

The Spreads and the Uniqueness of the Controversial Toxic Pharmaceutical Contrast Agents and Their Remediation.

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Abstract

The ongoing gadolinium toxicity concerns have resulted in progressive regulations and restrictions of gadolinium-based contrast agents (GBCAs). However, there are no regulations regulating Gd levels in the water sector to date. Therefore, the fast spreading of the anthropogenic Gd in the various hydrosphere, which serves as a source of drinking water for the populace, is worrisome. Evidently, with no hope of breaking this increasing trend any time soon due to the increasing demand for MRI administration. Sadly, conventional wastewater and advanced water treatment do not adequately remove GBCAs from water. Instead, it risks transforming them into a more toxic Gd from its chelated complex through unintentional degradation. This transformation led to undue exposure to its potential ecotoxicity and adverse human health effects like acute renal adverse reactions, acute non-renal adverse reactions, body pains, chronic skin changes, twitching or weakness, chronic eyes, and cognitive, flu-like symptoms, and digestive symptoms. Therefore, an affordable and manageable hybrid water treatment system is proposed suitable for reclamation of free and chelated Gd in aquatic environments.

1. Introduction

In recent years, the increasing spread of anthropogenic gadolinium (Gdanth) into different water sources is an emerging concern for water specialists. The chelated Gd metal initially considered safe is now detected as a micro-contaminant in rivers, surface water, lake water, seawater, Groundwater, estuaries, coastal water, municipal tap water, and more precariously in soft drinks. Aside from the river Berlin in Germany, where it was first detected, its presence in water has been reported worldwide from different countries and rural communities (Kulaksiz and Bau, 2011a; Kulaksiz and Bau, 2011b; Tepe et al., 2014; Brünjes et al., 2016; Brünjes and Hofmann, 2020). Contrary to earlier reports restricting anthropogenic Gd contamination to megacities with highly evolved health care systems, recent researches have confirmed its presence in wastewater obtained from low populated rural communities without MRI equipment or with less advanced health facilities (Rabiet et al., 2009; Fox-Rawlings and Zuckerman, 2019; Atinkpahoun et al., 2020)

The application of magnetic flux and gradients provided by gadolinium is the earliest diagnostic imaging modality for several indications providing detailed anatomical details with a high spatial resolution (Wang et al., 2021) ACR Manual On Contrast Media, 2021; Smeraldo et al., 2020; Enterline et al., 2020; Fox-Rawlings and Zuckerman, 2019; Kanal and Tweedle, 2015). A recent example is the use of enhanced MRI to assess the degree of cardiovascular sequelae among student-athletes who have recently recovered from COVID-19-related infection (Renaud-Picard et al., 2020; Huang et al., 2020; Nicol et al., 2020; Clark et al., 2020). Medically, Gd used for image enhancement in MRI is chelated to mitigate against its toxicity and was therefore considered safe (Siew et al., 2020; Bellin and Van Der Molen, 2008). However, clinical observations and reports have changed this long-held safety perception of all GBCAs (Penfield and Reilly, 2007; Runge, 2018; Baranyai et al., 2012). Administered GBCAs are now being implicated for causing acute renal adverse reactions, acute non-renal adverse reactions, delayed adverse reactions (nephrogenic systemic fibrosis), and problems at the site of injection (Local necrosis) regardless of the patient kidney health (Catherine et al., 2020; Nakajima and Lamid-Ochir, 2020; McDonald and McDonald, 2020; McDonald et al., 2018; Nehra et al., 2018; McDonald et al., 2017a; McDonald et al., 2017b; Rogosnitzky and Branch, 2016; McDonald et al., 2015; Bellin and Van Der Molen, 2008; Hao et al., 2012). Following these discoveries and clinical reported concerns, countries and regulatory agencies such as the European Union (E.U.) and the United States Food and drug administration (USFDA) have either suspended the use of some of the GBCAs or issued updated Medication Guides concerning their use (Fox-Rawlings & Zuckerman, 2019). Similarly, attempts to remove Gd from patients with impaired renal function following administration of GBCAs through dialysis as a preventive measure were reported by (Yantasee et al., 2010) and (Ngamcherdtrakul et al., 2019).

