		- 9.3	+ 4.6

Table B.6: Effects of rare earths (RE) on feed intake (in g), body weight (kg), body weight gain (BWG in g/animal/d) and feed conversion (kg/kg) of piglets; RE A 300 mg/kg of 99.7 % $LaCl_3 \cdot 6H_2O$, < 2.5 % $CeCl_3 \cdot 6H_2O$, < 0.3 % $PrCl_3 \cdot 6H_2O$, RE B: 300 mg/kg of 38.0 % $LaCl_3 \cdot 6H_2O$, 52.01 % $CeCl_3 \cdot 6H_2O$, 3.02 % $PrCl_3 \cdot 6H_2O$; mean value ± standard deviation; ^{a,b} values without the same superscripts differ significantly $p < 0.05$; n: number of animals per group (Recht, 2005).

	Control	RE chlorides 200 mg/kg
	First field trial	
n	48	49
initial weight (kg)	11.15	10.59
end weight (kg)	18.96	18.47
FI (g/d)	707	764
BWG (g/d)	474	484
FCR (kg/kg)	1.61	1.46
Improvements (%)		
FI		8.0
BWG		2.1
FCR		9.3
	Second field trial	
n	61	115
initial weight (kg)	8.31	8.71
end weight (kg)	20.43	20.60
FI (g/d)	589	634
BWG (g/d)	374	412
FCR (kg/kg)	1.58	1.54
Improvements (%)		
FI		7.6
BWG		10.2
FCR		2.5

Table B.7: Effects of rare earth elements on body weight gain (BWG in g) and feed conversion (FC in kg/kg) under field conditions; n: number of animals in each experimental group (Eisele, 2003), (Zehentmayer, 2002).

	Control	RE 50 mg/kg	RE 100 mg/kg	RE 200 mg/kg
n	7	7	7	7
		Feed Intake (g/animal/d)		
1. week	367 ± 83	366 ± 99	337 ± 70	469 ± 120
2. week	680 ± 148	808 ± 178	718 ± 206	836 ± 213
3. week	1020 ± 101	942 ± 43	995 ± 115	1155 ± 52
4. week	1197 ± 207	1165 ± 231	1301 ± 265	1340^{*} ± 207
5 1/2. week	1245 ± 77	1258 ± 79	1441^{*} ± 66	1513^{*} ± 62
1. - 6. week	870 ± 144	1557 ± 395	913 ± 152	1020 ± 137
		Body weight (kg)		
initial BW	8.6 ± 0.8	8.6 ± 0.7	8.6 ± 1.1	8.6 ± 1.3
BW day 20	13.7 ± 1.9	14.4 ± 1.9	14.6 ± 1.6	15.7 ± 2.7
BW day 38	25.7 ± 3.5	26.1 ± 3.2	27.4 ± 3.7	30.1 ± 5.0
		Body weight gain (g/animal/d)		
1. week	232 ± 94	229 ± 132	249 ± 72	365 ± 98
2. week	432 ± 82	495 ± 93	512 ± 95	512 ± 109
3. week	655 ± 138	558 ± 117	621 ± 256	741 ± 164
4. week	734 ± 122	708 ± 137	738 ± 134	798 ± 140
5. week	593 ± 176	713 ± 146	832^{*} ± 146	898^{*} ± 176
1. - 6. week	523 ± 118	525 ± 123	568 ± 140	641 ± 134
		Feed conversion (kg/kg)		
1. week	1.59	1.60	1.35	1.29
2. week	1.57	1.46	1.40	1.63
3. week	1.56	1.69	1.60	1.56
4. week	1.63	1.65	1.76	1.68
5. week	2.10	1.77	1.73	1.68
1. - 6. week	1.65	1.62	1.56	1.56

Table B.8: Effects of rare earth (RE) citrates on feed intake (in g), body weight gain (BWG in g/animal/d) and feed conversion (kg/kg) of piglets; mean value ± standard deviation; values with an asterisk ($*$) differ significantly $p < 0.05$; n: number of animals per group (Knebel, 2004).

	Control	RE citrate 200 mg/kg
Fattening period (in *days*)		
all animals	102	93
females	108	95
barrows	96	91
Daily body weight gain (in g)		
all animals	782	851
females	743	830
barrows	822	872
Feed consumption (in kg)		
all animals	199	192
females	205	189
barrows	194	195
Feed conversion rate (in kg/kg)		
all animals	2.52	2.43
females	2.56	2.40
barrows	2.47	2.46

Table B.9: Effects of rare earth citrates on performance of fattening pigs (Kessler, 2004).

	Control	RE citrate 300 ppm
n	10	10
BW 1. week	10.8 ± 4.8	11.6 ± 3.7
Rearing period		
1. - 3. week	468.9 ± 211.9	574.4 ± 176.5
4. - 7. week	$678.5^{ab} \pm 125.6$	$720.0^{b} \pm 159.2$
1. - 7. week	598.7 ± 147.9	664.5 ± 159.5
Compared to the control (%)		+ 11.0
Growing period		
8. - 11. week	622.6 ± 101.1	622.6 ± 48.3
12. - 15. week	$837.3^{ab} \pm 161.8$	$742.1^{a} \pm 71.5$
8. - 15. week	$728.1^{a} \pm 117.4$	$690.4^{b} \pm 53.0$
Compared to the control (%)		- 5.2
Fattening period		
16. - 18. week	$702.0^{ab} \pm 278.7$	$929.5^{b} \pm 79.1$
19. - 21. week	$718.8^{ab} \pm 190.7$	$534.4^{b} \pm 103.6$
16. - 21. week	709.1 ± 215.4	763.2 ± 82.8
Compared to the control (%)		+ 7.6

Table B.10: Effects of rare earth citrates on body weight gain (in g/d) growing and fattening Barrows; mean value ± standard deviation; ^{a,b} values without the same superscripts differ significantly $p < 0.05$; n: number of animals per group (Miller, 2006).

