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Evidence of high bioaccessibility of Gadolinium-contrast agents in natural waters after human oral uptake

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Abstract

Considering the large occurrence of anthropogenic Gd concentrations in natural waters, its continuous usage increase in technology developments and products and the lack of data on potential Gd human exposure due to ingestion of contaminated waters, it is urgently needed to understand how gadolinium contrast agents (Gd-CAs) reacts in the human digestive system. Here, we aimed to identify through in vitro bioaccessibility tests whether Gd-CAs can be potentially assimilated by humans after oral uptake and if there is a significant difference between contrast agents. We also roughly estimated the potential bioaccessibility of anthropogenic Gd for tap waters worldwide. Gd-CAs are highly bioaccessible (77 to 112%). The macrocyclic complexes pose the highest potential risk, because there are more

stable than linear complexes in the gastrointestinal tract and, as such, tend to remain in solution and thus might bring Gd at the intestinal barrier making it potentially bioavailable. The estimated range of potential intake of Gd varied from 13 to 4839 µg in a lifespan of 70 years. The high bioaccessibility of anthropogenic Gd in tap waters calls for appropriate actions to develop better practices to treat wastewater contaminated by Gd-CAs in order to safeguard population and ecosystem health.

Keywords: Bioaccessibility, gastrointestinal tract, anthropogenic Gd, natural waters, contrast agents, Gd complexes

1. Introduction

Gd^{3+} has unparalleled paramagnetic properties that can help increase clarity, contrast and detail for the differentiation of tissues in diagnostic medical imaging. Consequently, it is largely employed as a contrast agent in magnetic resonance imaging (MRI). However, Gd^{3+} is highly toxic and can precipitate in various biological tissues (e.g., liver, lymph nodes and bones), block the transport of calcium in muscle and nerve cells, and it also interferes with intracellular enzymes and cell membranes through transmetallation (Idée et al., 2006; Möller and Dulski, 2010a; Möller and Dulski, 2010b). For this reason, Gd^{3+} is administered chelated with large organic molecules, forming stable Gadolinium-contrast agents (Gd-CAs) that can be safely used as MRI contrast media (Rogosnitzky and Branch, 2016). Due to their high stability, the Gd-CAs are less allergenic and safer than other contrasts (Shellock and Spinazzi, 2008).

The Gd-CAs started to be used in 1988 and since then the growth in access to healthcare systems promoted an increase in the number of MRI exams performed worldwide (OECD, 2019). Since 2005, the number of exams increased by 50% (Idee et al., 2006; Ebrahimi and Barbieri, 2019). Countries with highly developed healthcare systems (e.g. Germany and Austria) perform more than 140 scans per 1,000 habitants yearly (Statista,

2020). This number may have been even higher in 2020-2021, since Gd-CAs have been used to detect heart damage caused by the SARS-COV-2 infection during the global COVID-19 outbreak (Huang et al., 2020). The Gd-CAs (0.1 mmol of Gd per kg of body weight) are applied in ~40% of MRI exams and are rapidly excreted from the human body via urine, usually in a period of less than 30h (Kümmerer and Helmers, 2000).

The very stable and non-reactive Gd-CAs, after human excretion, pass wastewater treatment plants (WWTP) mostly unhindered (Telgmann et al., 2012) and enter aquatic systems by the effluents, contaminating water systems and suppliers, thus been currently regarded as contaminants of emerging concern (e.g., Bau and Dulski, 1996; Kulaksız and Bau, 2011a; Künnemeyer et al., 2009; Lawrence, 2010; Lawrence et al., 2009; Verplanck et al., 2010; Hatje et al., 2016; Lerat-Hardy et al., 2019). Because of the stability of Gd-CAs and their potentially high half-lives (> 100 days) in the environment (Holzbecher et al., 2005), they can travel relatively long distances and may contaminate lakes (Bau et al., 2006; Merschel et al., 2015), rivers (Bau, Knappe and Dulski, 2006; Kulaksız and Bau, 2011b; Lawrence, 2010; Merschel and Bau, 2015; Parant et al., 2018; Rogowska et al., 2018; Inoue et al., 2020), groundwater and marine waters (Pedreira et al., 2017; Hatje et al., 2016; Johannensson et al., 2017; Andrade et al., 2020). Once in the environment, Gd-CAs can be used as a tracer of wastewater discharges and hydrological processes (Hatje et al., 2014; Hissler et al., 2014). Although Gd-CAs were first identified in natural waters 25 years ago (Bau and Dulski, 1996), their toxicity, fate, and degradability under natural conditions are poorly understood, which jeopardize the risk assessment of these metalorganic species in ecosystems and human health. These knowledge gaps possibly explain why Gd-CAs are not yet regulated in water quality standards.

