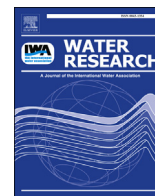




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Review

Anthropogenic gadolinium in freshwater and drinking water systems

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ARTICLE INFO

Article history:

Received 11 March 2020
 Received in revised form
 18 May 2020
 Accepted 19 May 2020
 Available online 29 May 2020

Keywords:

Anthropogenic gadolinium
 Gadolinium-based contrast agents
 Gadolinium anomaly
 Drinking water
 Micropollutants
 COVID-19

ABSTRACT

The increasing use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging is leading to widespread contamination of freshwater and drinking water systems. Contrary to previous assumptions that GBCAs are stable throughout the water cycle, they can degrade. The stability of GBCAs depends largely on their organic ligands, but also on the physicochemical conditions. There is specific concern regarding UV end-of-pipe water treatments, which may degrade GBCAs. Degradation products in drinking water supplies can increase the risk of adverse health effects. This is of particular relevance where the raw water for drinking water production has a higher proportion of recycled wastewater. GBCAs concentrations in aquatic systems, often referred to as anthropogenic gadolinium, are determined using a variety of calculation methods. Where anthropogenic gadolinium concentrations are low, the inconsistent use of these methods results in high discrepancies and high levels of uncertainty. The current COVID-19 crisis will, in the short-term, drastically decrease the input of GBCAs to freshwater systems. Temporal variations in anthropogenic gadolinium concentrations in river water can be used to better understand river-aquifer interactions and groundwater flow velocities. Collecting urine from all patients following MRI examinations could be a way forward to halt the generally increasing concentrations of Gd in drinking water systems and recover this technologically critical element.

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1. Magnetic resonance imaging and the increasing use of gadolinium-based contrast agents

Magnetic resonance imaging (MRI) is a versatile radiological tool for generating detailed images that can be used to assist in the

diagnosis of a variety of diseases affecting the brain, spinal cord, heart, blood vessels, bones, and joints; it can also be used to check the health of organs such as e.g. breasts, kidneys, ovaries, the liver, the pancreas, and the prostate. In contrast to X-rays and computerized tomography (CT) scans, MRI does not employ cell-damaging ionizing radiation, but the relaxation time of hydrogen nuclei excited by a strong external magnetic field to image organs and physiological processes in the body. Gadolinium-based contrast agents (GBCAs) are administered in MRI to increase the contrast of

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these images and allow radiologists to more accurately identify neoplastic, inflammatory, and functional abnormalities (Bellin, 2006).

GBCAs are strong chelate complexes in which the trivalent gadolinium ion (Gd^{3+}) is chelated by polyaminocarboxylic acid to avoid the toxic effects of free Gadolinium (Gd). Because the ionic radius of Gd is close to that of calcium (Ca) (107.8 pm for Gd^{3+} and 114 pm for Ca^{2+}), Gd inhibits physiological processes that rely on Ca (Bellin and Van Der Molen, 2008). Two general types of GBCA have been used to date: linear ("open chain") chelates and macrocyclic chelates, both of which can exist in either ionic or non-ionic forms (Fig. S1). The ligands of clinically approved GBCAs are all octadentate, with all donor atoms coordinated.

GBCAs shorten the longitudinal (T_1) and transverse (T_2 and T_2^*) relaxation time constants of adjacent hydrogen nuclei in MRI and thereby enhance contrast (Bellin and Van Der Molen, 2008; Caravan et al., 1999). Gd is specifically well suited for the desired signal enhancement due to its strong magnetic moment and the presence of an additional water molecule in the inner sphere, which completes the nine-fold coordination of Gd within GBCA complexes (Burai et al., 1997; Chan and Wong, 2007; Micskei et al., 1993). Because of its versatility, availability, and importance in modern diagnostics, the use of MRI and consequently also of GBCAs is constantly increasing (Organisation for Economic Cooperation and Development (OECD), 2017).

GBCAs are administered in 33–50% of all MRI examinations, either intravenously or by intra-articular injection (Idée et al., 2008; Thomsen, 2017). Due to their small size (around 500 Da), they are rapidly cleared from the intravascular space into the interstitial space, and their biodistribution is therefore non-specific (Bellin and Van Der Molen, 2008). GBCAs are eliminated unmetabolized, mostly by passive glomerular filtration in the kidney. The residence time of a GBCA within the body depends on the type of complex administered and the renal function of the patient. The plasma elimination half-lives of GBCAs range from 1.5 h for healthy individuals up to 34 h for patients with reduced renal function (Idée et al., 2008; Joffe et al., 1998).

GBCAs are generally considered to be safe and adverse effects are rarely observed (Kanda et al., 2016). However, in 2006 first links were established between nephrogenic systemic fibrosis (NSF) and GBCAs (Grobner, 2006; Marckmann, 2006). Concerns have since increased, especially as Gd deposits have been reported in brains, bone, skin, and other tissues following GBCA administration, even in healthy patients (Kanda et al., 2016; Le Fur and Caravan, 2019; Montagne et al., 2016; Nehra et al., 2018; Xia et al., 2010). The European Medicines Agency (EMA) therefore released a warning and suspended the use within the EU of certain linear GBCAs (Table 1) that are considered to present the highest risk of inducing NSF (European Medicines Agency, 2017). This has been legislated in all EU member states. The US Food and Drug Administration (FDA) has issued an update of their Medication Guides in relation to the use of GBCAs, requiring a new class warning especially for patients with kidney dysfunction (Food and Drug Administration, 2018, 2017). Other regulatory bodies in Australia, Japan, and Canada have also released revised precautionary advices (Le Fur and Caravan, 2019). The use of GBCAs is not recommended for patients with renal failure.