	Control	RE citrate 300 ppm
n	10	10
BW 1. week	10.6 ± 4.4	11.4 ± 3.9
BW 20. week	102.3 ± 17.3	99.4 ± 10.9
Rearing period		
1. - 3. week	463.6 ± 175.7	521.4 ± 130.5
4. - 7. week	616.6 ± 113.6	608.9 ± 112.5
1. - 7. week	558.3 ± 132.4	575.6 ± 113.5
Compared to the control (%)		+ 3.0
Growing period		
8. - 11. week	$562.1^{ab} \pm 112.4$	$556.0^{b} \pm 77.0$
12. - 15. week	821.4 ± 143.8	765.6 ± 157.5
8. - 15. week	$689.1^{ab} \pm 113.9$	$659.0^{ab} \pm 85.7$
Compared to the control (%)		- 4.4
Fattening period		
16. - 18. week	679.5 ± 149.8	806.8 ± 81.5
19. - 21. week	$875.0^{a} \pm 284.7$	$535.2^{b} \pm 113.8$
16. - 21. week	692.6 ± 278.0	692.4 ± 65.6
Compared to the control (%)		0

Table B.11: Effects of rare earth citrates on body weight gain (in g/d) female growing and fattening pigs; ^{a,b} values without the same superscripts differ significantly $p < 0.05$; n: number of animals per group (Miller, 2006).

	Control	RE Citrate
n	7	7
Feed Intake (g/animal/d)		
1. week	141 ± 26	159 ± 38
2. week	457 ± 78	413 ± 52
3. week	827 ± 143	797 ± 145
4. week	1185 ± 253	1187 ± 256
5. week	1442 ± 233	1451 ± 277
6. week	1657 ± 173	1555 ± 204
7. week	1582 ± 191	1608 ± 183
1. – 6. week	952 ± 190	927 ± 201
1. – 7. week	1042 ± 117	1024 ± 141
Compared to the control (%)		- 1.7
Body weight (kg)		
initial BW	8.7 ± 0.5	8.8 ± 0.7
BW day 48	37.4 ± 4.1	38.3 ± 2.5
Body weight gain (g/animal/d)		
1. week	84 ± 59	86 ± 51
2. week	325 ± 87	340 ± 77
3. week	536 ± 106	630 ± 131
4. week	635 ± 205	646 ± 124
5. week	811 ± 141	838 ± 87
6. week	904 ± 188	867 ± 59
7. week	940 ± 78	948 ± 96
1. – 6. week	549 ± 86	568 ± 50
Compared to the control (%)		+ 3.5
Feed conversion (kg/kg)		
1. – 2. week	1.45 ± 0.23	1.27 ± 0.36
3. week	1.55 ± 0.05	1.28 ± 0.19
4. week	1.95 ± 0.37	1.85 ± 0.31
5. week	1.80 ± 0.23	1.72 ± 0.18
6. week	1.86 ± 0.22	1.79 ± 0.18
7. week	1.72 ± 0.27	1.72 ± 0.30
1. – 6. week	1.72 ± 0.07	1.58 ± 0.10
1. – 7. week	1.72 ± 0.09	1.60 ± 0.12
Compared to the control (%)		- 7.0

Table B.12: Effects of rare earth (RE) citrate on feed intake (in g), body weight gain (BWG in g/animal/d) and feed conversion (kg/kg) of piglets; mean value ± standard deviation; ^{a,b} values without the same superscripts differ significantly $p < 0.05$; n: number of animals per group (Recht, 2005).

n	Control 16	100 mg RE 16	200 mg RE 16	400 mg RE 16	800 mg RE 16
Performance parameters					
end BW (kg)	17.1	17.7	16.1	15.2	16.7
BWG (g/d)	283^{ab}	301^{a}	254^{b}	258^{ab}	271^{ab}
Effects compared to the control (%)					
end BW		+ 3.5	- 5.8	- 11.1	- 2.3
BWG		+ 6.4	- 10.2	- 8.8	- 4.2

Table B.13: Effects of dietary rare earth (RE) supplementation on body weight (kg) and body weight gain (g per day); mean values ± standard deviation; ^{a,b} values without the same superscripts differ significantly $p < 0.05$; n: number of animals per group (Förster et al., 2006).

	Control	150 mg RE citrates	300 mg RE citrates	p-value
		BW (kg)		
day 9	1921 ± 144	2013 ± 184	2171 ± 200	0.85
day 26	1641 ± 134	1758 ± 163	1871 ± 173	0.90
day 40	618 ± 80	680 ± 131	786 ± 124	0.88
		DBWG (kg)		
P1	0.515 ± 0.10	0.494 ± 0.13	0.497 ± 0.15	0.89
P2	0.766 ± 0.15	0.736 ± 0.10	0.765 ± 0.11	0.81
P3	0.998 ± 0.08	1.044 ± 0.10	1.004 ± 0.07	0.47
MEAN	0.813 ± 0.07	0.817 ± 0.07	0.794 ± 0.07	0.95
		FI (kg)		
P1	0.77 ± 0.07	0.75 ± 0.32	0.74 ± 0.12	0.89
P2	1.23 ± 0.16	1.15 ± 0.26	1.22 ± 0.11	0.47
P3	1.99 ± 0.23	1.90 ± 0.24	1.96 ± 0.25	0.68
MEAN	1.46 ± 0.12	1.34 ± 0.16	1.40 ± 0.13	0.44
		FC (kg/kg)		
P1	1.51 ± 0.22	1.53 ± 0.11	1.49 ± 0.08	0.93
P2	1.61 ± 0.08	1.56 ± 0.09	1.60 ± 0.08	0.48
P3	2.00 ± 0.17	1.83 ± 0.09	1.96 ± 0.30	0.05
MEAN	1.79 ± 0.13	1.68 ± 0.16	1.77 ± 0.16	0.02

Table B.14: Effects of rare earth (RE) citrates on body weight (BW in kg), daily body weight gain (DBWG in kg), feed intake (FI in kg) and feed conversion (FC in kg/kg) of piglets with P1: after adaptation to first respiration period (day 10 - 25) P2: until 25 kg (day 26 - 40) P3: until slaughtered at 55 - 65 kg (day 40 - 62/69); mean values ± standard deviation; p-value significance (Prause et al., 2004).