The main human exposure of Gd-CAs is via venous injection, which in only exceptional cases may lead to the accumulation of Gd in tissues and brain after repeated MRI

treatments (Delfino et al., 2019) or in patients with renal disease history (Kanda et al., 2016). However, the worldwide occurrence of anthropogenic Gd in tap waters, surface waters and groundwaters used for domestic supply is a subject of increasing concern once it may be a pathway for anthropogenic Gd into the food chain. Contamination by Gd is not a local problem, but rather a common feature of tap water of cities with highly developed healthcare systems, such as Berlin (Bau and Dulski, 1996; Schmidt et al., 2019; Tepe and Bau, 2014; Kulaksiz and Bau, 2011b), London (Kulaksiz and Bau, 2011b), Prague (Möller et al., 2002), Dusseldorf, and Munchen (Schmidt, et al., 2019). Gd contamination has also been observed in tap water-based popular soft drinks (Coca Cola) from fast food franchises (Schmidt et al., 2019). The source of drinking water, including surface water, precipitation, shallow or deep groundwater, is a key factor to determine the quality of the tap water and its likelihood of contamination. Hence, consumption of low levels of Gd-CAs contaminated tap water may represent a new human exposure route that potentially place at risk consumers in the long run, particularly those at critical development stages, and for the more sensitive population, such as pregnant women and their fetuses.

Determining the amount of Gd-CAs that dissolves or remains dissolved in the gastrointestinal tract during digestion (i.e. oral bioaccessibility) and can be assimilated and reach the systemic circulation of an organism, is an important tool in health risk assessment. This tool provides valuable data that supports decision making regarding water consumption regulation. Yet, no studies have addressed the oral bioaccessibility of Gd-CAs in tap waters.

Considering the occurrence of anthropogenic Gd concentrations in tap water and beverages (e.g., Kulaksiz and Bau, 2011a; Tepe and Bau, 2014; Schmidt et al., 2019), the lack of data on potential Gd-CAs low-dosage exposure due to long-term ingestion of contaminated waters, and the absence of legal maximum threshold values available, it is urgently needed to understand how Gd-CAs reacts in the human digestive system. Here, we

aimed to i) identify through *in vitro* bioaccessibility tests whether Gd-CAs can be potentially assimilated by humans after orally ingestion; ii) evaluate if there is a significant difference in the oral bioaccessibility values between contrast agents; and iii) estimate the bioaccessibility of anthropogenic Gd already reported for tap waters.

2. Experimental section

2.1 Reagents, samples and solutions for the extraction

All solutions were prepared from analytical reagents using Milli-Q water (>18.2 MΩ•cm, Millipore, A10®, Germany). Polyethylene containers (Nest Scientific) and glassware were soaked in detergent (Extran®, Merck, Germany), and then soaked in 6 HCl solution, followed by a 6 M HNO_3 solution, for ca. 48 h each and rinsed three times with Milli-Q water pending use. Two linear chelates (i.e., ionic complex Magnevistan®-Bayer, and non-ionic complex Optimark®- Guerbet) and two macrocyclic chelates (i.e., ionic complex Dotarem®-Guerbet and non-ionic complex ProHance®-Bayers) commonly used as MRI contrast agents were obtained from hospitals in Bahia, Brazil for the bioaccessibility tests (Table S1). Although the European Medicines Agency (EMA) suspended the use of some linear Gd-CAs (i.e. gadodiamide, gadopentetic acid and gadoversetamide) and restricted the use of others (e.g. gadobenic acid) (European Medicines Agency, 2017). Brazil and other countries worldwide (e.g. USA; FDA, 2018) are still using linear complexes.