Since GBCA's use was first approved in 1988, more than 460 million doses have been administered worldwide up to 2018 (Gibby et al., 2019). In 2016, almost 200,000 MRI scans using GBCAs were conducted per day within the EU and the US combined (Organisation for Economic Cooperation and Development (OECD), 2017). In Germany, the country with the highest MRI use per capita (Fig. 1), more than 32,000 MRI scans are carried out per day, resulting in an estimated annual emission of 4 tons of gadolinium

(assuming 50% of all MRIs use GBCAs with 1.1 g Gd per MRI scan); the corresponding figure for the whole of the EU is 19 tons, 21 tons for the US, and 0.3 tons for Switzerland (data from 2016). Vriens et al. (2017) calculated a total river-borne discharge of 0.78 tons of Gd from the concentrations of the four major rivers leaving Switzerland, with a sewage treatment plant (STP) contribution of around 83% for the same year. Compared to the late 1990s, the Gd emission in Germany has doubled over the last 20 years (Bau and Dulski, 1996; Kümmerer and Helmers, 2000). Increasing concentrations of Gd, which can be attributed to the use of GBCAs, have been found in rivers, groundwater, and estuaries around the world (Hatje et al., 2016; Lerat-Hardy et al., 2019; Tepe et al., 2014). In the vicinity of STP outlets Gd concentrations are substantially higher than the geogenic background (in general about a few nanograms per liter) with up to 86 μg per liter (Parant et al., 2018).

At present, the global spread of the SARS-CoV-2 coronavirus and the COVID-19 disease lead to a temporal decrease in GBCAs use. The paralysis in economic production and socialization leaves strong signals in the environment (Callaway et al., 2020). In addition to the closure of factories and businesses, a major concern for all countries has been the drastic effect on their health systems. Hospitals around the world have been preparing for this unprecedented situation for weeks and ramped up the number of medical intensive care units (MICUs). Therefore, non-essential medical consultations, examinations and surgeries, including the use of MRI, have been postponed in order to free up hospital capacities and personnel. Medical facilities are currently performing about 80% fewer MRI examinations and a significant reduction of GBCA emissions is to be expected. This will result in a temporal reduction of Gd concentrations in freshwater systems (Fig. 2). Measuring and analyzing this transient Gd signal could improve our understanding of environmental systems and provide a better database for the risk assessment of waterworks regarding inputs of xenobiotics or pathogens.

In future, GBCA concentrations in aquatic environments are likely to continue to rise due to the constantly increasing use of MRI. Even though actual increasing GBCA concentrations are still low, this could become of concern in settings where drinking water is produced from raw water resources with a high proportion of recycled wastewater. In this paper, we review on the stabilities of GBCAs, their behavior in freshwater systems, and the importance of the method to differentiate between naturally occurring and anthropogenic Gd. We conclude our review by suggestions how to reduce GBCAs emissions.

2. Stability of gadolinium-based contrast agents determined by their organic ligands

It is not yet fully clear whether GBCAs themselves, their transformation products, or the release of free Gd are causing adverse health effects; these remain fundamental topics for a better risk assessment (Le Fur and Caravan, 2019). Every substitution of Gd^{3+} from GBCA complexes by other metal ions, known as transmetalation, can also increase the toxicity of GBCAs by releasing toxic Gd^{3+} . Iron (Fe^{3+}), zinc (Zn^{2+}) and copper (Cu^{2+}) in particular, are in focus to be possible substituents because of their similar (or higher) thermodynamic stability and *in vivo* concentrations (Le Fur and Caravan, 2019; Semelka et al., 2019; Swaminathan, 2016). The degree of transmetalation of GBCAs in humans has been assessed from zinc enhancement in urine following GBCA administration, which yielded evidence of possible reactions with other trace metals (Rogowska et al., 2018). The inner sphere coordination of a single water molecule within the Gd complex could be a critical aspect because it is potentially substituted by other, preferably negatively charged ligands (Burai et al., 1997). Whether this reduces

Table 1
Characteristics and stability properties of approved gadolinium-based contrast agents (worldwide).

Name	Acronym	Gd-DTPA	Gd-DTPA-BMA	Gd-DTPA-BMEA	Gd-BOPTA	Gd-EOB-DTPA	Gd-DOTA	Gd-HP-DO3A	Gd-BT-DO3A
	Generic name	Gadopentetate dimeglumine	Gadodiamide	Gadoversetamide	Gadobenate dimeglumine	Gadoxetate disodium	Gadoterate meglumine	Gadoteridol	Gadobutrol
	Trade name	Magnevist®	Omniscan®	OptiMARK®	MultiHance®	Primovist®/ Eovist®	Dotarem®/ Artirem®	ProHance®	Gadovist®/ Gadavist®
Manufacturer		Bayer HealthCare	GE Healthcare	Guerbet	Bracco	Bayer HealthCare	Guerbet	Bracco	Bayer HealthCare
Year of FDA approval		1988	1993	1999	2004	2008	2013	1992	2011
Current legal status (Europe)		restricted to intra-articular	suspended	suspended	restricted to liver scans	maintained	maintained	maintained	maintained
Type		linear	linear	linear	linear	linear	macrocyclic	macrocyclic	macrocyclic
Charge		di-ionic	non-ionic	non-ionic	di-ionic	di-ionic	ionic	non-ionic	non-ionic
Concentration	[M]	0.5	0.5	0.5	0.5	0.25	0.5	0.5	1
Standard dose	[mmol/kg]	0.1	0.1	0.1	0.1	0.025	0.1	0.1	0.1
Excess Ligand		0.10%	5%	10%	none	0.50%	none	0.10%	0.10%
log K_{therm}	[1]	22.1	16.9	16.6	22.6	23.46	25.6	23.8	21.8
log K_{cond}	[1]	17.7	14.9	15	18.4	18.7	19.3	17.1	14.7
log K_{cond}	[2]	18.4	14.9	15	18.4	18.7	17.2	17.1	16.1
log K_{cond} calculated for pH 4.0	[2]	11.2	10.8	10.8	11.1	11.5	9.5	9.9	9
log K_{cond} (modelled)	[3]	6.30	4.17	not available	not available	not available	7.24	not available	not available
Kinetic stability (dissociation half-life at pH 1.0)	[1]	10 min	35 s	not available	not available	not available	>1 month	3 h	24 h

Log K_{therm} and log K_{cond} are the thermodynamic and conditional stability constants, respectively; [1] [Morcos \(2008\)](#) and references therein, [2] [Le Fur and Caravan \(2019\)](#), [3] [Prybylski et al. \(2017\)](#).