Controversially, the implications of gadolinium retention in the human system remained obscured, and there are conflicting published research outcomes concerning the administration safety of GBCAs in humans. For example, Liu (2021), Soloff and Wang (2020), McDonald and McDonald (2020), (Cowling and Frey, 2019), Center for Drug Evaluation and Research (2015), and others had argued that there are too limited substantial clinical effects of Gd deposition and retention. They further believed that the benefits of GBCAs-MRI outweigh the statistically low reported popularly known “gadolinium deposition diseases” (GDD). Therefore, in their opinion, it may be too presumptuous to conclude on retained gadolinium safety. Unfortunately, despite the uncertainty about GBCAs safety in the human body, the controversial toxic metal has recently been identified as a hydrological

contaminant. They are reportedly detected in increasing amounts in rivers, estuarine waters, seawater, groundwater, lakes, and Municipal tap water worldwide (Zabrecky et al., 2021; Brünjes and Hofmann, 2020; Andrade et al., 2020; Ebrahimi and Barbieri, 2019; Thomsen, 2017; Brünjes et al., 2016; Bichler et al., 2016; Hatje et al., 2016)

Indeed, the consequences of the anthropogenic gadolinium anomaly in water over a significant period have remained vague. There is also a lack of extensive clinical evidence of gadolinium deposition and clinical studies' neurologic effects, establishing a link between gadolinium retention and clinical sequelae (Layne et al., 2020; Soloff and Wang, 2020; Choi and Moon, 2019; Kanal, 2016). The lack of sufficient data about the safety of gadolinium in the human system probably explains why the concentration of Gd in water has remained unregulated by any environmental or waste/drinking water standards. However, the absence of Gd regulation does not automatically imply its safety, even at its lowest concentration (Cyris, 2013). The fact that a single dose of gadolinium contrast agent can cause 'nephrogenic' systemic fibrosis in non-dialysis dependent patients several years after exposure coupled with the reported adverse events in patients with healthy renal function suggests that the physiological reactions are primarily unknown and, therefore, remained a potential risk that cannot be simply whisked away (Ngamcherdtrakul et al., 2019; Leyba and Wagner, 2019). More importantly, the potential risk of Gd ingestion, especially for pregnant or breastfeeding women or patients with cardiac and kidney disease, is never in dispute between the two opposing divides regarding its safety. Based on reported complaints from a subset of patients, researchers and practitioners unanimously agreed that multidisciplinary and substantial objective research data are required to establish a mutual position.

Sadly, while there are definite and proven, practical regulatory actions on the clinical administration procedures of the GBCAs regardless of its safety controversies, the water/wastewater standards have none. Consequently, people exposed to Gd-polluted water are at risk of ingesting the toxic metal, irrespective of their renal health status. Unfortunately, the quantity and concentration of toxic Gd that humans are potentially exposed to under such circumstances have remained virtually intractable. Anthropogenic Gd in the hydrosphere is undoubtedly mainly from the patient's excretes containing the contrast agents or hospital waste effluents (Pallares et al., 2020). Moreover, because Gd³⁺ is considered a fission product, excrement containing Gd can flow into local water sources through the sewer system, far or near the point of administration, vis-a-vis point- and nonpoint-source contaminants (Ahuja, 2019).

Previous studies have explored the potential dechelation, deposition, and health risk factors associated with the administration of GBCAs and call for caution in its clinical administrations (Penfield and Reilly, 2007; Mendichovszky et al., 2008; Ramalho and Ramalho, 2017; Ranga et al., 2017; Olchoway et al., 2017; Dekkers et al., 2018; Le Fur and Caravan, 2019; Thomsen et al., 2013; Strzeminska et al., 2020). Other authors have explored the various sources and fate of toxic Gdanth in the environment in relation to human and ecological threats (Ebrahimi & Barbieri, 2019). Recently and continuously, after being recognized as an emerging concern in aquatic systems, the anomaly presence of Gd from different locations have been reported (Rabiet et al., 2009; Amorim et al., 2019; Kulaksiz, 2012; Merschel and Bau, 2015; Houtman, 2010; Schmidt et al., 2019; Rogowska et al., 2018; de Campos and Enzweiler, 2016; Kim et al., 1991; Knappe et al., 2005). To salvage the reported continuous Gd contamination of water, Robert and Thilo (Brünjes and Hofmann, 2020; Silberzweig and Chung, 2009) had suggested ways to halt the release of GBCAs from the patient into the environment. Curiously, only limited studies have reported the most sought removal techniques for GBCAs, and the most efficient among them is the expensive reverse osmosis technique. Hence, based on the inherent limitation identified in the few techniques used, there is a need to search for a more manageable, effective, and affordable remediation technology for GBCAs, which is of great interest.

