Original Article

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Measurement, model prediction and uncertainty quantification of plasma clearance of cerium citrate in humans

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Abstract Double tracer studies in healthy human volunteers with stable isotopes of cerium citrate were performed with the aim of investigating the gastro-intestinal absorption of cerium (Ce), its plasma clearance and urinary excretion. In the present work, results of the clearance of Ce in blood plasma are shown after simultaneous intravenous and oral administration of a Ce tracer. Inductively coupled plasma mass spectrometry was used to determine the tracer concentrations in plasma. The results show that about 80% of the injected Ce citrate cleared from the plasma within the five minutes post-administration. The data obtained are compared to a revised biokinetic model of cerium, which was initially developed by the International Commission on Radiological Protection (ICRP). The measured plasma clearance of Ce citrate was mostly consistent with that predicted by the ICRP biokinetic model. Furthermore, in an effort to quantify the uncertainty of the model prediction, the laboratory animal data on which the ICRP biokinetic Ce model is based, was analyzed. The measured plasma clearance and its uncertainty was also compared to the plasma clearance uncertainty predicted by the model. It was found that the measured plasma clearance during the first 15 minutes after administration is in a good agreement with the modelled plasma clearance. In general, the measured clearance falls inside the 95% confidence interval predicted by the biokinetic model.

Keywords*:* Cerium, Biokinetics, Systemic model, Speciation, Internal dosimetry, Uncertainty analysis

Introduction

Cerium (Ce), a lanthanide, is the most abundant rare-earth element (REE) found in nature. As Ce is of wide interest for industry, medicine and agriculture, excessive mining to extract Ce (and the other REEs) from mineral ores and their processing leads to a growing environmental pollution and, therefore, to an increasing human exposure possibly involving health effects (Pagano et al. 2015; EPA 2012). The production of REE-rich phosphate fertilizers and their application increase the REE concentration in soil, plants, and ground/surface water (Tyler 2004; Li et al. 2013). Hence, the daily intake of cerium by food ingestion (up to 35 µg) is expected to rise steadily (Wappelhorst et al. 2002; Stanek et al. 1997; Linsalata et al. 1986). Besides very low Ce concentrations in human blood of less than 0.008 – 0.07 µg L^{-1} (Höllriegl et al. 2010; Heitland and Köster 2006), much higher values up to 603 µg L^{-1} could be found in exposed humans living near mining areas or regions with naturally high background of Ce (Li et al. 2014).

Cerium is also of interest for radiation protection, due to its radioactive isotopes ^{141}Ce and ^{144}Ce, which are beta/gamma-emitters with physical half-lives of 33 days and 284 days, respectively. Radionuclides of Ce are produced in ^{235}U/^{239}Pu nuclear power and processing plants and may be released during nuclear accidents (Zheltonozhsky et al. 2001). These radionuclides may pose serious health risks to workers and members of the public, depending on the amount released into the environment. Incorporation of Ce radionuclides into the human body may occur by inhalation or ingestion, or through absorption by the skin or by wounds. A biokinetic and dosimetric model for the calculation of doses from intakes of radionuclides of lanthanides (including cerium) was developed by the International Commission on Radiological Protection (ICRP) (ICRP 1989, 1993). This model is mainly based on data from studies with animals which had incorporated lanthanides or their chemical analogues (actinides). Unfortunately, for humans there are not much data on the biokinetic behaviour of Ce published. Based on the reviews of Taylor and/or Leggett (Leggett et al. 2014; Taylor and Leggett 2003) improvements of the biokinetic ICRP Ce model will be published soon in the Occupational Intakes of Radionuclides Series (OIR) of the ICRP (in preparation).

It is further noted that most of the biokinetic experiments that were performed in the past to provide data for Ce biokinetic modelling used Ce (and/or other lanthanides) in chemical forms without considering any chemical speciation; therefore, the currently available biokinetic models are non-specific. However, as clearly stated by Paquet et al. (2003), “in the case of internal contamination with radionuclides, speciation studies could help to improve both the biokinetic and dosimetric models for radionuclides” (Paquet et al. 2003). Therefore, further biokinetic studies with human volunteers are

required to obtain reliable data describing the biokinetics of Ce in humans, ideally considering the chemical speciation of the administered substances.