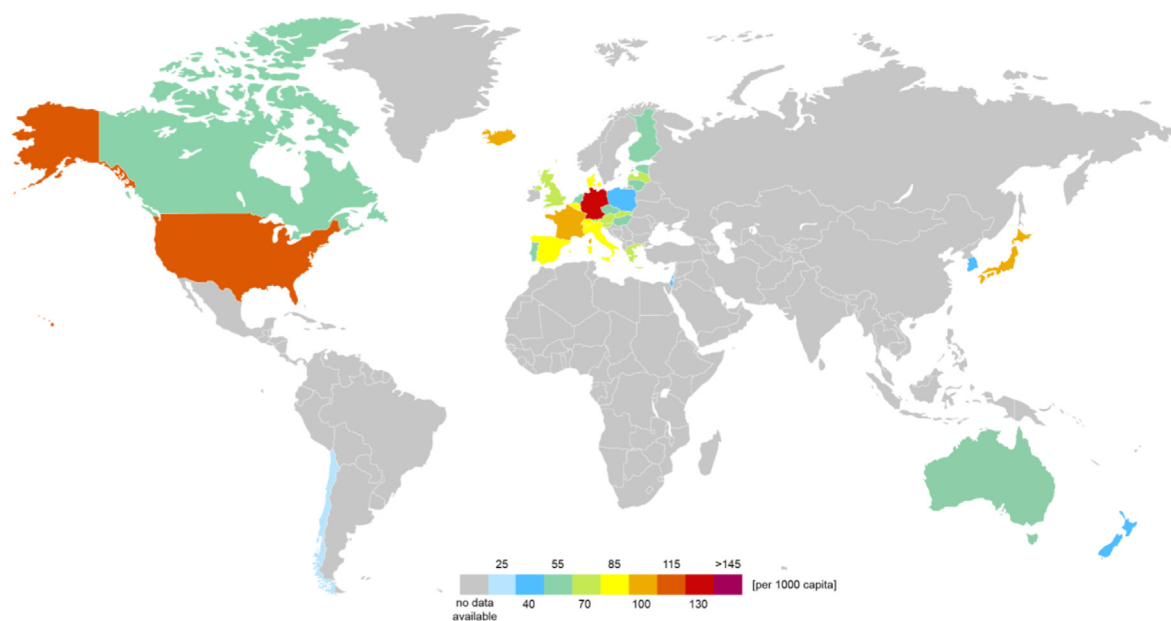


Fig. 1. Total annual MRI examinations: global distribution based on the latest data available ([Organisation for Economic Cooperation and Development \(OECD\), 2017](#)). Data from Austria, Great Britain, New Zealand, Switzerland, and Portugal are restricted to in-hospital data.

the stability of GBCAs remains unclear and would be an important subject for future research. Gd complexes are susceptible to dissociation and *in vivo* dissociation can be favored by any interaction with biological competitors for the original GBCA ligands, such as the adenosine triphosphate (ATP) present in human serum ([Bazzicalupi et al., 2012](#); [Port et al., 2008](#)). The same principle also applies in freshwater systems, where other competitive ligands exist.

The kinetic, thermodynamic, or conditional stabilities of GBCAs are measures that are often used to compare different species of GBCAs regarding their possible transformation, but their use is inconsistent and questionable. The thermodynamic stability of Gd complexes in solution is described as an equilibrium between Gd ions [Gd], their ligands [L], and the complexed form [GdL]. For all GBCAs the number of involved ligands is one, which simplifies the equation to:

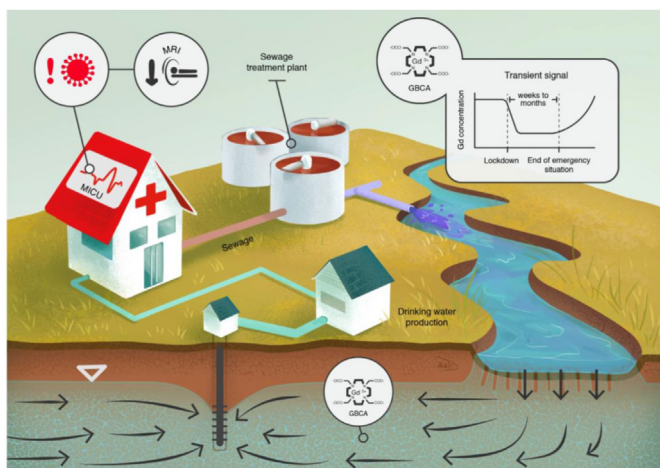


Fig. 2. Due to COVID-19 and its implications, changing anthropogenic gadolinium concentrations in surface water and groundwater could be used to improve the understanding of complex environmental systems.