Therefore, we reviewed an up-to-date environmental spread of GBCAS across the continents, the current technologies available for GBCAs remediation, and proposed a hybrid treatment technique that can be explored to treat Gd- GBCAs contaminated water. The review also described the uniqueness of gadolinium chelates for enhanced M.R. diagnosis that suggests its future continual usage relative to its current regulatory status due to the lack of a better alternative.

2. Gadolinium Chelates Application In Enhanced Mri Diagnostics

Gadolinium is a unique, rare-earth element that orders magnetically when close to room temperature and is considered a simple Heisenberg ferromagnet. The paramagnetic cum ferromagnetic phase transition follows a second-order phase transformation

due to seven unpaired 4f electrons with a total angular momentum of $J = 7/2$ with a hexagonal close-packed structure crystal (Dan'kov et al., 1998). The Magnetic and electronic properties of the bulk and the surface of Gadolinium metal in its ferromagnetic ground state and paramagnetic high-temperature phase are represented in Figure 1.

Figure 1: (a) and (b) illustrate the spin-resolved spectral DOS of the ferromagnetic state and total spectral DOS of the paramagnetic state of bulk gadolinium at the Fermi energy, respectively, as projected to the 2D Brillouin zone. The darker region depicts the bigger values of the spectral DOS. Gadolinium ortho-aluminate is an example of rare earth compounds, ABO_3 , where A is a rare-earth ion and B represents another trivalent ion, e.g., Fe^3 or Al^{3+} , which crystallize in a tinkered perovskite structure (space group $D'' - P6mm$) which shows the orthorhombic unit cell and also the pseudocubic cell. The orthorhombic cell dimensions of $GdAlO_3$ are $a = 0.5247$ nm, $b = 0.5304$ nm, $c = 0.7447$ nm, in such a way that the shift of the pseudocubic cell is very little ($a' = 0.3730$ nm, $b' = 0.3730$ nm, $c' = c = 0.3723$ nm, and the angle, $\alpha = -90.60^\circ$). This dimension is significant because, for a cubic lattice, the magnetic dipole interaction field on a particular ion disappears in both the ferromagnetic state (all magnetic moments parallel) and for the simple antiferromagnetic state (all nearest neighbors antiparallel) as a result of the ions in a spherical sample (Oroszlány et al., 2015). The detailed structure was described by Geller and Bala in 1956 as reported by (Cashion et al., 1970) and shown diagrammatically in Figure 2.

Gd^{3+} is located in a local environment of low symmetry, with just a mirror plane perpendicular to the c-axis. The supposed crystalline electric field acting on the Gd^{3+} ions in gadolinium aluminate has not been directly verified yet; however, the experiments reported in 1964 by White R.L. and his team on electron spin resonance of gadolinium ions in the isomorphous diamagnetic host yttrium aluminate indicate that the anisotropy forces in the antiferromagnetic are as a result of the crystalline electric field effects state. (Cashion et al., 1970). MRI scanning involves applying proton nuclear magnetic resonance (NMR) for medical tomography; the protons scanned are those of the water molecules in the scanned region. A critical factor influencing the scanned image quality is the rate at which excited protons in the scanned area relax, emitting radiofrequency photons as they fall from the upper to the lower energy state in the magnetic field. The shorter the relaxation time takes, the better the quality of the image (Cash, 2016). Gadolinium is the first pure element to exhibit ferromagnetic at near ambient temperature, except for the other three 'classic' metals, nickel, cobalt, and iron. This distinctive magnetic feature of Gd has found relevant industrial applications such as magnetic refrigerators and enhanced M.R. diagnostics. For example, its application in MRI provides high-quality images with a non-invasive diagnosis of myocardial, oncologic, inflammatory, orthopedic, and neurological vascular diseases (Nakajima and Lamid-Ochir, 2020; McDonald and McDonald, 2020; McDonald et al., 2018; Center for Drug Evaluation and Research, 2015; Nitz et al., 2010; Parizel et al., 2010; Fischer, 2010; Kauczor and Van Beek, 2010; Schmidt et al., 2010; Reimer et al., 2010; Penfield and Reilly, 2007; Eberhardt et al., 2006).