Biorelevant digestive fluid surrogates under fed-state (saliva, gastric fluid, gastrointestinal fluid and bile) were composed of salts, organic reagents and enzymes, as previously described by Versantvoort et al. (2005). All digestive fluids were subjected to agitation (100 rpm for 3 h) in order to dissolve the salts along with the enzyme constituents and they were kept overnight at room temperature. The digestive fluids were then heated to 37 ± 2 °C for 1 h to activate the enzymes and used on the same day of *in vitro* tests. Bidistillated nitric acid (Merck, Germany) was used for microwave-assisted digestion of (i) the water samples, (ii)

the bioaccessible fractions and (iii) the residual (non-bioaccessible) fractions of Versantvoort's test for the mass balance validation studies. Detailed information on the chemical reagents are given in Table S2.

2.3 Analytical procedures

Tap water was collected in the laboratory of CIEnAm-UFBA and was filtered with a cellulose acetate membrane filter (0.2 µm) in a vacuum filtration system. Then, the water samples were enriched with 500 µg L^{-1} (final concentration) of the Gd-CAs (Dotarem®, Magnevistan®, Optimark® and Prohance®), one at a time, for the bioacessibility tests.

The *in vitro* gastrointestinal digestion test was adapted from Versantvoort et al. (2005) and consisted of three consecutive steps: (I) salivary fluid was incorporated to the sample, (II) gastric fluid was added to the first step, and (III) duodenal and bile fluid were added to the second step. All steps were carried out in an incubator (ACB LABOR, model RE120, Germany) at 37 ± 2 °C under magnetic stirring at 55 rpm. To this end, 20 mL of tap water were spiked with 500 µg L^{-1} (final concentration), one at a time of Gd-CA in polypropylene flasks (50 mL). The volume of 20 mL was used following previous tests that evaluated bioaccessibility in liquid samples (Schimite et al., 2019; Quan et al., 2020; de Andrade et al., 2020). Then, 3 mL of salivary solution (pH 6.8 ± 0.2) were added and the mixture was incubated for 5 min. Subsequently, 6 mL of gastric fluid (pH 1.30 ± 0.02) were added, and the mixture was incubated for 2 h. Finally, 6 mL of duodenal fluid (pH 8.1 ± 0.2), 3 mL of bile (pH 8.2 ± 0.2), and 1.0 mL of 1.0 mol L^{-1} of HCO_3^- were consecutively added, and the mixture was incubated for another 2 h. The final pH of each step, when necessary, was adjusted using small volumes of 1 mol L^{-1} of HCl or NaOH. All experiments were run in at least triplicates.

The gastrointestinal extracts were filtered through 0.45 µm PVDF syringe filters and the filter membranes containing the residue were dried at room temperature at least 72 h in a

desiccator. The original tap water samples, the gastrointestinal bioaccessible fractions and the residual (non-bioaccessible) fractions were subjected to microwave-assisted digestion (Anton Paar, Multiwave PRO, Austria) using 6 mL of nitric acid (bidistilled acid, Merck), as described by Bendakovsk et al. (2016). Acid decomposition tests with oxidants were also carried out to evaluate the effect of hydrogen peroxide in the digestion of the gastrointestinal bioaccessible fraction from the *in vitro* oral bioaccessibility tests of tap water samples enriched with 500 μg L^{-1} of Dotarem®. There was no significant difference ($p > 0.05$) in the digestion efficiency with or without the use of 2 mL of H_2O_2 (Table S3). Therefore, H_2O_2 was not used in the following experiments. Quality control of the *in vitro* bioaccessibility test was performed via mass balance validation. The average of the sum of the Gd gastrointestinal bioaccessible fraction and the Gd residual fraction was compared against the total Gd concentration in the raw sample. For validation of the acid digestion procedure in raw samples, addition and recovery tests were performed with 100 and 200 μg L^{-1} of a gadolinium standard (High-Purity Standards, Charleston, SC, USA) (Table 1). The real sample concentration without addition of Gd was 0.46 ± 0.05 μg L^{-1}. The recovery tests for the gadolinium standard addition showed good recovery percentages, ranging from 105 ± 2 to 109 ± 1 % (Table 1). Besides, we analyzed samples of a certified reference material (Mussel tissue – BCR 668, IRMM, Belgium) and recoveries for Gd were 98 ± 5%.