and the thermodynamic stability constant K_{therm} is defined as

$$K_{\text{therm}} = \frac{[GdL]}{[Gd] * [L]} \quad \text{Equation 2}$$

The kinetic stability depends on the activation energy (E_a) and Gd complexes are kinetically stable/inert if E_a is high enough to prevent the formation of any other complexes. The “inertness” or “stability” of metal complexes is operationally defined. [Beyer and Angulo Cornejo \(2012\)](#) regard metal complexes to be inert if the exchange of ions takes longer than a minute at 25 °C. Because the E_a cannot include any possibly present catalyst which potentially lower reaction barriers, [Morcos \(2007\)](#) used the dissociation half-life at pH 1.0 to assess and quantify the kinetic stability of GBCAs. The half-lives vary from a few seconds to more than one month ([Table 1](#)). It may be convenient to compare kinetic stabilities with biological half-lives, but neither is able to indicate whether or not GBCAs are transformed within the human body not to quantify the extent of such processes. The dissociation half-life depends on both pH and temperature. For example, the dissociation half-life of the macrocyclic Gd-DOTA at pH 1 is 26.4 h at 37 °C but 338 h at 25 °C ([Idée et al., 2009](#)), and the DOTA ligand has a dissociation half-life of 85 days at pH 2 and more than 200 days at pH 5 ([Wang et al., 1992](#)). [Idée et al. \(2009\)](#) used a comparative subdivision of the kinetic inertness (into low, medium, or high) to compare different GBCAs, but cannot resolve the question of GBCA transformation within the human body.

The toxicological need for a measure that applies at the physiological pH of 7.4 has been tackled using the concept of conditional stability, expressed as K_{cond} . It can be measured *in vivo* and considers the protonation constants of the ligand. These constants can vary slightly, depending on the methods used, i.e., potentiometric measurement or competition experiments ([Idée et al., 2009](#)). [Frenzel et al. \(2008\)](#) confirmed K_{cond} as a good indicator for the *in vivo* stability of GBCAs based on the release kinetics in human serum at physiological temperature and pH. [Prybylski et al. \(2017\)](#) came to a different conclusion; remodeling the data from [Frenzel et al. \(2008\)](#) using the dissociation rate and the balancing aspect of the association between Gd and the GBCA ligand, they found that GBCAs were less stable in humans than previously indicated by

K_{cond} .

The stability constants in [Table 1](#) show that macrocyclic GBCAs are more stable than linear GBCAs, and that the linear ionic GBCAs are more stable than linear non-ionic GBCAs. The weakness in all stability concepts, however, is the assumption of equilibrium conditions since environmentally relevant conditions are likely to be more complex and not always in equilibrium ([Prybylski et al., 2017](#)). The inversely proportional relationship between the release of Gd from GBCAs and their stability is generally accepted, but the extent to which GBCAs can be transformed within the human body and the exact processes involved still remains unresolved.

3. The concentration of gadolinium-based contrast agents is increasing in freshwater environments

Following their excretion via urine after the MRI, GBCAs enter the sewage system and are released into surface waters as they are not removed by conventional sewage treatment plants. Anomalous occurrences of Gd in rivers were first reported in 1996 ([Bau and Dulski, 1996](#)). Since then GBCAs have been found in the effluents from hospitals, sewage water treatment plants, as well as other surface waters ([Birka et al., 2013](#); [Künemeyer et al., 2009](#); [Lindner et al., 2013](#)). Increased Gd concentrations have even been reported in rural areas where there are no MRI facilities in the catchments of the local sewage treatment plants ([Brünjes et al., 2016](#); [Rabiet et al., 2009](#)). This is due to the large number of patients who receive MRI scans as outpatients and are then sent home. Elevated Gd concentrations have been found in drinking water and are of increasing concern to waterworks, as well as to the general public ([Kulaksiz and Bau, 2011a](#); [Lindner et al., 2015](#); [Morteani et al., 2006](#); [Richardson and Kimura, 2016](#); [Schmidt et al., 2019](#); [Tepe et al., 2014](#)). Gadolinium originating from GBCAs is one of a series of emerging contaminants released from sewage systems, which makes it a suitable indicator for other sewage water-borne xenobiotics ([Reoyo-Prats et al., 2018](#)).

In general, most studies in freshwater systems pool GBCAs under the term “anthropogenic Gd” (Gd_{anth}), which does not imply the transformation of GBCAs. We hereafter refer to Gd_{anth} when we do not distinguish between GBCAs and their transformation products. Anthropogenic Gd has been globally detected, mainly in densely populated areas with highly developed health systems; in Europe ([Bau and Dulski, 1996](#); [Dia et al., 2000](#); [Elbaz-Poulichet et al., 2002](#); [Knappe et al., 2005](#); [Möller et al., 2003, 2000](#); [Petelet-Giraud et al., 2009](#)), in North America ([Barber et al., 2006](#); [Bau et al., 2006](#); [Hatje et al., 2016](#); [Verplanck et al., 2005](#)), in Oceania ([Lawrence et al., 2009](#); [Lawrence and Bariel, 2010](#); [Lawrence and Kamber, 2006](#)), in South America ([de Campos and Enzweiler, 2016](#); [Merschel and Bau, 2015](#)), Africa ([Atinkpahoun et al., 2020](#)), and in Asia ([Nozaki et al., 2000](#); [Ogata and Terakado, 2006](#); [Song et al., 2017](#)).

Due to the widespread contamination of freshwater environments with Gd_{anth} , a variety of hydrogeological investigations have used it as an ideal tracer in different hydrochemical settings, assuming that all types of GBCAs do not undergo degradation once released from STPs ([Barber et al., 2006](#); [Bichler et al., 2016](#); [Klaver et al., 2014](#); [Möller et al., 2011, 2000](#); [Petelet-Giraud et al., 2009](#)). Depending on the operating mode of an STP, the effluent Gd concentration may show a temporal variation (daily to weekly) because most MRI scans are carried out during the daytime from Monday to Friday ([Telgmann et al., 2012](#)). This transient signal can propagate into the groundwater and can be used to calculate groundwater transit times ([Brünjes et al., 2016](#)).