Besides gadolinium, manganese (Mn), a transition metal, has the second-highest paramagnetic moment because the Mn^{2+} ion has 5 unpaired electrons in its 3d shell. Based on this property, an attempt was made to use manganese as a chelated paramagnetic contrast agent called mangafodipir trisodium (Mn-DPDP) and commercially named Teslascan®. However, the manganese chelate was withdrawn from the U.S. and the E.U. marketplace in 2003 and 2010. The withdrawal was due to unsatisfactory clinical performance and concerns over its toxicity, resulting in poor patronage. Thus, to date, the gadolinium-based contrast agent remained the most popular and utilized contrast agent. Unarguably, many crucial life-saving medical information that is otherwise impossible with other imaging modalities have been obtained by physicians using Gadolinium-based contrast-enhanced MRI for diagnostic imaging since 1988, and it is still considered relatively safer and preferred over iodinated contrast used in computed tomography (Catherine et al., 2020; Ebrahimi and Barbieri, 2019; McDonald et al., 2018; Caravan et al., 1999).

Nonetheless, the toxicity of gadolinium salts also requires that the chelation of Gd^{3+} ions with appropriate multidentate for its safe usage in biomedical applications and to improve its water solubility (Lohninger, 2020; Fox-Rawlings and Zuckerman, 2019; McDonald et al., 2018; Penfield and Reilly, 2007). The bounded complexes, also known as "Gadolinium-based contrast agents (GBCAs)," contain gadolinium ions and a chelate / a ligand / a carrier, which secures the gadolinium ion firmly. This adjunct typically formed the different nomenclature of commercial GBCAs (Kanda et al., 2016).

However, despite the chelation of gadolinium ions, GBCAs also degrade invitro through transmetallation with a higher degradation and deposition incidence in the brain (Penfield & Reilly, 2007). Higher degradation susceptibility is associated more with the linear GBCA chelates than the macrocyclic chelates due to their transmetalation in vitro. The macrocyclic GBCAs chelates are technically more resistant to transmetalation (crowling and Frey, 2019; Aime, 2019; Val M. Runge, 2018; Lohrke et al., 2017; Sieber et al., 2008; Port et al., 2008b; Idée et al., 2006; Laurent et al., 2006). Several clinical observations showed that the linear nonionic chelates retain more gadolinium than the linear ionic chelates (R. J. McDonald, McDonald, Dai, et al., 2017). Notwithstanding, all brands of GBCAs chelates are susceptible to deposition, dechelation, and release of toxic Gd metal since they all contain the same toxic gadolinium metal (Fox-Rawlings and Zuckerman, 2019; Rasschaert et al., 2018; McDonald et al., 2017a; Lohrke et al., 2017; Baranyai et al., 2012).

Approved Commercial chelated gadolinium can be grouped according to some critical molecular design parameters which are responsible for the differences in their thermodynamic stability constants and kinetic stability; (a) Type of the chelating moiety: the linear open-chain molecules chelate, or the macrocyclic molecules chelates where Gadolinium ion is enclosed in the pre-organized cavity of the ligand, (b) ionicity: the ionicity of the complex varies from neutral to tri-anionic agents, and (c) the presence or absence of an aromatic lipophilic residue required for protein binding (Port et al., 2008). There are reported differences in the thermodynamic and kinetic behaviors, even among contrast of same chelation type. It is, therefore, complicated to assume similar kinetic and thermodynamic behaviors invitro of GBCAs of the same chelate type as strongly argued by the proponent of GBCAs safety. The kinetic stability of a gadolinium complex, rather than its thermodynamic stability, dictates its in vivo toxicity (Sherry et al., 2009; Boyken et al., 2019). The idea of kinetic and thermodynamic stability of GBCAs is currently under critical discussion, being a controversial topic that has birthed a renewed curiosity in the physicochemical characteristics of gadolinium chelates administered during contrast-enhanced MRI (Port et al., 2008).