After microwave-assisted decomposition, the solutions were made up to 50 mL with Milli-Q water and Gd was measured by an inductively coupled plasma-mass spectrometer, ICP-MS (Thermo Scientific™, iCAP RQ, Germany). The instrumental conditions are summarized in Table S4. Polyatomic and isobaric interferences were monitored. Two solutions composed of Tb and Gd, and La, Ce, Pr, Nd, Sm, and Ba, all at 1 μg L^{-1}, were run every 20 samples to monitor oxide formation. The concentrations of Gd were not corrected for oxide formation because their occurrence was not significant. Calibration curves spanning from 0.05 to 5.00

μg L^{-1} were used for the quantification of Gd. The final Gd concentrations in the measured samples were ca. 2.0, 1.0 and 0.2 μg L^{-1} for the tap water, bioaccessible fraction and residue, respectively. For each solution, the dilution factors were ca. 260, 450, and 10-fold, respectively. The difference in the dilution factor between tap water and bioaccessible fraction was approximately 2-fold considering the final volume of the gastrointestinal extract. Besides, the dilution factor for the gastrointestinal fluids should be greater to avoid matrix effect. Indium was used as the internal standard (1 μg L^{-1}, final concentration).

3. Results and discussion

For the first time, an oral bioaccessibility test was herein employed to determine the gastrointestinal bioaccessible fraction of Gd in tap water samples enriched with the most employed Gd-CA contrasts using in MRI (i.e., Dotarem®, Magnevistan®, ProHance® and Optimark®). The oral bioaccessible fraction was calculated as follows equation:

$$Bioaccessibility\ (\%) = \frac{\text{Gd bioaccessible concentration}}{\text{Gd concentration in the raw sample}}\ x\ 100$$

The results showed that the contrast with the greatest Gd gastrointestinal bioaccessibility was Dotarem® (112%), which is in good agreement with the finding that the residual fraction was below the limit of quantification (LOQ), followed by ProHance® (91%), Optimark® (84%), and Magnevistan® (77%), as shown in Table 2. Differences in bioaccessibility were significant between Dotarem® (macrocyclic) and all other contrasts (ANOVA, $p<0.05$). The ProHance® (91%) (macrocyclic) also presented significantly (ANOVA, $p<0.05$) larger bioaccesibility than the Magnevistan® (linear). The difference between the ProHance® and Optimark® was not significant (ANOVA, $p>0.05$). The linear complexes had lower bioaccessible Gd values (77 to 84%) than the macrocyclic complexes (91 to 112%). These results reflect differences in the stability of the complexes in the gastrointestinal tract. The macrocyclic complexes are more stable (Rogosnitzky and Branch, 2016) and, thus, they remain solubilized for longer time intervals and might act as carriers for

Gd towards the intestinal barrier, making it potentially bioavailable. Our bioaccessibility results are in good agreement with the fact that macrocyclic Gd ionic complexes (e.g., Dotarem®) are more stable than non-ionic counterparts (e.g., ProHance®) due to the superior ion-ligand bonding energy despite of its allergenic potential (Yon et al., 2019). On the other hand, in the gastrointestinal tract, the Gd(III) released from the less stable linear Gd-CAs tends to precipitate as oxide, and consequently the Gd coming from these complexes is less bioaccessible in the gastrointestinal phase.