	Control	RE 300 mg/kg RE chlorides	LaCe I 100 mg/kg $LaCl_3$ 200 mg/kg $CeCl_3$	LaCe II 200 mg/kg $LaCl_3$ 100 mg/kg $CeCl_3$
n	12	12	12	12
Body weight (kg)				
initial BW	18.0 ± 2.0	18.0 ± 2.3	18.1 ± 2.7	18.3 ± 1.8
BW day 41	37.4 ± 3.6	35.8 ± 3.5	37.9 ± 4.1	37.5 ± 4.9
final BW 12 weeks	67.3 ± 7.5	65.0 ± 7.0	67.6 ± 5.6	66.4 ± 6.6
Daily feed intake (g/d)				
1. - 2. week	672 ± 40	676 ± 52	692 ± 47	678 ± 39
3. - 4. week	1056 ± 76	1023 ± 119	1082 ± 114	1079 ± 151
5. - 6. week	1332 ± 92	1297 ± 117	1339 ± 117	1327 ± 181
7. - 8. week	1742 ± 235	1665 ± 171	1777 ± 117	1724 ± 224
9. - 10. week	2082 ± 333	2006 ± 241	2075 ± 212	1976 ± 238
11. week	2276 ± 444	2202 ± 311	2222 ± 248	2182 ± 224
1.- 11. week	1480 ± 158	1432 ± 137	1489 ± 105	1452 ± 127
Daily body weight gain (g/d)				
1. - 2. week	314.4 ± 60.7	251.4 ± 50.5	323.3 ± 74.4	291.9 ± 62.6
3. - 4. week	506.5 ± 54.8	489.3 ± 75.7	526.4 ± 61.8	499.3 ± 112.2
5. - 6. week	611.3 ± 83.2	565.5 ± 63.5	612.9 ± 79.8	621.4 ± 109.1
7. - 8. week	794.6 ± 168.5	775.5 ± 117.5	816.4 ± 83.9	777.9 ± 138.7
9. - 10. week	908.3 ± 189.7	863.8 ± 139.8	859.3 ± 137.1	829.2 ± 110.2
11. week	861.5 ± 198.0	896.4 ± 148.9	891.6 ± 126.2	912.9 ± 113.8
1.- 11. week	657.3 ± 87.4	626.8 ± 77.0	660.4 ± 59.1	641.1 ± 70.0
Feed conversion (kg/kg)				
1. - 2. week	2.21 ± 0.42	2.77^{*} ± 0.47	2.22 ± 0.45	2.40 ± 0.40
3. - 4. week	2.09 ± 0.11	2.11 ± 0.14	2.06 ± 0.15	2.20 ± 0.23
5. - 6. week	2.20 ± 0.21	2.31 ± 0.22	2.20 ± 0.17	2.16 ± 0.22
7. - 8. week	2.25 ± 0.35	2.17 ± 0.18	2.19 ± 0.16	2.24 ± 0.29
9. - 10. week	2.32 ± 0.18	2.34 ± 0.16	2.45 ± 0.30	2.40 ± 0.22
11. week	2.72 ± 0.69	2.47 ± 0.12	2.50 ± 0.18	2.40 ± 0.19
1.- 11. week	2.26 ± 0.09	2.29 ± 0.08	2.26 ± 0.10	2.27 ± 0.07

Table B.15: Effects of rare earth elements (REE) on feed intake (FI in g/animal/day), body weight gain (BWG in g/animal/d) and feed conversion (kg/kg) of piglets, first trial; mean value ± standard deviation; values with an asterisk ($*$) differ significantly $p < 0.05$; n: number of animals per group (Eisele, 2003).

	Control	RE citrate	p-value
n	28	28	
initial BW (kg)	5.22 ± 0.54	5.23 ± 0.57	$p > 0.05$
final BW (kg)	22.04 ± 1.62	22.19 ± 2.45	$p > 0.05$
Results of the first four weeks			
BWG (g/d)	288 ± 34	302 ± 38	$p > 0.05$
FI (g/d)	364 ± 28	369 ± 37	$p > 0.05$
FCR (kg/kg)	1.27 ± 0.07	1.23 ± 0.07	$p > 0.05$
Comparison to the control			
FCR (%)		- 3	
Results of the last two weeks			
BWG (g/d)	626 ± 45	608 ± 78	$p > 0.05$
FI (g/d)	889 ± 67	928 ± 113	$p > 0.05$
FCR (kg/kg)	1.42 ± 0.08	1.53 ± 0.08	$p < 0.01$
Comparison to the control			
FCR (%)		+ 8	
Results of the experimental period over six weeks			
BWG (g/d)	400 ± 30	404 ± 47	$p > 0.05$
FI (g/d)	539 ± 37	555 ± 55	$p > 0.05$
FCR (kg/kg)	1.35 ± 0.05	1.38 ± 0.08	$p > 0.05$
Comparison to the control			
FCR (%)		+ 3	

Table B.16: Effects of dietary supplementation of rare earth citrate on body weight (BW in kg), daily body weight gain (BWG in g per animal and day) and feed conversion rate (FCR in kg/kg) of piglets first trial; mean value ± standard deviation; n: number of animals per group; p-value: significance (Kraatz et al., 2004).

n	Control 14	RE citrate 28	Na citrate 14
initial BW (kg)	8.26 ± 0.50	8.26 ± 0.59	8.26 ± 0.56
final BW (kg)	28.91 ± 1.49	28.20 ± 2.00	28.48 ± 1.41
Results of the first four weeks			
BWG (g/d)	371 ± 22	352 ± 80	338 ± 33
FI (g/d)	486 ± 32	459 ± 48	441 ± 33
FCR (kg/kg)	1.31 ± 0.09	1.35 ± 0.23	1.31 ± 0.10
Comparison to the control			
FCR (%)		+ 3	- 3
Results of the experimental period over six weeks			
BWG (g/d)	492 ± 28	475 ± 37	481 ± 40
FI (g/d)	733 ± 19	702 ± 43	696 ± 20
FCR (kg/kg)	1.49 ± 0.08	1.48 ± 0.09	1.46 ± 0.14
Comparison to the control			
FCR (%)		- 1	- 2