The ligand on a linear chelate has a tail that wraps partially enclosing the atomic Gd, which is a flexible structure and facilitates the easy release of free Gd. In contrast, the ligand on a macrocyclic chelate produces a cast-iron-like structure that completely embeds the Gd atom (Fox-Rawlings & Zuckerman, 2019). Thus, the four covalent bonds in a cyclic chelate must be simultaneously broken before Gd can be freed. The linear and macrocyclic structures are depicted in Figure 3. (a) Macrocyclic Gadovist chelate and (b) Linear Magnevist chelate.

Consequent to this finding, the macrocyclic GCBAs, and selected linear ionic GCBAs are more favorably disposed to by the regulatory agencies to use as contrast agents in recent times. Presently, efforts are in place to phase out linear GBCAs from medical treatment and their replacement by the macrocyclic and nonionic forms to reduce the chance of its de-chelation and potential toxicity (Choi and Moon, 2019; Guo et al., 2018). As a result, a total decline of 70% in sales of linear GBCAs between 2009 and 2016 was observed using 10-year data from hospitals and pediatric clinics in 2017. On the other hand, the sales of the macrocyclic GBCAs rose to 82 % within the same period, 2018), as presented in Figure 4. Compared to the macrocyclic chelates, the low administration of the linear chelates probably accounts for the observed higher occurrence of the latter in surface and drinking water in recent times (Rogowska et al., 2018).

3. Current Gbcas Approval Status

In conjunction with the European Union in a swift reaction to the concerns about Gd toxicity, the European Medicine Agency has restricted or / suspended the sales and use of certain linear GBCAs in all its member states since 2017 (Fox-Rawlings and Zuckerman, 2019 Dekkers et al., 2018; McDonald et al., 2018; Agency, 2017a; Agency, 2017b). Presently, Gadoversetamide (OptiMARK, Guerbet, which is previously known; as Mallinckrodt) and Gadopentetate dimeglumine (Magnevist, Bayer + generic products such as Magneqita, Agfa), Gadodiamide (Omniscan, GE Healthcare) are no longer permitted for intravenous administration in Europe. Gadoteric acid (Primovist, Bayer) and gadobenate dimeglumine (MultiHance, Bracco) are still allowed, but only for liver imaging. Gadopentetate dimeglumine 2 mmol/l solution for intra-articular injection (Magnevist, Bayer), a low dose, dilute solution of Magnevist specifically formulated for intra-articular injection during MRI arthrography is still retained. Gadoteric acid (Dotarem, Guerbet, and Clariscan, GE Healthcare), Gadoteridol (ProHance, Bracco), and Gadobutrol (Gadovist, Bayer) are also permitted at the lowest effective dose and only when its use becomes indispensable for essential diagnostic

information (Soloff and Wang, 2020; Royal College of Radiologists, 2019; Fox-Rawlings and Zuckerman, 2019; Nacif et al., 2012; Aime and Caravan, 2009).

On the other hand, the US FDA initially declined to restrict using any of the Nine (9) different GBCAs, including those reportedly linked to higher gadolinium retention in the brain. The US FDA's position was due to a lack of substantial evidence on the effect of gadolinium on the human body, even though its advisory body held a contrary view. However, after a series of meetings to address these concerns between 2006 and 2010, it mandated that all approved GBCAs add some specific changes to its labeling in clinical Pharmacology and the Patient instruction sections bearing a warning precaution concerning its retention in patients having unhealthy kidneys (glomerular filtration rate or GFR < 30 mL/min/1.73m²) and adverse reactions in Pregnancy (Fox-Rawlings and Zuckerman, 2019; Choi and Moon, 2019; Runge, 2018; Medical Association, 2017; Agency, 2017a; Kanda et al., 2017). Thus, recognizing that NFS is associated with gadolinium retention, this mandate was updated in December 2017 with a new class alert for all GBCAs, particularly for patients with renal dysfunction. However, it still refrained from restricting any GBCAs (Fox-Rawlings and Zuckerman, 2019; FDA, 2018; Center for Drug Evaluation and Research, 2015). Finally, in May 2018, to allay the uncertain concerns of patients who may require contrast-enhanced MRI, the FDA updated its recommendation. Presently, the FDA no longer requires patients to be given any medication guide before administration except for the outpatients on their first visit to receive a GBCA injection or when the information is substantially changed (Fox-Rawlings & Zuckerman, 2019).