[Holzbecher et al. \(2005\)](#) assumed an environmental half-life of 130 days for Gd-DTPA from modelling breakthrough curves of column experiments. Based on these findings, [Massmann et al.](#)

(2008) used this half-life to calculate groundwater residence times from the attenuation of the Gd_{anth} signal in the aquifer. Predictions based on this approach depend on the precise quantification of the hydrodynamic dispersion and dilution, which can be susceptible to large errors. Further, the degradation of the ligand DTPA and its inorganic complexes is in general thought to be photochemical (Hinck et al., 1997; Means et al., 1980; Metsärinne et al., 2004).

Gd-DTPA appeared relatively inert, for example in column experiments carried out over a 70 day period under a range of redox conditions (Dulski et al., 2011; Menahem et al., 2016). In the presence of other metal ions, especially Fe^{3+} , Zn^{2+} , Cu^{2+} , other heavy lanthanides, or Yttrium (Y^{3+}), transmetallation can be slow due to the low concentrations involved, but it cannot be neglected over long time scales (Möller et al., 2011; Möller and Dulski, 2010). A modeling study by Schijf and Christy (2018) has shown that elevated concentrations of calcium and magnesium can destabilize Gd-DTPA in seawater.

4. Determination of anthropogenic gadolinium and differentiation from naturally occurring gadolinium

Gadolinium is also naturally occurring in the environment as a result of the dissolution of minerals. It is one of the elements in the lanthanide series. These elements are frequently referred to as the rare earth elements (REE), a term that usually also includes the elements scandium (Sc) and yttrium (Y). Except for two elements, all lanthanides exist only in a trivalent oxidation state. Cerium (Ce) can exist as both Ce^{3+} and Ce^{4+} and europium (Eu) as both Eu^{2+} and Eu^{3+} , which affects their solubility and melting temperature. Due to their different redox behavior, these two elements are decoupled from the coherent chemical behavior of the rest of the lanthanides (Goldstein and Jacobsen, 1988; Möller et al., 2002). The abundance of lanthanides follows the Oddo-Harkins rule; elements with even atomic numbers are naturally more abundant than those with odd atomic numbers. This leads to a typical zig-zag shape on logarithmic plots of concentration versus atomic number. To avoid this zig-zag shape, lanthanide concentrations are usually normalized against a geological reference which allows anthropogenically induced anomalies to be detected, as has been demonstrated for Gd, lanthanum (La) and samarium (Sm) in aqueous samples (Kulaksiz and Bau, 2013, 2011b).

For water samples, reference compositions such as those of the Post-Archean Australian Shale (PAAS) composite (McLennan, 1989), the North American Shale Composite (NASC) (Gromet et al., 1984), the Upper Continental Crust (UCC) (Taylor and McLennan, 1985), or (rarely) the Mud of Queensland (MUQ) (Kamber et al., 2005) compositions, have been used for normalization. The choice of geological reference has been a matter of debate. The use of a newly defined European Shale (EUS) reference has been recommended recently for European water samples to increase acceptance by national regulatory authorities (Bau et al., 2018). Averaging data from PAAS, NASC and EUS, the same authors have also suggested a World Shale (WSH) (Bau et al., 2018). Global-scale investigations could benefit from worldwide use of the WSH reference. However, for investigations of local element enrichment phenomena, site-specific geological reference compositions may be more appropriate as they better represent the natural background.

At present, inductively coupled plasma mass spectrometry (ICP-MS) is the technique most commonly used to measure lanthanides. To increase the analytical sensitivity and ensure precise measurements of low lanthanide concentrations in aqueous solutions with complex matrices, liquid chromatography (LC) can be directly coupled to ICP-MS systems for matrix removal and lanthanide preconcentration (Brünjes et al., 2016; Hathorne et al., 2012; Lagerström et al., 2013). Offline or online preconcentration

methods often use ion exchange resins with iminodiacetate functional groups for the enrichment of lanthanides (Pyrzyska et al., 2016). A crucial step before any preconcentration by ion exchange resins is the degradation of the GBCAs, e.g., by UV and H_2O_2 . Due to their chemical properties, GBCAs are not retained unless the chelate complexes are degraded and the Gd ions are released.

More specialized LC systems are equipped with hydrophilic interaction chromatography (HILIC), size exclusion chromatography (SEC), or reversed-phase chromatography (RPC) columns which can be coupled with MS-systems to enable the direct measurement of specific GBCAs species and transformation products (Birka et al., 2016; Clases et al., 2018b; Künnemeyer et al., 2009; Telgmann et al., 2012). The location of Gd precipitated in brains, other human tissue, or other species has commonly been determined by laser ablation coupled with ICP-MS (Clases et al., 2018a, 2018b; Fingerhut et al., 2018; Lingott et al., 2016).

In many investigations total Gd (Gd_{total}) is measured. Because the anthropogenic component Gd_{anth} cannot be measured directly, the geogenic Gd (Gd^*) background needs to be subtracted (Equation (3)). The advantage of this approach is that it has a significant lower limit of detection than methods that measure individual species of GBCAs.

$$Gd_{anth} = Gd_{total} - Gd^* \quad \text{Equation 3}$$

There is no standard methodology on how to quantify Gd^* in an aqueous sample, which brought up a variety of different approaches. All calculations to determine Gd_{anth} are based on either interpolations or extrapolations of Gd^* from the shale-normalized lanthanides (Ln_{SN}) by means of linear, logarithmic, geometric equations, or third-order polynomial fit (Table 2). Slight differences, apart from the mathematical methods, consist in the assumption of the specific behavior of Gd compared to the other lanthanides. While Bau and Dulski (1996) and Kulaksiz and Bau (2011a) assume that Gd behaves as a light lanthanide in freshwater systems and preferably use the light lanthanides (praseodymium (Pr), neodymium (Nd), Sm and terbium (Tb)) within their equations, Hissler et al. (2015) and Ogata and Terakado (2006) include the heavier lanthanide dysprosium (Dy). The approach from Möller et al. (2002) is the only one with no implicit assumption about the behavior of Gd compared to that of lighter, middle or heavier lanthanides and includes all lanthanides, besides Ce and Eu due to their natural occurring anomalies (Lawrence et al., 2009).