Table B.17: Effects of dietary supplementation of rare earth citrate on body weight (BW in kg), daily body weight gain (BWG in g per animal and day) and feed conversion rate (FCR in kg/kg) of piglets second trial; mean value ± standard deviation; n: number of animals per group (Kraatz et al., 2004).

n	Control 3	La chloride 3	RE nitrate 3	RE citrate 3	RE ascorbate 3
BWG (g/day)	896	864	864	866	886
FCR (kg/kg)	2.62	2.72	2.72	2.71	2.65

Table B.18: Effects of dietary supplementation of rare earths on body weight (BW in kg), daily body weight gain (BWG in g per day) and feed conversion rate (FCR in kg/kg) of pigs; n: number of animals per experimental group (Böhme et al., 2002a).

	Control	150 mg La	300 mg La	150 mg RE	300 mg RE
n	12	12	12	12	12
FI (g/d)	90.5 ± 7.5	88.2 ± 5.32	87.2 ± 4.7	87.7 ± 12.59	87.6 ± 7.59
BWG (g/d)	50.3 ± 8.45	49.11 ± 3.75	48.9 ± 3.6	47.4 ± 6.22	47.4 ± 5.97
FCR (kg/kg)	1.80 ± 0.31	1.80 ± 0.07	1.85 ± 0.20	1.85 ± 0.30	1.85 ± 0.15

Table B.19: Performance parameters of broilers including feed intake (FI in g per broiler and day), body weight gain (BWG in g per broiler per day) and feed conversion (FCR in kg/kg) with and without dietary supplementation of lanthanum chloride (La) or rare earth chlorides (RE) on of broiler; mean values ± standard deviation; no significance between the different experimental groups; n number of animals testes (Schuller, 2001).

	Control	Sorbic acid	RE ascorbate	RE citrate	La chloride
end BW (g)	1909 ± 270	1999 ± 230	1964 ± 221	1943 ± 243	1915 ± 279
Over the whole experimental period					
FI (g/day)	91.2 ± 5	90.9 ± 3	88.7 ± 4	86.7 ± 7	86.4 ± 5
FCR (kg/kg)	$1.694^{a} \pm 0.071$	$1.622^{b} \pm 0.064$	$1.613^{b} \pm 0.5$	$1.588^{b} \pm 0.064$	$1.472^{b} \pm 0.02$

Table B.20: Effects of different rare earth (RE) compounds and lanthanum (La) chloride on feed intake (FI in g per broiler day), body weight (BW in g/broiler), daily body weight gain (BWG in g per broiler day) and feed conversion rate (FCR in kg/kg) in broiler, second experiment; ^{a,b,c} values without the same superscripts differ significantly $p < 0.05$ (Halle et al., 2003c) and (Halle et al., 2004).

	Control	RE ascorbate	RE citrate	RE nitrate	La chloride
n	137	40	42	38	40
end BW (g)	$2024^{c} \pm 229$	$2169^{a} \pm 163$	$2157^{ab} \pm 159$	$2074^{bc} \pm 246$	$2124^{ab} \pm 184$
improvements BW (%)		+ 7	+ 6.5	+ 2	+ 5
During the first three week of the experiment					
BWG (g/day)	$34.3^{b} \pm 3.6$	$38.1^{a} \pm 1.9$	$36.0^{ab} \pm 3.1$	$36.2^{ab} \pm 2.6$	$35.6^{ab} \pm 3.4$
FI (g/day)	$47.2^{b} \pm 3.9$	$50.0^{ab} \pm 2.8$	$49.8^{ab} \pm 3.8$	$50.7^{a} \pm 3.3$	$49.3^{ab} \pm 4.1$
FCR (kg/kg)	$1.369^{a} \pm 0.071$	$1.290^{b} \pm 0.024$	$1.370^{a} \pm 0.051$	$1.391^{a} \pm 0.034$	$1.399^{a} \pm 0.061$
During the last two weeks of the experiment					
BWG (g/day)	$90.0^{c} \pm 5.8$	$95.3^{ab} \pm 4.7$	$97.1^{a} \pm 1.9$	$90.5^{bc} \pm 5.4$	$95.2^{ab} \pm 4.1$
FI (g/day)	$148.2^{b} \pm 6.3$	$156.9^{a} \pm 4.6$	$156.9^{a} \pm 3.2$	$149.2^{ab} \pm 4.7$	$151.1^{ab} \pm 9.6$
FCR (kg/kg)	1.647 ± 0.098	1.656 ± 0.053	1.607 ± 0.028	1.656 ± 0.086	1.582 ± 0.066
Over the whole experimental period					
BWG (g/day)	$56.6^{c} \pm 2.0$	$61.0^{a} \pm 1.9$	$60.5^{a} \pm 1.8$	$57.9^{bc} \pm 1.8$	$59.4^{ab} \pm 3.4$
FI (g/day)	$87.6^{b} \pm 4.2$	$92.8^{a} \pm 1.8$	$92.5^{a} \pm 2.8$	$90.1^{ab} \pm 3.2$	$90.0^{ab} \pm 6.1$
FCR (kg/kg)	$1.480^{a} \pm 0.035$	$1.442^{b} \pm 0.032$	$1.464^{ab} \pm 0.02$	$1.497^{a} \pm 0.035$	$1.472^{ab} \pm 0.020$

Table B.21: Effects of different rare earth (RE) compounds and lanthanum (La) chloride on feed intake (FI in g per broiler day), body weight (BW in g/broiler), daily body weight gain (BWG in g per broiler day) and feed conversion rate (FCR in kg/kg) in broiler, first experiment; ^{a,b,c} values without the same superscripts differ significantly $p < 0.05$; n: number of animals per experimental group (Halle et al., 2002a).

