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- 5 Measurement, model prediction and uncertainty quantification of plasma clearance of cerium citrate

6 in humans

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21 Abstract Double tracer studies in healthy human volunteers with stable isotopes of cerium citrate were 22 performed with the aim of investigating the gastro-intestinal absorption of cerium (Ce), its plasma 23 clearance and urinary excretion. In the present work, results of the clearance of Ce in blood plasma are 24 shown after simultaneous intravenous and oral administration of a Ce tracer. Inductively coupled 25 plasma mass spectrometry was used to determine the tracer concentrations in plasma. The results show 26 that about 80% of the injected Ce citrate cleared from the plasma within the five minutes post-27 administration. The data obtained are compared to a revised biokinetic model of cerium, which was 28 initially developed by the International Commission on Radiological Protection (ICRP). The measured 29 plasma clearance of Ce citrate was mostly consistent with that predicted by the ICRP biokinetic model. 30 Furthermore, in an effort to quantify the uncertainty of the model prediction, the laboratory animal 31 data on which the ICRP biokinetic Ce model is based, was analyzed. The measured plasma clearance 32 and its uncertainty was also compared to the plasma clearance uncertainty predicted by the model. It 33 was found that the measured plasma clearance during the first 15 minutes after administration is in a 34 good agreement with the modelled plasma clearance. In general, the measured clearance falls inside the 95% confidence interval predicted by the biokinetic model. 35

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

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40 Introduction

41 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 42 43 REEs) from mineral ores and their processing leads to a growing environmental pollution and, 44 therefore, to an increasing human exposure possibly involving health effects (Pagano et al. 2015; EPA 45 2012). The production of REE-rich phosphate fertilizers and their application increase the REE 46 concentration in soil, plants, and ground/surface water (Tyler 2004; Li et al. 2013). Hence, the daily 47 intake of cerium by food ingestion (up to $35 \mu g$) 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 48 49 than $0.008 - 0.07 \mu g L^{-1}$ (Höllriegl et al. 2010; Heitland and Köster 2006), much higher values up to 603 50 µg L⁻¹ could be found in exposed humans living near mining areas or regions with naturally high 51 background of Ce (Li et al. 2014).

Cerium is also of interest for radiation protection, due to its radioactive isotopes ¹⁴¹Ce and ¹⁴⁴Ce, which 52 53 are beta/gamma-emitters with physical half-lives of 33 days and 284 days, respectively. Radionuclides of Ce are produced in ²³⁵U/²³⁹Pu nuclear power and processing plants and may be released during 54 55 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. 56 57 Incorporation of Ce radionuclides into the human body may occur by inhalation or ingestion, or through 58 absorption by the skin or by wounds. A biokinetic and dosimetric model for the calculation of doses 59 from intakes of radionuclides of lanthanides (including cerium) was developed by the International 60 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). 61 Unfortunately, for humans there are not much data on the biokinetic behaviour of Ce published. Based 62 63 on the reviews of Taylor and/or Leggett (Leggett et al. 2014; Taylor and Leggett 2003) improvements of 64 the biokinetic ICRP Ce model will be published soon in the Occupational Intakes of Radionuclides Series (OIR) of the ICRP (in preparation). 65

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 nonspecific. 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 thechemical speciation of the administered substances.

74 Consequently, a human study on the biokinetics of Ce was initiated including two isotopically enriched 75 stable tracers of Ce with the aim to describe the gastrointestinal absorption of Ce, its distribution 76 throughout the human body and its urinary excretion (Keiser et al. 2011). The isotopes chosen, ¹³⁶Ce 77 and ¹³⁸Ce, were simultaneously administered to human volunteers as Ce-III-citrate complexes, one 78 orally and the other intravenously. This double tracer technique was introduced by De Grazia et al. 79 (De Grazia et al. 1965) as an effective method for the determination of the fractional absorption of an 80 ingested substance, and for the determination of the clearance from the plasma and of the urinary 81 excretion rate of an ingested and injected substance. Over the last years, this technique was modified 82 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 83 to elements with more than one stable isotope, if the natural isotopic composition of this element is 84 known. For cerium this was the case. The tracer concentrations should be as low as possible, in order 85 86 not to disturb the normal metabolism of the naturally occurring substance. Therefore, very low 87 concentrations of the tracer substance in plasma or urine samples have to be measured, which is 88 technically challenging. In addition, sources of interferences during the measurement must be avoided 89 or at least be controllable. In the present study, initially thermal ionization mass spectrometry (TIMS) 90 was considered as a suitable measurement technique. Unfortunately, this technique failed to 91 eliminate the known interferences from barium (Ba) at the isotope masses 136 and 138, in spite of 92 intensive sample preparation and purification (Pourmand and Dauphas 2010). As alternative method, 93 inductively coupled plasma sector field mass spectrometry (ICP-SF-MS) was chosen, although the 94 same interferences from Ba could also disturb the ICP-SF-MS measurements. However, to solve this interference problem, the ¹⁴⁰Ce concentration of the plasma samples were measured as the relative 95 abundance of ¹⁴⁰Ce was also substantial in both applied tracers enriched in ¹³⁶Ce or ¹³⁸Ce (Table 1). 96