Most calculation methods are avoiding these elements with naturally occurring anomalies. As an exception, the method developed by Kulaksiz and Bau (2013) uses the redox-sensitive element Eu excluding slightly acidic colloid-rich conditions, and enrichments in the middle lanthanides. The use of lanthanides with any anomalous concentrations, however, limits the applicability of the method.

In order to compare and evaluate the different approaches, we used published data on lanthanides in freshwater systems under a variety of hydrochemical conditions. We compared the Gd anomaly, defined as the ratio between the shale-normalized measured Gd concentration and the shale-normalized geogenic background concentration (Gd_{SN}/Gd^*_{SN}), and the concentrations obtained for Gd_{anth} using the different normalization and interpolation/extrapolation approaches.

The results of our analysis clearly show that the geological reference used for normalization has only a minor effect up to 7% on the calculated Gd_{anth} concentration (Fig. 3b and c; Table S1). The comparison also elucidates that the smaller the Gd anomaly, the less important is the choice of geological reference. Nevertheless, the different approaches resulted in a broad range of amplitudes for Gd anomalies (Fig. 3a). Gadolinium anomalies calculated for

Table 2
Selected methods for calculating Gd_{anth} , elements and approaches used.

Reference	Elements used	Interpolation/extrapolation	Specifics
Bau and Dulski (1996)	Sm, Tb	linear	Gd behaves as a LREE ^a
Hissler et al. (2015)	Nd, Dy	linear	Gd behaves as a MREE
Ogata and Terakado (2006)	Sm, Dy	logarithmic	Gd behaves as a HREE
Kulaksiz and Bau (2013)	Eu, Nd	logarithmic	Not usable if MREE are enriched or water is slightly acidic, rich in organic colloids
Kulaksiz and Bau (2011a)	Pr, Nd, Sm	geometric	Gd behaves as a LREE
Möller et al. (2002)	all Ln except Ce, Eu	third grade polynomial fit	no implicit assumption about the behavior of Gd

^a No specifics stated in the original manuscript but implied in (Bau et al., 2006); LREE - light rare earth element, MREE - middle rare earth element, HREE - heavy rare earth element (terminology is referring to the original literature).

Wiembach Creek varied only within a range of 4%, while those in samples from Guériniec groundwater (GW) and the Delaware River varied by up to 28% and 24%, respectively.

Any Gd anomaly greater than 1.0, in theory, implies that Gd_{anth} is present in the sample. However, this threshold is misleading for most of the samples selected from the published literature since the authors assumed that the samples contained no Gd_{anth} (Fig. 3a). To avoid overestimation of Gd_{anth} , some investigators have used Gd anomaly thresholds of 1.2, 1.3, 1.4, or 1.5 (Bau et al., 2006; Petelet-Giraud et al., 2009; Rabiet et al., 2009; Rozemeijer et al., 2012). Others adjusted the geogenic Gd concentration by a factor of 1.1, 1.15, or 1.2 (Lawrence, 2010; Lawrence et al., 2009; Möller et al., 2003, respectively). Often this is justified by natural Gd anomalies found in Gd_{anth} -uncontaminated waters, particularly in acid mine drainage environments and seawater (De Baar et al., 1985; Migaszewski and Gałuszka, 2015). However, from the above cited studies which use corrections, only Lawrence (2010) is working with seawater conditions. To avoid any bias we did not include a correction factor to our calculations.

In contrast to all other methods, the calculations based on the two methods by Kulaksiz and Bau resulted in Gd anomalies closest to 1.0, in agreement with the assumptions by the authors that no anthropogenic Gd was present in the samples (Fig. 3b; Table S1). The largest Gd anomalies were obtained using the approaches from Hissler et al. (2015), Ogata and Terakado (2006), and Möller et al. (2002), with exceptions for the Han and Elbe rivers (Fig. 3b and c). Comparing the methods, Gd anomaly differences are particularly high if concentrations of the higher lanthanides Tb and Dy are more abundant compared to the lighter lanthanides Nd and Sm (Fig. 3a, Table S1). While the influence of Tb and Dy can be decisive using approaches from Hissler et al. (2015) or Ogata and Terakado (2006), the advantage of the third-grade polynomial fit approach by Möller et al. (2002) is the larger number of elements included. This reduces the influence of minor anomalies and element-specific measurement errors on the interpolated geogenic Gd.

5. Measures to halt the increase in gadolinium concentrations in freshwater environments

Once GBCAs reach the aquatic environment, they are diluted to ng/L or to $\mu\text{g/L}$ levels, which is at least an order of magnitude below the free Gd toxicity level for humans (Merbach et al., 2013). However, the potential toxicity of Gd needs to be considered together with that of the entire lanthanum series, as they form a uniform group of elements (Blinova et al., 2018). Anthropogenically elevated concentrations of other lanthanides further increase the risks to aquatic ecosystems, because aquatic organisms absorb lanthanides through their skin, gills, and digestive systems (Kulaksiz, 2012; Kulaksiz and Bau, 2013; Lingott et al., 2016).