	Control	RE chloride 40 mg/kg	RE citrate 70 mg/kg	p-value
n	12	12	12	
Body weight				
initial BW (g)	41.3	41.5	41.6	0.616
BW after 3 weeks	761.2	771.1	777.5	0.745
final BW	2039.1^{a}	2111.8^{ab}	2139.3^{b}	0.035^{*}
Results over the first three weeks				
BWG (g/day)	720.1	729.6	735.9	0.749
FI (g/day)	1043.6	1051.9	1067.2	0.733
FCR (kg/kg)	1.454	1.447	1.456	0.822
Results compared to the control				
BWG (%)		+ 1.3	+ 2.2	
FI (%)		+ 0.8	+ 2.3	
FCR (%)		- 0.5	+ 0.1	
Result over the last two weeks				
BWG (g/day)	1278.0^{a}	1340.7^{b}	1362.0^{b}	0.004^{**}
FI (g/day)	2084.0^{a}	2171.6^{b}	2227.7^{b}	0.007^{**}
FCR (kg/kg)	1.633	1.621	1.636	0.822
Results compared to the control				
BWG (%)		+ 4.9	+ 6.6	
FI (%)		+ 4.2	+ 6.9	
FCR (%)		- 0.7	+ 0.2	
Over the whole experimental period				
BWG (g/day)	1997.9^{a}	2070.3^{ab}	2097.8^{b}	0.035^{*}
FI (g/day)	3127.6^{a}	3223.5^{ab}	3295.0^{b}	0.007^{*}
FCR (kg/kg)	1.566	1.558	1.571	0.711
Results compared to the control				
BWG (%)		+ 3.6	+ 5.0	
FI (%)		+ 3.1	+ 5.4	
FCR (%)		- 0.5	+ 0.3	

Table B.22: Effects of different rare earth (RE) compounds and lanthanum (La) chloride on feed intake (FI in g per animal day), body weight (BW in g/animal), daily body weight gain (BWG in g per animal day) and feed conversion rate (FCR in kg/kg) of broiler; ^{a,b} values without the same superscripts differ significantly: with one asterisk ($*$): ($p < 0.05$), with two asterisks ($**$): ($p < 0.01$) (He et al., 2006a).

	Control	200 mg RE per kg MR
Feed intake		
Milk replacer (MR)	553 ± 14	560 ± 10
pelleted Concentrates	156 ± 125^a	161 ± 95^a
Hay	182 ± 64^b	100 ± 24^a
Total	890 ± 157^a	821 ± 81^a
Body weight		
initial BW	43.4 ± 3.4^a	41.4 ± 5.6^a
end BW	58.4 ± 6.1^a	58.5 ± 7.1^a
Average daily body weight gain (g) over the whole experimental period		
	356 ± 118^a	408 ± 92^a

Table B.23: Effects of dietary supplementation of rare earth (RE) citrates to milk replacer on feed intake (FI in g dry matter per day) and body weight (BW in kg) of Holstein calves; ^{a,b} values without the same superscripts differ significantly $p < 0.05$ (Meyer et al., 2006).

	Control	75 mg La	150 mg La	75 mg RE	150 mg RE	p-value
Over the whole experimental period						
FI ($g/rat/day$)	12.4^a	12.0^a	12.0^a	13.2^b	11.8^a	< 0.03
BWG (g/day)	5.31	5.51	5.59	5.77	5.70	0.32
FCR (kg/kg)	2.34^a	2.21^{ab}	2.14^b	2.28^a	2.08^b	< 0.01
Comparison with the control						
FI (%)		-3	-3	$+6$	-5	
BWG (%)		$+4$	$+5$	$+9$	$+7$	
FCR (%)		-6	-8	-3	-11	

Table B.24: Effects of dietary supplementation of rare earth (RE) chlorides and lanthanum (La) chloride at different concentrations on Feed intake (FI in g per rat and day), Body weight gain (BWG in g per day), Feed conversion rate (FCR in kg/kg) of rats; p-value: significance; ^{a}, ^{b} values without the same superscripts differ significantly $p < 0.05$ (He et al., 2003a).

APPENDIX C

RARE EARTH CONCENTRATIONS

	Control	RE ascorbate	RE citrate	RE nitrate	Lanthanum chloride
Lanthanum					
Liver	7.5	32	32	47	147
Kidney	-	-	-	-	-
Heart	6.4	8	19	57	57
Muscle (Breast)	5	14	14	19	45
Thigh	-	-	-	-	-
Skin	7	15	21	25	107
Fat	14	188	147	103	1650
Cerium					
Liver	19	42	42	55	15
Kidney	-	-	-	-	-
Heart	7.6	13	27	71	14
Muscle (Breast)	7	25	28	33	13
Thigh	-	-	-	-	-
Skin	10	24	38	38	25
Fat	20	322	248	141	155
Praseodymium					
Liver	3.0	6.6	6.6	8.1	4.0
Kidney	-	-	-	-	-
Heart	2.8	2.7	5.3	9.2	3.3
Muscle (Breast)	2.7	4.3	4.6	5.7	3.8
Thigh	-	-	-	-	-
Skin	3.3	4.3	6.5	7.0	5.1
Fat	4.1	33	29	18	16
Neodymium					
Liver	7.7	12	12	20	11
Kidney	-	-	-	-	-
Heart	7.8	9	12	47	9
Muscle (Breast)	12	17	19	14	9
Thigh	-	-	-	-	-
Skin	12	12	14	12	15
Fat	14	101	41	32	31

Table C.1: Rare earth contents (μg/kg) in tissue samples of broilers fed different rare earth (RE) compounds or lanthanum (La) chloride, first trial (Fleckenstein et al., 2004).