Consequently, a human study on the biokinetics of Ce was initiated including two isotopically enriched stable tracers of Ce with the aim to describe the gastrointestinal absorption of Ce, its distribution throughout the human body and its urinary excretion (Keiser et al. 2011). The isotopes chosen, ^{136}Ce and ^{138}Ce, were simultaneously administered to human volunteers as Ce-III-citrate complexes, one orally and the other intravenously. This double tracer technique was introduced by De Grazia et al. (De Grazia et al. 1965) as an effective method for the determination of the fractional absorption of an ingested substance, and for the determination of the clearance from the plasma and of the urinary excretion rate of an ingested and injected substance. Over the last years, this technique was modified and applied to several elements (Cantone et al. 1993; Cantone et al. 1998; Giussani et al. 2008; Greiter et al. 2011; Roth et al. 1999; Veronese et al. 2001; Höllriegl et al. 2006). The technique can be applied to elements with more than one stable isotope, if the natural isotopic composition of this element is known. For cerium this was the case. The tracer concentrations should be as low as possible, in order not to disturb the normal metabolism of the naturally occurring substance. Therefore, very low concentrations of the tracer substance in plasma or urine samples have to be measured, which is technically challenging. In addition, sources of interferences during the measurement must be avoided or at least be controllable. In the present study, initially thermal ionization mass spectrometry (TIMS) was considered as a suitable measurement technique. Unfortunately, this technique failed to eliminate the known interferences from barium (Ba) at the isotope masses 136 and 138, in spite of intensive sample preparation and purification (Pourmand and Dauphas 2010). As alternative method, inductively coupled plasma sector field mass spectrometry (ICP-SF-MS) was chosen, although the same interferences from Ba could also disturb the ICP-SF-MS measurements. However, to solve this interference problem, the ^{140}Ce concentration of the plasma samples were measured as the relative abundance of ^{140}Ce was also substantial in both applied tracers enriched in ^{136}Ce or ^{138}Ce (Table 1).

Recently, results from the same human cohort on the excretion of Ce citrate in urine were presented (Höllriegl et al. 2017). The results showed excretion rates of Ce that were higher as compared to those calculated with the systemic model for cerium proposed by Taylor and Leggett (Leggett et al. 2014). This difference was attributed to the specific chemical form of the cerium administered to the human volunteers, which could not be adequately considered in the biokinetic model. In contrast, the present work shows the plasma clearance of the administered Ce citrate in humans as compared to that predicted by the biokinetic Ce model of Taylor and Leggett.

Biokinetic models are essential for calculation of internal radiation dose and associated risk for occupational workers, members of the public and patients exposed to radionuclides; consequently, such models underpin regulatory policy decisions in radiation protection. However, the required model parameters are derived mostly from experimental data obtained from laboratory animals and from analyses of accidental human contamination cases. According to ISO/IEC 17025 (ISO 2005), the uncertainty of the measurement results is necessary to be reported for uncertainty quantification of further derived quantities. The above mentioned parameters are often subject to significant uncertainties, due to the physiological variability of individuals, the uncertainty in the extrapolation of animal data to humans, uncertainties in measurement techniques, the sparsity of and/or inconsistency in the reported data, and the choice of parameter values (NCRP 1996, 1998, 2009; IAEA 1998; Leggett 2001; Li et al. 2015). The uncertainty of these model parameters should be provided according to ISO GUM (ISO et al. 1995).

Materials and Methods

Biokinetic investigations

Recently, a biokinetic study based on the use of two stable isotopes of cerium citrate as tracers was initiated in healthy adult volunteers, to obtain biokinetic data in humans (Keiser et al. 2011). The study was performed according to a protocol approved by the Ethical Committee of the Technical University Munich, Germany. Written consent was obtained from the volunteers before each investigation.

Briefly, 100 µg (0.7 µmol) ^{136}Ce and 1 µg (0.007 µmol) ^{138}Ce tracer as Ce-III-citrate complexes were simultaneously administered orally and intravenously, respectively. The applied Ce-III-citrate complexes were very stable with a formation constant of log beta2 of about 11.2 (Ohyoshi et al. 1972). Citrate complexes were used because citrate is a common chelating substance and present in the blood plasma as buffering material. Besides, citrate is also present naturally in many geologic fluids and, due to its strong chelating properties, it is used in the decontamination of nuclear facilities (Prakash et al. 2013). The quantity of the administered Ce tracers needed for the study was estimated based on natural intake values of Ce, its concentration in blood or daily excretion, and some toxicological considerations (Linsalata et al. 1986; Wappelhorst et al. 2002; Sabbioni et al. 1982; Minoia et al. 1990; Jakupec et al. 2005; Health Effects Institute 2001). After administration, 10 mL blood samples were taken via an in-dwelling catheter (heparinized) at fixed times post-administration. More specifically, the intended time schedule was 5′, 10′, 15′, 30′, 60′, 2h, 3h, 4h, 6h, 8h, and 24h; the exact time of blood drawing was recorded and used for further calculations; for example, the