97 Recently, results from the same human cohort on the excretion of Ce citrate in urine were presented 98 (Höllriegl et al. 2017). The results showed excretion rates of Ce that were higher as compared to those 99 calculated with the systemic model for cerium proposed by Taylor and Leggett (Leggett et al. 2014). 100 This difference was attributed to the specific chemical form of the cerium administered to the human 101 volunteers, which could not be adequately considered in the biokinetic model. In contrast, the present 102 work shows the plasma clearance of the administered Ce citrate in humans as compared to that 103 predicted by the biokinetic Ce model of Taylor and Leggett. 104 Biokinetic models are essential for calculation of internal radiation dose and associated risk for 105 occupational workers, members of the public and patients exposed to radionuclides; consequently, 106 such models underpin regulatory policy decisions in radiation protection. However, the required model 107 parameters are derived mostly from experimental data obtained from laboratory animals and from 108 analyses of accidental human contamination cases. According to ISO/IEC 17025 (ISO 2005), the 109 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 110 uncertainties, due to the physiological variability of individuals, the uncertainty in the extrapolation of 111 112 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 113 114 2001; Li et al. 2015). The uncertainty of these model parameters should be provided according to ISO GUM (ISO et al. 1995). 115

116 Materials and Methods

117 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) ¹³⁶Ce and 1 µg (0.007 µmol) ¹³⁸Ce tracer as Ce-III-citrate complexes were 122 123 simultaneously administered orally and intravenously, respectively. The applied Ce-III-citrate 124 complexes were very stable with a formation constant of log beta2 of about 11.2 (Ohyoshi et al. 1972). 125 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 126 127 and, due to its strong chelating properties, it is used in the decontamination of nuclear facilities 128 (Prakash et al. 2013). The quantity of the administered Ce tracers needed for the study was estimated 129 based on natural intake values of Ce, its concentration in blood or daily excretion, and some 130 toxicological considerations (Linsalata et al. 1986; Wappelhorst et al. 2002; Sabbioni et al. 1982; 131 Minoia et al. 1990; Jakupec et al. 2005; Health Effects Institute 2001). After administration, 10 mL 132 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; 133 134 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).

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144 Inductively coupled plasma mass spectrometry

145 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 146 147 oven for 45 minutes at 60 bar and 240 °C, with a maximum energy of 600 W. After the microwave digestion procedure, the ¹³⁶Ce, ¹³⁸Ce, ¹⁴⁰Ce and ¹⁴²Ce concentrations were measured with a NexION 350X 148 149 mass spectrometer (Perkin Elmer). Instrument parameters are given in Table 3. Unfortunately, ¹³⁶Ce and ¹³⁸Ce could not be quantified because of known barium interferences at masses 136 and 138 150 (Höllriegl et al. 2017). For further analysis, the measured ¹⁴⁰Ce concentrations were used, because ¹⁴⁰Ce 151 was present in both applied tracers (Table 1). Three measurements were made per sample, and the 152 153 mean value and the standard deviation were calculated. The limit of detection (LOD) was 0.01 μ g L⁻¹ and the limit of quantification (LOQ) was 0.05 µg L⁻¹ (Currie 1968). These values were mainly governed 154 by the digestion procedure and the sample dilution necessary for the ICP-MS measurement. 155

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157 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 halflife 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 165 equilibration of Ce with the extra-cellular fluid (ECF) which is part of the plasma; in the biokinetic model 166 the ECF is modelled by the soft tissue compartment STO (Fig. 1). Recycling of Ce between the tissue 167 compartments and blood plasma is included in the model allowing for different biological half-lives. The 168 model parameters (transfer coefficients) were taken from Leggett et al. (2014) and implemented in the 169 SAAM II ver2.3 computer program (Barrett et al. 1998). For the simulations, 1 µg Ce for the injection 170 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 171 172 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, 173 174 this value was taken for the simulations instead of 3.0 L.