	Control	RE ascorbate	RE citrate	Lanthanum chloride
Lanthanum				
Liver	19	26	40	56
Kidney	9.6	97	108	136
Heart	-	-	-	-
Muscle (Breast)	15	27	20	28
Thigh	15	13	24	16
Skin	-	-	-	-
Fat	-	-	-	-
Cerium				
Liver	25	36	62	12
Kidney	10.7	167	194	24
Heart	-	-	-	-
Muscle (Breast)	21	43	36	19
Thigh	17	15	39	13
Skin	-	-	-	-
Fat	-	-	-	-
Praseodymium				
Liver	3.9	4.8	7.9	2.2
Kidney	2.1	18	23	3.6
Heart	-	-	-	-
Muscle (Breast)	3.2	5.3	4.5	2.8
Thigh	2.6	2.7	5.3	2.2
Skin	-	-	-	-
Fat	-	-	-	-
Neodymium				
Liver	9.2	15	12	4.4
Kidney	4.5	58	18	8.4
Heart	-	-	-	-
Muscle (Breast)	10	14	8.8	8.7
Thigh	10	6.0	6.8	3.7
Skin	-	-	-	-
Fat	-	-	-	-
Samarium				
Liver	3.1	2.8	3.0	1.8
Kidney	1.9	3.6	3.0	2.0
Heart	-	-	-	-
Muscle (Breast)	1.8	1.6	1.7	1.9
Thigh	2.2	1.7	1.5	1.5
Skin	-	-	-	-
Fat	-	-	-	-

Table C.2: Rare earth contents (μg/kg) in tissue samples of broilers fed different rare earth (RE) compounds or lanthanum (La) chloride, second trial (Fleckenstein et al., 2004).

	Control	RE ascorbate	RE citrate	RE nitrate	La chloride
n	10	6	6	6	6
breast muscle	14.4 ± 1.7	14.9 ± 0.5	14.7 ± 2.1	15.1 ± 2.4	14.0 ± 1.6
haunch	19.8 ± 1.6	19.6 ± 1.3	19.8 ± 1.0	20.2 ± 1.0	20.1 ± 1.0
liver	$2.5^{a} \pm 0.3$	$2.1^{b} \pm 0.3$	$2.2^{ab} \pm 0.2$	$2.3^{ab} \pm 0.4$	$2.1^{b} \pm 0.2$
heart	0.7 ± 0.1	0.7 ± 0.0	0.8 ± 0.4	0.7 ± 0.1	0.6 ± 0.1
abdominal fat	1.2 ± 0.3	1.4 ± 0.4	1.4 ± 0.1	1.5 ± 0.3	1.5 ± 0.3
breast skin	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.2	0.7 ± 0.1
total body *	69.4 ± 2.0	69.8 ± 1.5	69.2 ± 1.2	70.4 ± 1.8	69.5 ± 1.5

Table C.3: Excavation results of broiler - effects of different rare earth (RE) compounds and lanthanum (La) chloride on the amount of different muscle and organ tissue of broiler, first experiment; mean values (g/100g body weight) ± standard deviation; ^{a,b} values without the same superscripts differ significantly $p < 0.05$; * total body without giblets n: number of animals per experimental group (Halle et al., 2002a).

	Control	75 mg La	150 mg La	75 mg RE	150 mg RE
			Lanthanum		
Feed	200	59 000	134 000	23 000	45 000
Muscle^{a}	7.7	4.6	8.3	7.8	5.3
Liver	1.1	6.2	12	2.1	5.5
Kidney	<2.2	<1.7	<2.3	<1.0	<1.8
			Cerium		
Feed	400	600	900	30 000	61 000
Muscle^{a}	<27	<21	<25	<25	<21
Liver	<17	<27	<20	<17	<28
Kidney	<12	<20	<13	<12	<21

Table C.4: Lanthanum and cerium contents (μg/kg dry matter or feed) in pooled tissue samples (the organ samples were pooled from 12 piglets of each group) of piglets and in their feed diets with and without supplementation, ^{a} muscle samples taken from musculus longissiumus dorsi (piglets) (Rambeck et al., 1999a).

	Control	150 mg La	300 mg La	150 mg RE	300 mg RE
Lanthanum					
Muscle ^{a}	< 33	< 36			
Liver	< 52	< 47			
Kidney	< 34	< 36			
Muscle	7.5	9.4	11.0	8.9	10.0
Liver	5.1	29.0	40.0	12.0	14.0
Kidney	26				250
Cerium					
Muscle ^{a}	$< 44^b$	$< 58^b$	$< 49^b$	$< 52^b$	$< 85^b$
Liver	$< 43^b$	$< 63^b$	$< 52^b$	$< 58^b$	$< 61^b$
Kidney	$< 540^b$				$< 490^b$

Table C.5: Lanthanum and cerium contents (μg/kg dry matter) in tissue samples of chickens fed a lanthanum chloride (La) or rare earth (RE) chlorides supplemented diet compared to the control; ^{a} muscle samples taken from musculus pectoralis; ^{b} limit of detection because of interference with other elements present in the sample, actual concentration may be considerably lower (Schuller et al., 2002).

	Control	300 mg RE
Lanthanum		
MI feed	170	36393
MII feed	178	43074
Muscle^a	3.0	19.0
Liver	2.8	53.4
Kidney	< 3	22.3
Cerium		
MI feed	315	49156
MII feed	296	57699
Muscle^a	< 33	< 36
Liver	< 52	< 47
Kidney	< 34	< 36

Table C.6: Lanthanum and cerium contents (μg/kg dry matter or feed) in tissue samples of pigs and in their feed diets with and without supplementation; ^{a} muscle samples taken from musculus glutaeus (He et al., 2001), (Borger, 2003).

	Control	RE
Lanthanum		
kidney	< 0.02	< 0.02
liver	< 0.02	< 0.02
chop	< 0.02	< 0.02
leaf fat	< 0.03	< 0.03
Cerium		
kidney	< 0.02	< 0.02
liver	< 0.02	< 0.02
chop	< 0.02	< 0.02
leaf fat	< 0.03	< 0.03

Table C.7: Concentrations of lanthanum and cerium (mg/kg dry matter) in liver, kidney, muscle (chop) and fat (leaf fat) of fattened pigs after dietary supplementation of rare earths determined by ICP - MS (Böhme et al., 2002a).