blood collection of one specific data set started always 1.5 minutes later than intended. One blood sample (blank) was taken a few minutes before Ce administration, and the first few milliliters of blood were discarded, in order to eliminate any possible contamination of the catheter needle. The blood samples were centrifuged at 3000 rotations per minute (rpm) for 10 minutes and the plasma was collected. All plasma samples were stored frozen until analysis. After thawing, the plasma samples were prepared and analysed using inductively coupled plasma mass spectrometry (ICP-MS).

Table 2 presents the characteristics of the ten volunteers (two females, eight males). The plasma volumes of the volunteers were calculated based on their body masses (Moore et al. 1963).

Inductively coupled plasma mass spectrometry

For the ICP-MS measurements, the 3.5 mL plasma samples were first transferred to microwave plastic tubes, and 3 mL 65 % HNO_3 and 100 µL H_2O_2 were added. The samples were then treated in a microwave oven for 45 minutes at 60 bar and 240 °C, with a maximum energy of 600 W. After the microwave digestion procedure, the ^{136}Ce, ^{138}Ce, ^{140}Ce and ^{142}Ce concentrations were measured with a NexION 350X mass spectrometer (Perkin Elmer). Instrument parameters are given in Table 3. Unfortunately, ^{136}Ce and ^{138}Ce could not be quantified because of known barium interferences at masses 136 and 138 (Höllriegl et al. 2017). For further analysis, the measured ^{140}Ce concentrations were used, because ^{140}Ce was present in both applied tracers (Table 1). Three measurements were made per sample, and the mean value and the standard deviation were calculated. The limit of detection (LOD) was 0.01 µg L^{-1} and the limit of quantification (LOQ) was 0.05 µg L^{-1} (Currie 1968). These values were mainly governed by the digestion procedure and the sample dilution necessary for the ICP-MS measurement.

Biokinetic modelling

The biokinetic model of cerium proposed by Taylor and Leggett (Taylor and Leggett 2003; Leggett et al. 2014) was applied to simulate the plasma clearance of Ce and to compare the model data with the experimental results obtained in the present study. The structure of the systemic model for cerium used here is shown in Fig. 1. After its injection, cerium is cleared from the circulation with a biological half-life of approximately 30 minutes. Subsequently, Ce is homogenously distributed in organs and tissues, mainly in the liver (50%) and bone (30%). About 2% of injected Ce from plasma is excreted into urine within the biological half-life of 30 minutes. The plasma clearance is influenced by the rapid

equilibration of Ce with the extra-cellular fluid (ECF) which is part of the plasma; in the biokinetic model the ECF is modelled by the soft tissue compartment ST0 (Fig. 1). Recycling of Ce between the tissue compartments and blood plasma is included in the model allowing for different biological half-lives. The model parameters (transfer coefficients) were taken from Leggett et al. (2014) and implemented in the SAAM II ver2.3 computer program (Barrett et al. 1998). For the simulations, 1 µg Ce for the injection and 100 µg Ce for the ingestion were used, as well as two different plasma volumes of 3.6 L (for the male volunteers) and of 2.4 L (for the females) (see Table 2). Although the reference plasma volumes proposed by the ICRP are 3.0 L for males and 2.4 L for females (ICRP 1989), the mean plasma volumes of the participating male volunteers was 3.6 L and higher than the ICRP reference value. Consequently, this value was taken for the simulations instead of 3.0 L.