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176 Uncertainty analysis

177 According to the ISO Guide (ISO 1995), the measurement uncertainty is the parameter associated with 178 the result of a measurement that characterizes the dispersion of the values that could reasonably be 179 attributed to the measurand. Uncertainty analysis requires computation of the total uncertainty 180 induced in the output of a simulation. This in turn requires quantification of the input and model 181 uncertainties, and the attributes of the relative importance of the input uncertainties in terms of their 182 contributions to the output (Morgan and Henrion 1990). The method can be applied both to measured 183 data and model parameters. To quantify the measurement uncertainties, the standard deviation of 184 plasma clearance as deduced from the ICP-MS measurements was used in the present study. The 185 uncertainty of parameters of the ICRP Ce biokinetic model was analyzed by evaluating the animal data 186 on which the ICRP biokinetic Ce model used in the present study was based. In addition, according to 187 the results of the parameter uncertainty analysis, the model parameters were sampled and imported 188 as input to the computer code BIOKINDOS. This code was developed for internal dosimetry uncertainty 189 analysis (Li et al. 2011; Li et al. 2015). The uncertainty of the model prediction was calculated from the 190 computer-simulated outputs and was compared to the uncertainty of the measured human data (partly 191 mean values with standard deviation). The biokinetic parameters (transfer coefficients) k_{ij} were 192 calculated by Eq. 1:

$$k_{ij} = \frac{\ln 2}{T_j} a_{ij} \tag{1}$$

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.

195 Numerical values of the variables k_{ij} , T_j , a_{ij} can be found in the literature (Taylor and Leggett 2003, 196 1998; Leggett et al. 2014; ICRP 1989). It was assumed that the values of these variables follow a normal 197 distribution. For those biokinetic parameters for which the available experimental data did not allow 198 estimation of any uncertainty, a coefficient of variation (cv) of 20% was assumed here. The cv is 199 considered to be one of the most widely used statistical measures of the relative dispersion. Values for 200 the cv of 16%, 17% and 31% were obtained from cited references by evaluating the animal data on 201 which the ICRP biokinetic Ce model was based (ICRP 1989; Taylor and Leggett 1998, 2003; Leggett et al. 202 2014). For the confidence interval of 95%, a coefficient of variation of 20% corresponds to a coverage 203 probability of more than 99.2% (Sappakitkamjorn and Niwitpong 2013). In the present work, the mean 204 values of these transfer coefficients k_{ij} were set to be the values reported by Leggett et al. (2014). The 205 standard deviation σ can be calculated for all statistical values based on Eq. 2:

$$cv = \frac{\sigma}{\mu} \tag{2}$$

206 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):

$$Minimum = \mu - 1.96\sigma \tag{3}$$

$$Maximum = \mu + 1.96\sigma \tag{4}$$

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

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214 Results and Discussion

215 Measurements of the normal cerium concentrations in blood plasma resulted in very low values (<0.008 216 $- 0.07 \ \mu g \ L^{-1}$) (Höllriegl et al. 2010; Heitland and Köster 2006). In the present study, the cerium 217 concentrations in the plasma (before administration of the Ce tracers) were less than 0.05 μ g L⁻¹, which 218 means that most of the measured values were below the LOQ.

219 Table 5 presents the results of the plasma concentration of Ce at fixed time points post-administration 220 for all ten human volunteers. At five minutes after injection, only half of the samples showed 221 measurable Ce concentrations, while the other samples showed values below the LOQ of 0.05 μ g L⁻¹; 222 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 ¹³⁸Ce, and not from 223 the orally administered ¹³⁶Ce, as a single oral Ce citrate administration (of 100 µg) would not result in 224 a significant increase of the Ce concentration in plasma, due to the low gastrointestinal absorption 225 226 factor for Ce of 5 x 10^{-4} (Leggett et al. 2014). It is noted that thermal ionisation mass spectrometry 227 (TIMS) would allow measurement of a very low mass of Ce tracers in human plasma, i.e. about 1 ng 228 per sample, and thus, detection of a small increase in Ce concentration after ingestion of 100 µg of Ce 229 citrate. As mentioned above, although the plasma samples were intensively processed (Pourmand and 230 Dauphas 2010), the sources of interferences from barium in these samples could not be removed in 231 the present study. The fact that Ce concentrations were too low to be detected in many of the 232 investigated samples is certainly a drawback of the present study. Nevertheless, it is obvious that the 233 plasma clearance of Ce citrate of the volunteers was very fast. On average, within the first five minutes 234 more than 80% of Ce disappeared from the plasma. To better follow the rapid decrease of Ce in the 235 plasma during the early phase after injection, blood collection starting about one minute after tracer injection would have been preferable. 236