The inadvertent oral intake of Gd-CAs favors the release of Gd^{3+} from linear complexes due to their greater dissociation (as compared to the macrocyclic counterparts) at low pH. However, at the gastrointestinal pH, the Gd^{3+} released is involved in precipitation equilibria, making it less bioaccessible. It is known that a number of cations, such as Cu^{2+}, Fe^{3+}, Ca^{2+} and Zn^{2+} compete with the Gd^{3+} for the ligand (Rogosnitzky and Branch, 2016) and a number of other anions, such as PO_4^{3-}, CO_3^{2-}, and OH^- can compete with the ligand for Gd^{3+} in a process known as transmetallation (Ideè *et al*., 2006). From the point of view of the intravenous administration of Gd complexes, at physiological pH, the concentrations of Cu^{2+} and Zn^{2+} in the bloodstream, for example, have a strong affinity for the chelate with the consequent release of free Gd in the medium. However, it is still unclear whether the Gd-CA, its transformation products or release of Gd^{3+} are in fact posing issues to human health (Brünjes and Hofmann, 2020).

It is worth noting that the information presented herein in relation to oral ingestion does not invalidate the discussions in the literature on intravenous administration, since they evaluated different routes of exposure to Gd-CAs. However, the contrasting results highlight the importance of the exposure routes and potential associated risks. From a pharmacological point of view, venous administration of macrocyclic complexes is less harmful than by oral administration.

The in vitro physiologically-based tests are important tools to evaluate the behavior of Gd in the gastrointestinal medium and to comprehend its absorption/toxicity in the human body. Moreover, the human feeding can directly interfere in the bioaccessibility of the complex. For example, if the diet is rich in Cu, Fe, Ca, and Zn, or if the daily intake of metal-laden foods is concomitant with the contaminated water, it could alter the competitiveness by the ligand and this risk can be worsened. Another important consideration is that the complexes are prepared with an excess of chelator agent to quickly capture the released gadolinium. On the other hand, in the environment, the excess of the chelator added to the medication will be diluted, which then makes the dissociation of gadolinium in its ionic form easier.

The validation of the *in vitro* bioaccessibility test was performed by mass balance (bioaccessible plus residual fractions compared to the total content). The recoveries of Gd varied between 80±3 to 112±4 % (Table 2). These results showed good recoveries and demonstrate that there is no significant matrix interfering effects in the determination of the oral bioaccessible fraction of Gd by ICP-MS, once these were eliminated by the use of microwave-assisted digestion.

Our data shows that a large part of the anthropic Gd resulting from the use of Gd-CAs remains bioaccessible in the gastrointestinal tract after oral ingestion. Thus, drinking Gd-CAs contaminated tap water can potentially promote the accumulation of Gd in the human body, even in individuals who have never undergo a MRI exam with a Gd-CA.

A rough estimation of the potential intake (PI) of anthropogenic Gd by humans consuming Gd contaminated tap waters under chronic scenarios (Table 3) were performed using the minimum and maximum values of bioaccessibility of Gd obtained in our study (i.e., 77 and 100%). Although we just provide rough estimates in a risk assessment/exposure framework, we believe that our conservative/worst case scenario results underscore the

potential dimensions of the increasing problem associated with the Gd-CAs contamination in surface and groundwaters that are used as source drinking water. We have considered local tap water concentrations of Gd as reported in the literature (Table 3); the time span of 70 years (global average life expectancy); and the daily ingestion of 2 liters of water, which is the minimum water intake recommended by the WHO (2005) for PI estimation.

$$PI=\frac{CTW\ x\ \%\ MIPB\ or\ MAPB\ x\ 2L/day\ x\ 70\ years}{1000}$$

Where PI is the potential intake of Gd in µg, CTW is the Gd concentration in tap water in ng L^{-1}, MIPB is the minimum percentage of bioaccessibility and the MAPB is the maximum percentage bioaccessibility. Although natural Gd is also included in the total concentrations of Gd presented in Table 3, we assumed that the overall Gd concentrations are associated with Gd-CAs, then providing a conservative, upper limit estimation.