Uncertainty analysis

According to the ISO Guide (ISO 1995), the measurement uncertainty is the parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand. Uncertainty analysis requires computation of the total uncertainty induced in the output of a simulation. This in turn requires quantification of the input and model uncertainties, and the attributes of the relative importance of the input uncertainties in terms of their contributions to the output (Morgan and Henrion 1990). The method can be applied both to measured data and model parameters. To quantify the measurement uncertainties, the standard deviation of plasma clearance as deduced from the ICP-MS measurements was used in the present study. The uncertainty of parameters of the ICRP Ce biokinetic model was analyzed by evaluating the animal data on which the ICRP biokinetic Ce model used in the present study was based. In addition, according to the results of the parameter uncertainty analysis, the model parameters were sampled and imported as input to the computer code BIOKINDOS. This code was developed for internal dosimetry uncertainty analysis (Li et al. 2011; Li et al. 2015). The uncertainty of the model prediction was calculated from the computer-simulated outputs and was compared to the uncertainty of the measured human data (partly mean values with standard deviation). The biokinetic parameters (transfer coefficients) k_{ij} were calculated by Eq. 1:

$$k_{ij} = \frac{ln2}{T_j} a_{ij} \qquad (1)$$

where T_j is the removal half-life (d) from the compartment j; and a_{ij} is a fraction of activity in compartment j transferred to compartment i.

Numerical values of the variables k_{ij}, T_j, a_{ij} can be found in the literature (Taylor and Leggett 2003, 1998; Leggett et al. 2014; ICRP 1989). It was assumed that the values of these variables follow a normal distribution. For those biokinetic parameters for which the available experimental data did not allow estimation of any uncertainty, a coefficient of variation (cv) of 20% was assumed here. The cv is considered to be one of the most widely used statistical measures of the relative dispersion. Values for the cv of 16%, 17% and 31% were obtained from cited references by evaluating the animal data on which the ICRP biokinetic Ce model was based (ICRP 1989; Taylor and Leggett 1998, 2003; Leggett et al. 2014). For the confidence interval of 95%, a coefficient of variation of 20% corresponds to a coverage probability of more than 99.2% (Sappakitkamjorn and Niwitpong 2013). In the present work, the mean values of these transfer coefficients k_{ij} were set to be the values reported by Leggett et al. (2014). The standard deviation σ can be calculated for all statistical values based on Eq. 2:

$$cv = \frac{\sigma}{\mu} \qquad (2)$$

Where μ is the mean value.

The standard deviation for any parameter was calculated using standard deviations for the variables T_i, a_{ij} and applying the propagation of uncertainty. Based on a normal distribution and a confidence interval of 95%, the minimum and maximum values (97.5th and 2.5th percentiles of the normal distribution) of the model parameters k, which are used for the Latin hypercube sampling (LHS) (Iman and Shortencarier 1984) technique, were calculated as follows (Eqs. 3 and 4):

$$Minimum = \mu - 1.96\sigma \qquad (3)$$

$$Maximum = \mu + 1.96\sigma \qquad (4)$$

The model parameters and the uncertainties are presented in Table 4.

Results and Discussion

Measurements of the normal cerium concentrations in blood plasma resulted in very low values (<0.008 – 0.07 µg L^{-1}) (Höllriegl et al. 2010; Heitland and Köster 2006). In the present study, the cerium

concentrations in the plasma (before administration of the Ce tracers) were less than 0.05 µg L^{-1}, which means that most of the measured values were below the LOQ.

Table 5 presents the results of the plasma concentration of Ce at fixed time points post-administration for all ten human volunteers. At five minutes after injection, only half of the samples showed measurable Ce concentrations, while the other samples showed values below the LOQ of 0.05 µg L^{-1}; 30 minutes after administration, all Ce concentrations were below the LOQ. It can be assumed that the measurable Ce concentrations were derived from the intravenous injection of ^{138}Ce, and not from the orally administered ^{136}Ce, as a single oral Ce citrate administration (of 100 µg) would not result in a significant increase of the Ce concentration in plasma, due to the low gastrointestinal absorption factor for Ce of 5×10^{-4} (Leggett et al. 2014). It is noted that thermal ionisation mass spectrometry (TIMS) would allow measurement of a very low mass of Ce tracers in human plasma, i.e. about 1 ng per sample, and thus, detection of a small increase in Ce concentration after ingestion of 100 µg of Ce citrate. As mentioned above, although the plasma samples were intensively processed (Pourmand and Dauphas 2010), the sources of interferences from barium in these samples could not be removed in the present study. The fact that Ce concentrations were too low to be detected in many of the investigated samples is certainly a drawback of the present study. Nevertheless, it is obvious that the plasma clearance of Ce citrate of the volunteers was very fast. On average, within the first five minutes more than 80% of Ce disappeared from the plasma. To better follow the rapid decrease of Ce in the plasma during the early phase after injection, blood collection starting about one minute after tracer injection would have been preferable.