237 In fact, animal studies on the blood clearance of Ce showed indeed an extremely fast clearance during 238 the first minutes after intravenous injection. For example, Aeberhardt et al. found that 50% of Ce 239 (administered as colloidal Ce) disappeared from the blood of rats already one minute after tracer 240 injection; and after five minutes, about 91% of Ce was cleared from the blood (Aeberhardt et al. 1962). 241 Similarly, Durbin et al. reported an almost complete disappearance of Ce during the first five minutes 242 after injection of Ce citrate in rats (Durbin et al. 1955). An initial removal half-life from blood plasma of 243 one minute was discussed, which was assumed to represent the equilibration time of the administered 244 Ce in plasma with the extracellular fluid (ECF) and highly vascularized tissues. A second but longer half-245 life of 17 minutes from 5-60 minutes post-administration was assumed to represent the uptake of Ce 246 in organs and tissues, the urinary excretion, and the re-entry of Ce into the plasma from other tissues. 247 Obviously, these animal studies show fast clearance rates similar to those observed in the present 248 human study.

Figure 2 presents the plasma clearance measured in the present study and, for comparison, the 249 250 clearance predicted by the biokinetic model of Leggett (Leggett et al. 2014). Two model curves are 251 shown, one applying a plasma volume of 2.4 L, the other a plasma volume of 3.6 L. The model curves at 252 5-10 minutes after injection are largely consistent with the measured data that are above LOQ. It is 253 noted that the only value above the model curves was obtained from a female volunteer. It is also noted 254 that the results for those volunteers for which all results were below LOQ (one female, four males) are 255 not shown in Fig. 2. The biokinetic model curves suggest a slow plasma clearance of Ce between 5 and 256 120 minutes post-administration reaching a plasma level of 5% L⁻¹ after about 84 minutes. In contrast, 257 all experimental values except one reached the LOQ (which corresponded to $5\% L^{-1}$) much earlier (after 258 about 15 minutes). Although the experimental data obtained in the present study are limited, they 259 suggest a more rapid Ce removal from plasma than the model of Taylor and Leggett implies, which 260 assumed a biological removal half-life from blood of 30 minutes (Taylor and Leggett 2003). Because of 261 the many data, which were below LOQ (Table 5), a corresponding removal rate from plasma, was 262 difficult to calculate, although it will be certainly less than 30 minutes. A half-life of around 10 minutes 263 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 264 265 from the plasma to other compartments of the human body or to a higher urinary excretion than those 266 of a lower complexed or ionic Ce salt. This was already addressed by Höllriegl et al. (Höllriegl et al. 2017). 267 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 268 269 Taylor and Leggett, which is a systemic model without any consideration of chemical speciation (Taylor 270 and Leggett 1998, 2003).

271 For many years, speciation studies using complexes of REEs (including Ce but also other elements like 272 the actinides) with citrate or with other stable chelating agents like DTPA or EDTA, have been 273 performed, and their results compared particularly with the behaviour of the corresponding inorganic 274 salts (chlorides, nitrates, carbonates) of these elements (Spencer 1963; Aeberhardt et al. 1962; Rosoff 275 et al. 1963; Turner and Taylor 1968; Durbin et al. 1955). It was observed that after intravenous injection, 276 the plasma level of elements in the form of stable chelate complexes decreased at a higher rate than 277 those of elements present in their ionic forms. Depending on the chemical form and stability of the 278 complexes, their distribution in organs or tissues (e.g. liver, bone) as well as their urinary excretion was 279 different (Zhang and Chai 2004; Rosoff et al. 1963). A recent human study demonstrated the influence 280 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, whileinorganic Ru remained longer in the systemic circulation (Veronese et al. 2004).