	Control	RE 300 mg/kg RE chlorides	LaCe I 100 mg/kg $LaCl_3$ 200 mg/kg $CeCl_3$	LaCe II 200 mg/kg $LaCl_3$ 100 mg/kg $CeCl_3$
Liver				
La	25.3	101.0	90.6	89.3
Ce	15.8	105.0	84.7	39.7
Pr	1.0	5.2	0.4	$<$ DL
Nd	2.2	1.2	1.1	0.9
Sm	$<$ DL	$<$ DL	$<$ DL	$<$ DL
Muscle				
La	11.6	6.7	3.7	5.3
Ce	13.9	5.4	1.9	4.4
Pr	0.3	0.5	$<$ DL	$<$ DL
Nd	1.4	1.8	0.7	1.1
Sm	$<$ DL	$<$ DL	$<$ DL	$<$ DL
DL	0.8	0.3	0.3	0.3

Table C.8: Concentrations of rare earth elements (μg/kg) in tissues of piglets; mean value ± standard deviation; DL: detection limit (Eisele, 2003).

	RE ascorbate	RE citrate	RE nitrate	La chloride
La	8.5	9.7	12.2	44.5
Ce	16.8	15.7	21.7	-
La and Ce	25.3	25.4	33.9	44.5

Table C.9: Analysis of Chinese rare earth samples and of lanthanum chloride, concentrations in %, first experiment (Halle et al., 2002a).

	RE citrate concentrate (%)	Control diet (mg/kg)	Experimental diet (mg/kg)
Lanthanum	23.3	0.48	11.09
Cerium	68.2	0.86	32.17
Praseodymium	8.0	< 0.02	3.62
Neodymium	0.4	0.22	0.47
RE (sum)	99.9	< 1.58	47.35

Table C.10: Content of rare earth elements in rare earth citrate concentrate (%) and feed samples (mg/kg) determined by ICP - MS (Kraatz et al., 2004).

APPENDIX D

MODE OF ACTION

	Control	150 mg RE citrates	300 mg RE citrates	p-value
		Energy		
intake	1921 ± 144	2013 ± 184	2171 ± 200	0.079
digestible	1641 ± 134	1758 ± 163	1871 ± 173	0.066
retained	618 ± 80	680 ± 131	786 ± 124	0.048
		Nitrogen		
intake	3.29 ± 0.23	3.43 ± 0.32	3.72 ± 0.36	0.075
digestible	2.75 ± 0.18	2.94 ± 0.26	3.13 ± 0.45	0.065
retained	2.36 ± 0.21	2.37 ± 0.24	2.74 ± 0.37	0.058

Table D.1: Effects of rare earth (RE) citrates on energy (kJ per day and kg BW) and nitrogen (g per day and kg BW) balance of piglets (first period 8.5 - 40 kg); mean values ± standard deviation; p-value: significance (Prause et al., 2004).

	Control	300 mg RE	p-value
	Growing period (full stomach)		
T_3 (nmol/l)	2.33 ± 0.68	1.65 ± 0.13	$p < 0.01$
T_4 (nmol/l)	50.4 ± 9.9	58.2 ± 14.6	$p > 0.05$
	Fattening period (empty stomach)		
T_3 (nmol/l)	1.82 ± 0.41	1.08 ± 0.31	$p < 0.01$
T_4 (nmol/l)	43.9 ± 10.6	45.0 ± 10.4	$p > 0.05$

Table D.2: Concentrations of thyroid hormones (nmol/l) in blood serum of pigs with and without rare earth supplementation; mean values ± standard deviation; p-value: significance (He et al., 2001).

	Control	RE 300 mg/kg RE chlorides	LaCe I 100 mg/kg $LaCl_3$ 200 mg/kg $CeCl_3$	LaCe II 200 mg/kg $LaCl_3$ 100 mg/kg $CeCl_3$
T_3	2.38 ± 0.49	2.22 ± 0.38	2.24 ± 0.48	2.17 ± 0.32
T_4	29.13 ± 7.54	22.15^{*} ± 8.63	19.28^{**} ± 3.55	24.82 ± 7.21

Table D.3: Effects of rare earth elements on thyroid hormones (nmol/l) of piglets; mean value ± standard deviation; values with an asterisk (∗) differ significantly $p < 0.05$ those with two differ significantly $p < 0.01$; n: number of animals per group (Eisele, 2003).

	Control	REE 300 mg/kg
n	8	8
Rearing period 1. - 8. week		
Na	165.31 ± 6.12	165.31 ± 6.23
K	6.77 ± 0.57	6.85 ± 0.54
Ca	3.20 ± 0.12	3.19 ± 0.16
Cl	112.33 ± 4.31	111.67 ± 2.05
P	3.74 ± 4.31	3.82 ± 0.37
AST	18.75 ± 7.07	19.75 ± 8.36
ALT	24.63 ± 1.73	28.13 ± 5.16
AST	303.25 ± 46.98	282.63 ± 44.28
Chol	2.76 ± 0.38	2.87 ± 0.43
Trig	0.37 ± 0.11	0.31 ± 0.08
TP	77.16 ± 7.95	76.03 ± 5.12
Alb	44.03 ± 2.13	45.77 ± 1.70
Gluc	6.78 ± 0.69	7.14 ± 1.11
T_3 (nmol/l)	2.38 ± 0.60	$1.65^* \pm 0.12$
T_4 (nmol/l)	53.35 ± 14.16	58.17 ± 13.64
Fattening period 8. - 12. week		
Na	158.66 ± 3.34	159.91 ± 7.94
K	5.88 ± 0.38	6.37 ± 0.40
Ca	2.89 ± 0.17	2.89 ± 0.21
Cl	108.29 ± 2.49	106.57 ± 3.54
P	3.81 ± 0.49	3.94 ± 0.50
AST	45.00 ± 9.49	61.75 ± 21.72
ALT	28.86 ± 5.99	32.38 ± 6.34
AST	324.14 ± 69.24	331.25 ± 44.36
Chol	3.22 ± 0.22	3.21 ± 0.29
Trig	0.61 ± 0.16	0.57 ± 0.12
TP	77.30 ± 4.79	79.44 ± 5.17
Alb	50.93 ± 4.93	48.84 ± 5.41
Gluc	6.51 ± 0.91	7.28 ± 0.95
T_3 (nmol/l)	1.28 ± 0.39	1.29 ± 0.36
T_4 (nmol/l)	55.55 ± 22.92	69.99 ± 7.86

Table D.4: Effects of rare earth elements (REE) on several blood parameters (electrolytes, liver enzymes, cholesterol, triglycerides, total protein, albumin, glucose) of piglets; mean value ± standard deviation; values with an asterisk ($*$) differ significantly $p < 0.05$; n: number of animals per group (Borger, 2003).