In fact, animal studies on the blood clearance of Ce showed indeed an extremely fast clearance during the first minutes after intravenous injection. For example, Aeberhardt et al. found that 50% of Ce (administered as colloidal Ce) disappeared from the blood of rats already one minute after tracer injection; and after five minutes, about 91% of Ce was cleared from the blood (Aeberhardt et al. 1962). Similarly, Durbin et al. reported an almost complete disappearance of Ce during the first five minutes after injection of Ce citrate in rats (Durbin et al. 1955). An initial removal half-life from blood plasma of one minute was discussed, which was assumed to represent the equilibration time of the administered Ce in plasma with the extracellular fluid (ECF) and highly vascularized tissues. A second but longer half-life of 17 minutes from 5-60 minutes post-administration was assumed to represent the uptake of Ce in organs and tissues, the urinary excretion, and the re-entry of Ce into the plasma from other tissues. Obviously, these animal studies show fast clearance rates similar to those observed in the present human study.

Figure 2 presents the plasma clearance measured in the present study and, for comparison, the clearance predicted by the biokinetic model of Leggett (Leggett et al. 2014). Two model curves are shown, one applying a plasma volume of 2.4 L, the other a plasma volume of 3.6 L. The model curves at 5-10 minutes after injection are largely consistent with the measured data that are above LOQ. It is noted that the only value above the model curves was obtained from a female volunteer. It is also noted that the results for those volunteers for which all results were below LOQ (one female, four males) are not shown in Fig. 2. The biokinetic model curves suggest a slow plasma clearance of Ce between 5 and 120 minutes post-administration reaching a plasma level of 5% L^{-1} after about 84 minutes. In contrast, all experimental values except one reached the LOQ (which corresponded to 5% L^{-1}) much earlier (after about 15 minutes). Although the experimental data obtained in the present study are limited, they suggest a more rapid Ce removal from plasma than the model of Taylor and Leggett implies, which assumed a biological removal half-life from blood of 30 minutes (Taylor and Leggett 2003). Because of the many data, which were below LOQ (Table 5), a corresponding removal rate from plasma, was difficult to calculate, although it will be certainly less than 30 minutes. A half-life of around 10 minutes may be estimated visually from the plotted data. This fast plasma clearance after intravenous injection of Ce citrate may be due to the very stable Ce citrate complex, which shows a more rapid transfer of Ce from the plasma to other compartments of the human body or to a higher urinary excretion than those of a lower complexed or ionic Ce salt. This was already addressed by Höllriegl et al. (Höllriegl et al. 2017). The initial chemical speciation of the administered Ce citrate complex can explain the difference between the clearance observed in the present study and that predicted by the biokinetic model of Taylor and Leggett, which is a systemic model without any consideration of chemical speciation (Taylor and Leggett 1998, 2003).

For many years, speciation studies using complexes of REEs (including Ce but also other elements like the actinides) with citrate or with other stable chelating agents like DTPA or EDTA, have been performed, and their results compared particularly with the behaviour of the corresponding inorganic salts (chlorides, nitrates, carbonates) of these elements (Spencer 1963; Aeberhardt et al. 1962; Rosoff et al. 1963; Turner and Taylor 1968; Durbin et al. 1955). It was observed that after intravenous injection, the plasma level of elements in the form of stable chelate complexes decreased at a higher rate than those of elements present in their ionic forms. Depending on the chemical form and stability of the complexes, their distribution in organs or tissues (e.g. liver, bone) as well as their urinary excretion was different (Zhang and Chai 2004; Rosoff et al. 1963). A recent human study demonstrated the influence of the chemical form of ruthenium (Ru) on its kinetics in plasma. It was found that Ru citrate complexes

were very rapidly cleared from the plasma with a characteristic half-life of about 17 minutes, while inorganic Ru remained longer in the systemic circulation (Veronese et al. 2004).

In the present study, the uncertainty in the predicted plasma clearance of Ce was calculated based on the uncertainties of the biokinetic model parameters (see Table 4), and compared to the measured human Ce clearance and its uncertainty (Fig. 2). Except for one value, the measured mean values are, especially during the early period at 5-10 minutes after tracer injection, within the 95% confidence interval provided by the biokinetic model. It is emphasised, however, that the data below the LOQ are not consistent with the model prediction, because the biokinetic model was assumed to follow a linear and first order kinetics resulting in a slow and smooth decline of plasma clearance. Therefore, the LOQ data cannot reliably be used to validate the model predictions and uncertainties. This calls for further biokinetic measurements with improved experimental techniques. Within the involved uncertainties, however, this study found reasonable agreement between predicted and measured plasma clearance of Ce in humans. This demonstrates that the biokinetic model of Ce can be applied to predict the fast component of plasma clearance after injection. Finally, the influence of the chemical speciation of administered Ce on its biokinetic behaviour in the body is important, and this aspect should be included in biokinetic modelling.