Unaltered GBCAs have been shown not to sorb to materials such as activated carbon (contrary to the findings of Elizalde-González et al., 2017), but once acidified, they release Gd^{3+} with a high

sorption affinity to many adsorbers (Anastopoulos et al., 2016; Elizalde-González et al., 2017; Kovalova et al., 2013; Patra et al., 2017). The sorption of Gd^{3+} onto activated carbon strongly depends on the pH of the solution (Pourret and Houben, 2018). The environmental mobility of Gd^{3+} is similar to that of the other lanthanides and mainly involves complexation with dissolved organic carbon (DOC) under slightly acidic or neutral conditions (Pédrot et al., 2010). This complexation is based on electrostatic interactions and multidentate bonding between positively charged Gd^{3+} and inorganic anions, or negatively charged organic ligands (Byrne and Kim, 1990; Davranche et al., 2015; Luo and Byrne, 2004).

In contrast to natural lanthanides, GBCAs have so far not been reported in sewage sludge, even though coagulation-flocculation is reported to remove at least some of the linear GBCAs (Lawrence et al., 2010; Neubert, 2008; Telgmann et al., 2012; Verplanck et al., 2010). Most of the commercially used coagulants are based on ferric or aluminum salts (e.g. FeCl_3 and $\text{Al}_2(\text{SO}_4)_3$), which are Lewis acids and form acidic microenvironments (Lee et al., 2014). Under these conditions, linear GBCAs are destabilized resulting in rapid transmetalation (Rabiet et al., 2014). The formation of Fe-oxide flocs further assists in the removal of Gd^{3+} from solution due to the high sorption affinity of lanthanides towards iron phases (Davranche et al., 2008, 2004). Once Gd^{3+} is released from GBCA complexes, this sorption affinity could be utilized to recover Gd from sewage water (Nassar et al., 2015; Stepka et al., 2018).

Water suppliers and STPs seek to eliminate GBCAs (Lingott et al., 2016; Rogowska et al., 2018; Thomsen, 2017). Promising results have been achieved using advanced oxidation processes based on *in situ* formation of $\cdot\text{OH}$ radicals by means of various chemical, photochemical, sonochemical, or electrochemical reactions (Oturán and Aaron, 2014). While direct reactions between GBCAs and ozone are insignificant, the $\cdot\text{OH}$ radicals they produce can result in degradation of GBCAs (Cyril et al., 2013). Treatment with a combination of UV-C irradiation and hydrogen peroxide (H_2O_2) effectively degrades GBCAs within 24 h (Bichler et al., 2016). Low energy (15 W) irradiation with UV-C over long periods of time (>12 h) has been shown to degrade all types of GBCAs, but these conditions cannot be met by most commercial water sanitation facilities (Brünjes et al., 2017). Birka et al. (2016) reported a series of degradation products from the linear Gd-BOPTA complexes after applying UV-irradiation, while other complexes such as the macrocyclic Gd-DOTA and Gd-BT-DO3A, and the linear Gd-DTPA showed no degradation even after 300 min. Because of this duration of exposure to UV, the study does not simulate conditions found in natural environments, STPs, or end-of-pipe treatments of drinking water purification (Birka et al., 2016; Thomsen, 2017). So far, there is no systematic study on the stability of GBCAs regarding end-of-pipe UV treatments. Since the human uptake of potential harmful GBCA transformation products is of special concern, further studies are recommended.

To reduce GBCAs contamination of drinking water, a few starting points can be considered. During drinking water production,