	Control	100 mg RE	200 mg RE	400 mg RE	800 mg RE
T_3 $(nmol/l)$	0.73 ± 0.14	1.20 ± 0.21	1.26 ± 0.74	1.20 ± 0.25	1.53 ± 0.35
T_4 $(nmol/l)$	$36.0^{b} \pm 3.4$	$42.5^{ab} \pm 3.8$	$45.0^{a} \pm 5.2$	$42.5^{ab} \pm 2.8$	$43.8^{a} \pm 5.2$

Table D.5: Effects of dietary rare earth (RE) supplementation on the concentrations of thyroid hormones (nmol/l); mean values ± standard deviation; ^{a,b} values without the same superscripts differ significantly $p < 0.05$ (Förster et al., 2006).

	Control	$LaCl_3$ 100 mg/kg
n	30	30
GH peak (ng/ml)	3.43^{a}	6.19^{b}
GH base	1.13^{a}	1.94^{b}
GH average	1.89^{a}	3.11^{b}
Improvements in BWG and FCR compared to the control		
BWG (%)		+ 6.30 ($p < 0.01$)
FCR (%)		- 10.29

Table D.6: Effects of dietary supplementation of lanthanum chloride on growth hormone (GH) levels (ng/ml) of pigs; n: number of animals per experimental group; ^{a,b} values without the same superscripts differ significantly $p < 0.05$ (Liu, 2005).

	Control	75 mg La	150 mg La	75 mg RE	150 mg RE	p-value
Glucose (mmol/l)	1.59^{a}	1.34^{ab}	1.51^{a}	1.22^{b}	1.14^{b}	< 0.05
Cholesterol (mmol/l)	2.75	2.53	2.77	2.95	2.75	0.16
Total triglyceride (mmol/l)	1.28^{ab}	1.33^{ab}	1.55^{b}	1.40^{b}	1.09^{a}	< 0.03
Total protein (g/l)	65.4	58.7	61.1	67.5	63.0	0.44
Albumin (g/l)	25.5	28.3	27.3	26.1	28.7	0.47
Creatinine (mg/l)	1.85^{a}	2.08^{a}	1.95^{a}	1.90^{a}	2.50^{b}	< 0.01
Urea nitrogen (mmol/l)	7.70	7.86	8.31	8.03	8.47	0.54
ALT (mmol/l)	24.4^{a}	44.3^{b}	57.0^{c}	57.8^{c}	57.9^{c}	< 0.01
AST (mmol/l)	260	326	339	343	291	0.12
AP (mmol/l)	209^{a}	254^{ab}	328^{b}	262^{ab}	296^{b}	< 0.04
Thymus (g/100g BW)	0.20	0.20	0.22	0.20	0.20	0.09
Spleen (g/100g BW)	0.26	0.26	0.26	0.26	0.25	0.74

Table D.7: Effects of dietary supplementation of rare earth (RE) chlorides and lanthanum (La) chloride at different concentrations on blood serum parameters (in mmol/l, g/l, mg/l) and the weight of thymus and spleen (in g per 100 g body weight (BW)) of rats; p-value: significance; ^{a,b,c} values without the same superscripts differ significantly p < 0.05 (He et al., 2003a).

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ACKNOWLEDGEMENTS

I wish to express my gratitude to the scholars who advised me on this dissertation and to my friends and relatives who supported me in many ways.

In the first place, I owe many thanks to Prof. Walter Rambeck, who drew my attention to the field of rare earths, suggested the dissertation and guided me through the various stages. Being himself an eminent scholar in this innovative field, he passed on his enthusiasm in finding the current studies and generously gave his professional advice on structuring and evaluating the materials.

This professional support was supplemented by the often informal talk to Dr. Herfried Richter, who also is a specialist on rare earths and gave his advice freely and liberally. His expertise in chemistry has specifically helped me to organize the chapters on the spectrum of disciplines which, today, participate in the research on rare earths, chemistry, physics, medicine, pharmacology and agriculture.

I am similarly indebted to Dr. Ulrich Wehr, who advised me on the sources of materials and their presentation.

Since the early research on rare earths was done in Chinese and China is still a major contributor to the research in this field, my work would not only be incomplete, but miss its objective without the help of Dr. Moalong He, who not only adviced me on the access to Chinese research but, in conjunction with Mrs. He, spent a great amount of time on translating Chinese articles in order to make them accessible. 非常感谢你的帮忙！

My research was also facilitated by the personal help of the staff of the Bayrische Staatsbibliothek at Munich as well as of the staff of the University Libraries at Stuttgart-Vaihingen and Stuttgart-Hohenheim, who introduced me to electronic search systems and made distant materials accessible.

Furthermore I wish to express personal thanks to my relatives, Patrick, Steffi, Gernot, who have already completed their theses and encouraged me, to Tiff, a native speaker of English who proofread the rather extensive work and especially to my uncle Julius, who is professor of Anglistics, for his encouragement, proofreading and valuable advices.

Thanks also go to my good friends Nadina and Florian for being just that.

Most dearly I thank my Mum and Dad for getting me at the point where I could write this thesis as well as for their continued support, encouragement and love. This would not have been possible without your help.

Finally a very special thankyou goes to Ingo, whose love, patient help, knowledge of LaTeX and proofreading were indispensable for this study.