Conclusion

The present human Ce study provided new results on the biokinetic behaviour of cerium citrate in blood plasma. After intravenous injection, plasma clearance was very fast within the first few minutes after administration. Given the involved uncertainties, data measured in the present study suggested a faster plasma clearance of Ce than predicted by the biokinetic model of Ce developed by Taylor and Leggett (Taylor and Leggett 1998). The present study suggested an influence of the chemical form of the administered cerium on its plasma clearance rate. Consequently, the importance of the chemical speciation should also be taken into account for biokinetic and dosimetric modelling. Furthermore, additional biokinetic measurements of Ce in blood and various organs and tissues, and urinary excretion of Ce, in particular at times later than those chosen in the present study, are called for. This would need use of advanced technologies offering the possibility to measure lower concentrations than those that could be measured in the present study. This, together with better Ce intake information, would allow further validation and improvement of the current systemic biokinetic model of Ce.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of interest: The authors declare that they have no conflict of interest.

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462 **Table 1** Isotopic composition of the administered cerium tracers as compared to that of natural

463 cerium and barium

	Relative isotope abundances (atom %)			
	136	138	140	142
natural cerium	0.185	0.25	88.45	11.11
oral ^{136}Ce tracer	30.6	0.7	64.2	4.5
intravenous ^{138}Ce tracer	0.04	41.6	55.81	2.55
natural barium	7.85	71.69		

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466 **Table 2** Data of human volunteers who participated in the present study. M – male; F – female.

Volunteer ID	Sex (F/M)	Age (y)	Mass (kg)	Plasma volume (L)
Ce7	M	31	115	4.55
Ce8	M	54	70	3.13
Ce9	F	48	66	2.56
Ce10	M	22	130	5.02
Ce11	M	30	84	3.57
Ce12	M	28	75	3.29
Ce13	M	30	82	3.51
Ce14	M	27	87	3.66

Ce15	F	62	75	2.79
Ce17	M	44	82	3.51

Table 3 Instrument parameters used for the inductively coupled plasma mass spectrometry (ICP-MS) measurements

Instrument	NexION 350X, Perkin Elmer
RF power	1300 W
Plasma gas	15 L Ar/min
Nebulizer gas	0.93 – 0.98 L Ar/min
Isotope	^{140}Ce
Internal standard	^{103}Rh, at 5 µg/L
Dwell time	50 ms
Replicates	3
Measurement time	2 min
Sample flow rate	250 µL/min
Calibration	
3-point calibration	1 ppt, 5 ppt, 10 ppt
4-point calibration	0.5 ppb, 1 ppb, 2 ppb, 5 ppb

Table 4 Uncertainty of the biokinetic parameters of Ce; Mean values represent k-values (k1-k28) reported by Leggett et al. (2014), and k-values (k29-k34) by ICRP 100 (ICRP 2006) ; Values of q2.5 and q97.5 are the 2.5th and 97.5th percentiles of the normal distribution, respectively; $\boldsymbol{cv}$ = coefficient of variation; SD – standard deviation