The estimated range of PI of Gd varied from 13 to 4839 µg in a lifespan of 70 years (Table 3). Despite the lack of toxicity guidelines as to the maximum allowed daily intake of Gd, the results are worrisome, once contamination by Gd in natural waters is ubiquitous and of increasing concern, although the concentrations measured in tap waters being still relatively low. Among the world regions for which there is contamination by Gd in tap waters, the highest risk was found for the tap water of Berlin (Table 3). Though we only present a rough estimate of human exposure to Gd, this clearly highlights the other two problems associated with the increasing use of Gd-CAs: i. the potential long-term exposure of humans to Gd, and ii. the need to develop novel technologies or improve those extant to eliminate Gd during wastewater treatment. Obviously the later does not only refer to Gd but all emerging organic and inorganic contaminants associated with the development of new technologies and products.

4. Conclusions

With the increasing use of RMI worldwide, which has escalated even more because

helps diagnose heart damage during the COVID-19 pandemic, our results (high Gd bioaccessibility) suggest that anthropogenic Gd should be evaluated more routinely in tap and superficial waters. In addition, appropriate actions to develop better practices to treat wastewater contaminated by Gd-CAs are called for in order to safeguard the population and the ecosystem's health.

Conflict Of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1. Concentration of Gd in tap water and recovery tests after microwave digestion (n = 3).

Sample	Real sample concentration ($\mu g\ L^{-1}$)	Added concentration of Gd ($\mu g\ L^{-1}$)	Recovery (%)
Tap water	0.46 ± 0.05	100	109 ± 1
		200	105 ± 2

Results are expressed as the mean of three replicates ± standard deviation.

Table 2. Gastrointestinal bioaccessible concentrations of Gd for Dotarem®, Magnevistan®, Optimark®, Prohance® samples and mass balance validation of the extraction system (n=4).

Sample	Gastrointestinal bioaccessibility ($\mu g\ L^{-1}$ and (%))	Residue ($\mu g\ L^{-1}$)	Total ($\mu g\ L^{-1}$)	Total microwave digestion ($\mu g\ L^{-1}$)	Recovery of mass balance (%)
Dotarem	406 ± 3 (112%)	<LOQ*	406 ± 3	373 ± 25	112 ± 4
Magnevistan	288 ± 9 (77%)	15 ± 1	300 ± 8	375 ± 7	80 ± 3
ProHance	370 ± 17 (91%)	1.5 ± 0.2	372 ± 17	402 ± 29	92 ± 8
Optimark	335 ± 29 (84%)	14 ± 2	335 ± 7	383 ± 35	88 ± 9

*LOQ = Limit of Quantification

Table 3. Total concentration, Gd anomaly, and minimum and maximum concentrations of bioaccessible Gd in tap water assuming a daily intake of 2L of water and a lifetime

span of 70 years.

Country	Location	Gd (ng L^{-1})	Min -Max conc. of Gd bioacessible in tap water (ng L^{-1})[1]	Min - Max daily Gd intake[2] (ng per day)	Min - Max cumulative lifetime potential intake[3] (µg in 70 years)	Refs.
England	**London**	1.9	1.5 – 1.9	3.0 – 3.9	76 - 99	Kulaksiz et al, 2011
Czech Republic	**Podoli prague**	0.6	0.5 – 0.6	0.9 – 1.2	24 - 31	Moller et al., 2002
	Zelivka prague	0.3	0.25 – 0.33	0.5 – 0.7	13 - 17	Moller et al., 2002
	Karany prague	2.5	1.9 – 2.5	3.9 – 5.0	98 - 128	Moller et al., 2002
Germany	**Mitte**	7.0	5.4 – 7.0	10.8 – 14.1	277 - 359	Kulaksiz et al., 2011
	Reichstag	18.1	13.9 – 18.1	27.8 – 36.2	712 - 924	Kulaksiz et al., 2011
	Reichstag 2	9.5	7.3 – 9.5	14.6 – 19.0	374 - 485	Kulaksiz et al., 2011
	Jungfernheide	0.6	0.4 – 0.6	0.8 – 1.1	22 - 28	Kulaksiz et al., 2011
	Zoologischer Garten	11.7	9.0 – 11.7	18.0 – 23.4	460 - 597	Kulaksiz et al., 2011
	Kurfürstendamm	6.0	4.6 – 6.0	9.2 – 12.0	235 - 305	Kulaksiz et al., 2011
	Schöneberg	2.7	2.0 – 2.7	4.1 – 5.3	105 - 136	Kulaksiz et al., 2011
	Neukölln	4.8	3.7 – 4.8	7.4 – 9.6	189 - 246	Kulaksiz et al., 2011
	Alt-Mariendorf	1.8	1.4 – 1.8	2.7 – 3.6	70 - 91	Kulaksiz et al., 2011
	Steglitz	1.2	0.9 – 1.2	1.8 – 2.3	46 - 60	Kulaksiz et al., 2011