283 In the present study, the uncertainty in the predicted plasma clearance of Ce was calculated based on 284 the uncertainties of the biokinetic model parameters (see Table 4), and compared to the measured 285 human Ce clearance and its uncertainty (Fig. 2). Except for one value, the measured mean values are, 286 especially during the early period at 5-10 minutes after tracer injection, within the 95% confidence 287 interval provided by the biokinetic model. It is emphasised, however, that the data below the LOQ are 288 not consistent with the model prediction, because the biokinetic model was assumed to follow a linear 289 and first order kinetics resulting in a slow and smooth decline of plasma clearance. Therefore, the LOQ 290 data cannot reliably be used to validate the model predictions and uncertainties. This calls for further 291 biokinetic measurements with improved experimental techniques. Within the involved uncertainties, 292 however, this study found reasonable agreement between predicted and measured plasma clearance 293 of Ce in humans. This demonstrates that the biokinetic model of Ce can be applied to predict the fast 294 component of plasma clearance after injection. Finally, the influence of the chemical speciation of 295 administered Ce on its biokinetic behaviour in the body is important, and this aspect should be included 296 in biokinetic modelling.

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298 Conclusion

299 The present human Ce study provided new results on the biokinetic behaviour of cerium citrate in 300 blood plasma. After intravenous injection, plasma clearance was very fast within the first few minutes 301 after administration. Given the involved uncertainties, data measured in the present study suggested 302 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 303 304 the administered cerium on its plasma clearance rate. Consequently, the importance of the chemical 305 speciation should also be taken into account for biokinetic and dosimetric modelling. Furthermore, 306 additional biokinetic measurements of Ce in blood and various organs and tissues, and urinary 307 excretion of Ce, in particular at times later than those chosen in the present study, are called for. This 308 would need use of advanced technologies offering the possibility to measure lower concentrations 309 than those that could be measured in the present study. This, together with better Ce intake 310 information, would allow further validation and improvement of the current systemic biokinetic 311 model of Ce.

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317 **Ethical approval**: All procedures performed in studies involving human participants were in 318 accordance with the ethical standards of the institutional and/or national research committee and 319 with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

320 Informed consent: Informed consent was obtained from all individual participants included in the321 study.

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

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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				

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

Volunteer	Sex (F/M)	Age (y)	Mass (kg)	Plasma volume (L)
ID				
	N.4	21	115	4.55
Ce/	IVI	31	115	4.55
Ce8	М	54	70	3.13
Ce9	F	48	66	2.56
		-		
Ce10	М	22	130	5.02
Ce11	М	30	84	3.57
Ce12	Μ	28	75	3.29
Ce13	М	30	82	3.51
6.14		27	07	2.55
Ce14	IVI	27	87	3.66

Cers	F	62	75	2.79	
Ce17	Μ	44	82	3.51	
ʿ able 3 Instrum neasurements	ent param	eters used fo	or the inductiv	vely coupled plasma ma	ass spectrometry
Instrument		Ne		erkin Elmer	
		10			
RF power		13	00 W		
Plasma gas		15	L Ar/min		
Nebulizer gas		0.9	93 – 0.98 L Ar,	/min	
Isotope		140	Ce		
Internal standa	ard	103	Rh, at 5 μg/L		
Dwell time		50	ms		
Replicates		3			
Measurement	time	2 r	nin		
Sample flow ra	ate	25	0 μL/min		
Calibration					
3-point calib	oration	1 f	opt, 5 ppt, 10	ppt	
	oration	0.5	5 ppb, 1 ppb, 2	2 ppb, 5 ppb	

476 **Table 4** Uncertainty of the biokinetic parameters of Ce; Mean values represent k-values (k1-k28)

477 reported by Leggett et al. (2014), and k-values (k29-k34) by ICRP 100 (ICRP 2006) ; Values of q2.5 and

478 q97.5 are the 2.5th and 97.5th percentiles of the normal distribution, respectively; cv = coefficient of

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

479 variation; SD – standard deviation

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

481 adult female)

483 **Table 5** Cerium concentration of intravenous tracer measured in plasma of ten human volunteers;

484 SD – standard deviation

	Ce concentration in plasma				
	μg L ⁻¹ (± SD)				
Post-	5 min	10 min	15 min	30 min –	
administration				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	0.220	0.207	<0.05	
	(0.199)	(0.083)	(0.065)		
Ce10*	0.336	<0.05	<0.05	<0.05	
	(0.036)				
Ce11	-	0.318	<0.05	<0.05	
		(0.059)			
Ce12	<0.05	<0.05	<0.05	<0.05	
Ce13	0.262	<0.05	<0.05	<0.05	
	(0.122)				
Ce14	0.342	0.319	<0.05	<0.05	
	(0.120)	(0.114)			
Ce15	<0.05	<0.05	<0.05	<0.05	
Ce17	<0.05	<0.05	<0.05	<0.05	

485 *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



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 + STO" 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 was applied; the solid red line represents the 50th percentile of prediction; the black dashed lines 504 denote the 2.5th and 97.5th percentiles. 505

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