	Transfer coefficients k (d^{-1})[a]					
	Distribution	q2.5	Mean	q97.5	$cv(\%)$	SD
k1	Normal	8.502×10^{-1}	11.65	22.44	30	3.490
k2	Normal	5.216×10^{-1}	9.981	19.48	31	3.070
k3	Normal	1.353×10^{-1}	1.853	3.570	30	5.560×10^{-1}
k4	Normal	3.400×10^{-2}	4.658×10^{-1}	8.976×10^{-1}	30	1.400×10^{-1}
k5	Normal	2.551×10^{-1}	3.494	6.732	30	1.050
k6	Normal	2.551×10^{-1}	3.494	6.732	30	1.050
k7	Normal	2.551×10^{-2}	3.494×10^{-1}	6.732×10^{-1}	30	1.050×10^{-1}
k8	Normal	1.020×10^{-1}	1.170×10^{-1}	2.693	30	4.190×10^{-1}
k9	Normal	8.502×10^{-3}	1.397	2.244×10^{-1}	30	3.490×10^{-2}
k10	Normal	5.930×10^{-4}	8.150×10^{-3}	1.571×10^{-2}	30	2.450×10^{-3}
k11	Normal	3.401×10^{-2}	4.658×10^{-1}	8.976×10^{-1}	30	1.400×10^{-1}
k12	Normal	3.620×10^{-4}	9.490×10^{-4}	1.536×10^{-3}	20	1.900×10^{-4}
k13	Normal	7.140×10^{-4}	2.310×10^{-3}	3.906×10^{-3}	23	5.170×10^{-4}
k14	Normal	7.923×10^{-3}	2.079×10^{-2}	3.367×10^{-2}	20	4.170×10^{-3}
k15	Normal	5.296×10^{-1}	1.386	2.243	20	2.770×10^{-1}
k16	Normal	7.250×10^{-4}	1.899×10^{-3}	3.072×10^{-3}	20	3.800×10^{-4}
k17	Normal	4.800×10^{-5}	1.280×10^{-4}	2.040×10^{-4}	20	2.530×10^{-5}
k18	Normal	2.901×10^{-3}	7.596×10^{-3}	1.229×10^{-2}	20	1.520×10^{-3}
k19	Normal	3.100×10^{-5}	8.200×10^{-5}	1.320×10^{-4}	20	1.640×10^{-5}
k20	Normal	1.500×10^{-5}	4.100×10^{-5}	6.600×10^{-5}	20	8.220×10^{-6}
k21	Normal	3.100×10^{-5}	8.200×10^{-5}	1.320×10^{-4}	20	1.640×10^{-5}
k22	Normal	2.901×10^{-3}	7.596×10^{-3}	1.229×10^{-2}	20	1.520×10^{-3}
k23	Normal	1.880×10^{-4}	4.930×10^{-4}	7.970×10^{-4}	20	9.860×10^{-5}
k24	Normal	9.400×10^{-5}	2.470×10^{-4}	3.990×10^{-4}	20	4.940×10^{-5}
k25	Normal	1.880×10^{-4}	4.930×10^{-4}	7.970×10^{-4}	20	9.860×10^{-5}
k26	Normal	3.783×10^{-2}	9.900×10^{-2}	1.602×10^{-1}	20	1.980×10^{-2}
k27	Normal	5.290×10^{-4}	1.386×10^{-3}	2.243×10^{-3}	20	2.770×10^{-4}
k28	Normal	1.450×10^{-4}	3.790×10^{-4}	6.140×10^{-4}	20	7.600×10^{-5}
k29	Normal	4.584	12.00	19.42	20	2.400
k30	Normal	7.052×10^{-1}	1.750[b]	2.204	17	2.430×10^{-1}
k31	Normal	8.273×10^{-1}	1.750[b]	2.427	16	2.590×10^{-1}
k32	Normal	8.273×10^{-1}	1.750[b]	2.427	16	2.590×10^{-1}
k33	Normal	1.926	6.000	6.350	17	7.160×10^{-1}
K34	Normal	1.236×10^{-3}	3.000×10^{-3}	4.764×10^{-3}	30	9.000×10^{-4}

[a] Numbering of transfer coefficients (k_i) see Fig. 1; [b] mean value of 2 (for adult male) and 1.5 (for adult female)

Table 5 Cerium concentration of intravenous tracer measured in plasma of ten human volunteers; SD – standard deviation

	Ce concentration in plasma µg L^{-1} (± SD)			
Post-administration time	5 min	10 min	15 min	30 min – 1,440 min
Volunteer ID				
Ce7	<0.05	<0.05	<0.05	<0.05
Ce8	<0.05	<0.05	<0.05	<0.05
Ce9	0.435 (0.199)	0.220 (0.083)	0.207 (0.065)	<0.05
Ce10*	0.336 (0.036)	<0.05	<0.05	<0.05
Ce11	-	0.318 (0.059)	<0.05	<0.05
Ce12	<0.05	<0.05	<0.05	<0.05
Ce13	0.262 (0.122)	<0.05	<0.05	<0.05
Ce14	0.342 (0.120)	0.319 (0.114)	<0.05	<0.05
Ce15	<0.05	<0.05	<0.05	<0.05
Ce17	<0.05	<0.05	<0.05	<0.05