	Adlershof	0.6	0.4 – 0.6	0.8 – 1.1	22 - 28	Kulaksiz et al., 2011
	Wedding	8.1	6.2 – 8.1	12.5 – 16.2	319 - 415	Kulaksiz et al., 2011
	Wittenau	8.5	6.5 – 8.5	13.0 – 16.9	333 - 432	Kulaksiz et al., 2011
	Tegel	9.2	7.1 – 9.2	14.2 – 18.5	363 - 472	Kulaksiz et al., 2011
	Spandau	0.6	0.4 – 0.6	0.9 – 1.1	22 - 29	Kulaksiz et al., 2011
	Zehlendorf	1.6	1.2 – 1.6	2.5 – 3.2	62 - 81	Kulaksiz et al., 2011
	Hohenzollerndamm	1.4	1.1 - 1,4	2.2 – 2.9	57 - 74	Kulaksiz et al., 2011
	McDonalds (Berlin, Zool, G,)	94.7	72.9 – 94.7	146 – 189	3726 - 4839	Schmidt et al., 2019
	McDonalds (Düsseldorf)	9.5	7.3 – 9.5	14.6 – 19.0	374 - 485	Schmidt et al., 2019
	McDonalds (Munich)	1.5	1.2 – 1.5	2.3 – 3.1	60 - 78	Schmidt et al., 2019
	McDonalds (Karlsruhe)	0.6	0.5 – 0.6	0.9 – 1.2	24 - 31	Schmidt et al., 2019
	McDonalds (Dresden)	2.1	1.6 – 2.1	3.3 – 4.2	84 - 108	Schmidt et al., 2019
	(Bremen)	0.8	0.6 – 0.8	1.2 – 1.6	32 - 41	Schmidt et al., 2019
	Berlin-Salzufer	44.0	33.9 – 44.0	67.8 – 88.0	1731 - 2248	Lindner et al., 2015
	Berlin-Westend	57.0	43.9 – 57.0	87.8 – 114.0	2243 - 2913	Lindner et al., 2015
	Berlin-Adlershof	2.0	1.5 – 2.0	3.1 – 4.0	79 - 102	Lindner et al., 2015
	Berlin-Steglitz	8.0	6.2 – 8.0	12.3 –	315 - 409	Lindner

				16.0		et al., 2015
	Spandau	1.1	0.8 – 1.1	1.6 – 2.1	42 - 54	Tepe et al., 2014
	Jungfernheide	4.0	3.1 – 4.0	6.2 – 8.0	158 - 205	Tepe et al., 2014
	Wedding	16.8	12.9 – 16.8	25.8 – 33.5	660 - 857	Tepe et al., 2014
	Alt-Tegel	25.0	19.3 – 25.0	38.6 – 50.1	986 - 1280	Tepe et al., 2014
	Wittenau	26.2	20.2 – 26.2	40.4 – 52.4	1031 - 1340	Tepe et al., 2014
	Neukölln	7.7	5.9 – 7.7	11.9 – 15.4	303 - 394	Tepe et al., 2014
	Schöneberg	11.4	8.8 – 11.4	17.5 – 22.7	447 - 581	Tepe et al., 2014
	Zehlendorf	2.2	1.7 – 2.2	3.4 – 4.5	88 - 114	Tepe et al., 2014
	Steglitz	2.2	1.7 – 2.2	3.4 – 4.5	88 - 114	Tepe et al., 2014
	Kurfürstendamm	15.8	12.2 – 15.8	24.3 – 31.6	622 - 808	Tepe et al., 2014
	Zoologischer Garten	17.7	13.7 – 17.7	27.3 – 35.5	698 - 906	Tepe et al., 2014
	Mitte	27.3	21.0 – 27.3	42.1 – 54.7	1075 - 1397	Tepe et al., 2014
	Hauptbahnhof	22.6	17.4 – 22.6	34.8 – 45.2	890 - 1156	Tepe et al., 2014