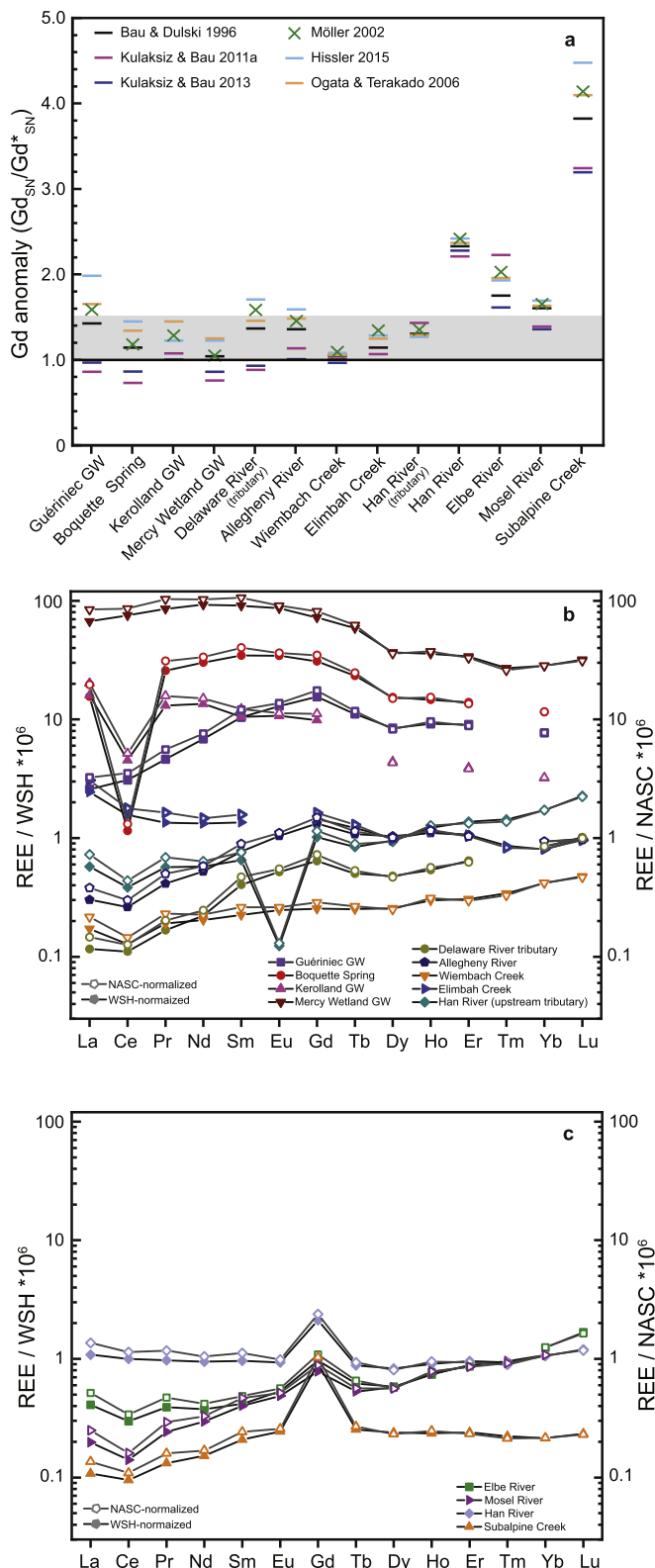


Fig. 3. a Calculated gadolinium anomalies in water samples using different interpolation or extrapolation methods. Grey shading: area of reported Gd anomalies (max. 1.5) that have been assumed to be natural; b published data from water samples with Gd anomalies of less than 1.5 (averaged over selected methods); c published data from water samples with Gd anomalies greater than 1.5 (averaged over selected methods).

improved water purification using expensive reverse osmosis would be required as this is the only efficient way to fully remove GBCAs (Lawrence et al., 2010). Reverse osmosis can be applied as drinking water treatment or as the last step of sewage water treatment to prevent Gd emissions into the aquatic environment. Because of the high percentage of outpatients undergoing MRI scans, treating only hospital effluents would not prevent the increasing input of GBCAs into freshwater water resources.

The simplest way to reduce the input of Gd into the aquatic environment and its potential health risk would be to collect urine from patients for at least 24 h following the administration of GBCAs. This would require urine collection not only in hospitals, but also at the patients' homes. Urine collection bags can be made leak-proof by including super absorbent polymers. A trial in Germany found that although medical staff were skeptical about integrating these bags into their existing routines, there was a high level of acceptance by patients (Niederste-Hollenberg et al., 2018).

Collecting urine would also allow to recover and recycle Gd from GBCAs and prevent the technologically critical element Gd from being lost into aquatic environments (Cobelo-García et al., 2015). Extraction procedures from polymer matrices would need to involve the degradation of GBCAs but benefit from the high concentrations of the recycling target. For example, GBCAs could be degraded by a combination of H₂O₂ and UV radiation and recovered by using a variety of existing green technology methods such as biosorption that are already used for lanthanides from wastewater (Pereao et al., 2018). In contrast, recovering diluted Gd in sewage systems or after STPs would be economically less attractive for recycling.

6. Conclusion

Due to their ability to significantly enhance the contrast of MRI scans there is currently no viable alternative to GBCAs for medical use. MRI will develop towards higher resolutions, but the use of Gd for MRI contrast agents remains necessary. In general, GBCAs are renally excreted with plasma elimination half-lives of 1.5–34 h, however, there is increasing evidence that some of the Gd may be retained in the human body, but so far, the exact processes and amounts remain unknown.

As conventional sewage water treatment cannot eliminate GBCAs, they contaminate freshwater systems which provide our drinking water resources. GBCA concentrations in drinking water, the main pathway for unintentional human intake, are still at the nanogram per liter levels but will further increase. As soon as they enter the stomach their stability is reduced by the acidity of the gastrointestinal fluids.

Unaltered GBCAs are highly mobile and neither retained by activated carbon filters nor present in sewage sludge. Promising results to degrade and remove GBCAs have been achieved using advanced oxidation processes. Macrocyclic GBCAs are more stable against degradation than linear GBCAs, but besides reverse osmosis, no other advanced water treatment technique is capable to fully eliminate GBCAs. UV radiation can alter GBCAs and their transformation products may enhance the risk of adverse health effects if the treatment is utilized as an end-of-pipe solution.

The amount of GBCA contamination in freshwater environments, also referred to as anthropogenic gadolinium, is determined using a variety of calculation methods. In water bodies with low concentrations of Gd_{anth} compared to the geogenic background concentration, the inconsistent use of these methods results in high discrepancies and high levels of uncertainty. Applying any

corrections to account for natural Gd anomalies should be based on site-specific conditions rather than on Gd anomalies from literature. In our comparison, the approach from Möller et al. (2002) is the most holistic using a larger number of elements which reduces the influence of minor anomalies and element-specific measurement errors. The assessment of Gd_{anth} in drinking water would benefit from a coordinated approach to determine Gd anomalies and Gd_{anth} concentrations. A recognized standard methodology would also be beneficial for the acceptance of Gd_{anth} as a sewage water indicator and quantitative tracer. Temporal changes of GBCA emission patterns in rivers can be used to determine groundwater residence times and river-aquifer interactions to improve our understanding of these complex subsurface aquatic systems.

Even if Gd emissions are temporarily reduced due to the COVID-19 pandemic, increasing emissions are expected in future if no measures are taken. At present, the technologically critical element Gd is being lost into the aquatic environment, for example 19 tons/year in the EU and 21 tons/year in the USA. Considering the total environmental burden of mining and extracting Gd from ore, and in the perspective of a circular economy, the collection and recycling of Gd from the urine of patients should be considered “best practice” in future.

Declaration of competing interest

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.

Acknowledgments

We acknowledge the illustration of Figure 2 by Audrey Desaulniers, Orcéine, Montreal, Canada.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.watres.2020.115966>.

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