*Post-administration time: always 1.5 min later than intended

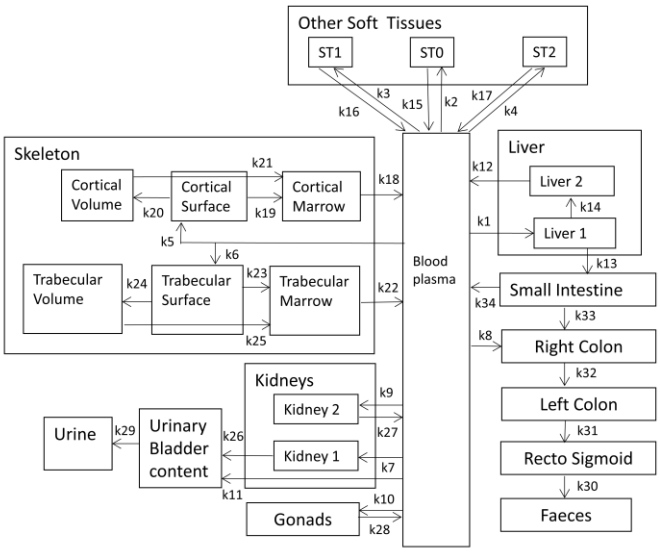
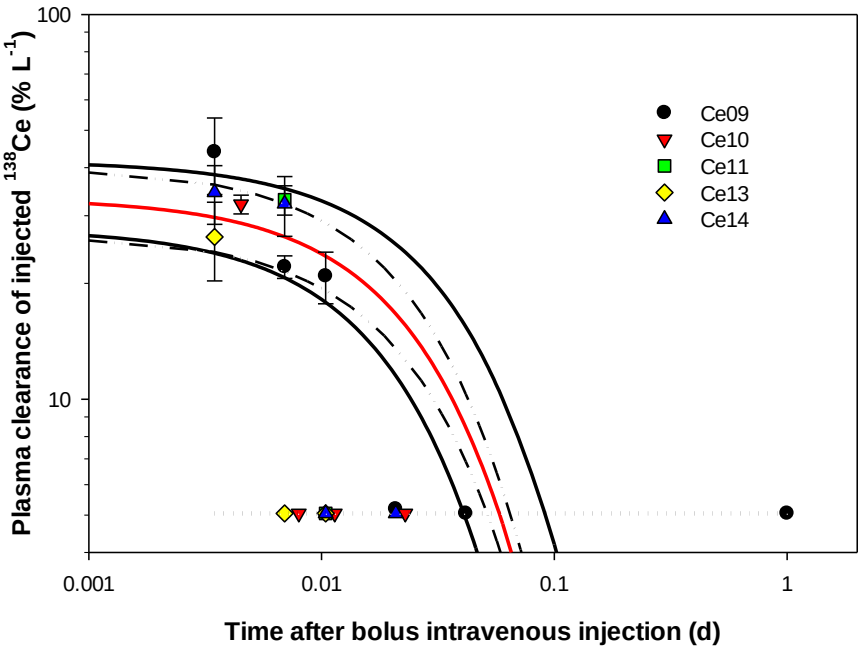


Fig. 1 Schematic presentation of the systemic model of cerium used in the present study (Leggett et al. 2014). The k_i-values represent the transfer coefficients (d^{-1}) between the different compartments of the model; ST = soft tissue



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494 **Fig. 2** Plasma clearance of cerium after intravenous injection of 1 µg (0.007 µmol) Ce-III-citrate. Tracer
495 concentrations are given as percent of administered tracer per liter plasma. Different symbols
496 correspond to data from five human volunteers (one female, four males), who showed measurable
497 values above limit of quantification (LOQ): Black circle – Ce09; red triangle down – Ce10; green square
498 – Ce11; yellow diamond – Ce13; blue triangle up – Ce14. Each data point represents the mean of three
499 measurements; error bars denote the corresponding standard deviation. Horizontal dotted line – LOQ
500 for Ce at 5.0% L^{-1}. Dashed-dotted lines – biokinetic model curves applying plasma volumes of 2.4 L (for
501 females, upper curve) and 3.6 L (for males, lower curve); the curves represent Ce concentrations in
502 plasma as "plasma", and not as "plasma + ST0" according to the biokinetic Ce model (Leggett et al.
503 2014). For the uncertainty of model prediction in the blood clearance of Ce, a plasma volume of 3 L
504 was applied; the solid red line represents the 50th percentile of prediction; the black dashed lines
505 denote the 2.5th and 97.5th percentiles.

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