[1] Estimated bioaccessible concentration of Gd using the reported concentration of Gd in tap water for each study and the max (100%) and the min (77%) bioaccessible fraction estimated in this study; [2] assuming daily consumption of 2L of tap water; [3] assuming 70 years life span drinking 2L of tap water daily

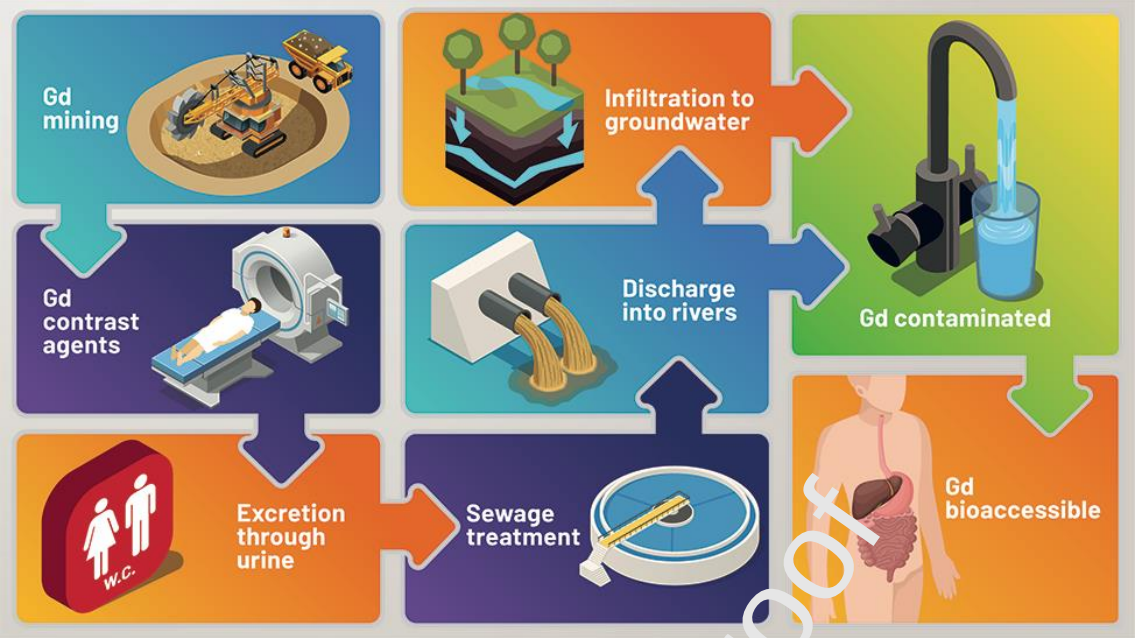
Declaration of competing interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Author Contributions

LAS: Conceptualization, laboratory experiments, data analysis, investigation, writing-original draft preparation, editing; V. Hatje: Conceptualization, data analysis, funding acquisition, investigation, writing-original draft preparation, writing-reviewing, supervision; RMAP: laboratory experiments, data analysis, writing-reviewing; MM: writing-reviewing.



Graphical abstract

Highlights

- Bioaccessibility of Gd-contrasts in tap water is reported for the first time
- Gd-contrast agents are highly bioaccessible (77 to 112%)
- Macrocyclic contrasts are more bioacessible than linear contrasts
- Gd-contrast agents can be assimilated by humans after oral ingestion
- The potential intake of Gd varied from 13 to 4839 µg in a lifespan of 70 years