Summarily, the updated list of the E.U. and USFDA permitted GBCAs is presented in Table1. The list includes gadobenate (MultiHance), gadobutrol (Gadavist), gadodiamide (Omniscan), gadopentetate (Magnevist), gadoterate (Dotarem), gadoteridol (ProHance), and Primovist (Gadoxetate disodium). The use of Ablavar (gadofosveset trisodium) and Opti Mark (gadoversetamide) was discontinued by the USFDA in February 2018 and February 2019, respectively (Fox-Rawlings and Zuckerman, 2019; Soloff and Wang, 2020; Enterline et al., 2020).

Table 1.

Gadolinium-based contrast agent code, generic names, brand names, and regulatory status update on MRI administration by the Food and Drug Administration (FDA) and the European Union (E.U.).

| Code name | Product name | Generic name | Ligand Type | Year approved. | EU | USFDA | References |
|---------------|--------------|---------------------------|--------------------|----------------|------------|-----------|-------------------------------------------------------------------------------------------------------------------------|
| Gd-DTPA | Magnevist | Gadopentetate dimeglumine | Linear (i.v) | 1988 | Suspended | Permitted | (Catherine et al., 2020; Enterline et al., 2020), |
| GD-DTPA | Magnevist | Gadopentetate dimeglumine | Linear (i.a) | 1988 | Permitted | Permitted | (McDonald et al., 2018; Rogowska et al., 2018) Radiologists, 2019); [46 - 48] |
| Gd-DOTA | Dotarem | Gadoterate meglumine | Macrocyclic (i. a) | 2013 | Permitted | Permitted | (Enterline et al., 2020; Catherine et al., 2020) |
| Gd-DOTA | Dotarem | Gadoterate meglumine | Macrocyclic (i.v) | 2013 | Permitted | Permitted | (Rogowska et al., 2018; Nacif et al., 2012) |
| Gd-DPTA-BMA | Omniscan | Gadodiamide | Linear (i.v.) | 1993 | Suspended | Permitted | (Leyba and Wagner, 2019; (Rogowska et al., 2018) College of Radiologists, 2019); (Catherine et al., 2020); (EAM, 2019). |
| Gd-HP-DO3A | Prohance | Gadoteridol | Macrocyclic (i.v.) | 1992 | Permitted | Permitted | (Rogowska et al., 2018; EAM, 2019) |
| Gd-DO3A-butro | Gadovist | Gadobutrol | Macrocyclic (i.v.) | 2011 | Permitted | Permitted | (Catherine et al., 2020; Sherry et al., 2009) |
| Gd-DTPA-BMEA | Optimark | Gadoversetamide | Linear (i.v.) | 1999 | Suspended | Removed | (McDonald et al., 2018; Enterline et al., 2020) |
| Gd-BOPTA | Multihance | Gadobenate disodium | Linear (i.v.) | 2004 | Restricted | Permitted | (Catherine et al., 2020; EAM, 2019) |

| | | | | | | | |
|-------------|-----------|------------------------|---------------|------|------------|-----------|-----------------------------------------------|
| Gd-EOB-DTPA | Primovist | Gadoxetate disodium | Linear (i.v.) | 2008 | Restricted | Permitted | (Fox-Rawlings and Zuckerman, 2019; EAM, 2019) |
| MS-325 | Vascovist | Gadofosveset trisodium | Linear (i.v.) | 2008 | N/A | Removed | (Enterline et al., 2020; Sherry et al., 2009) |

N/A= Not Applicable

4. Anthropogenic Gadolinium As A Global Threat In Water

Several constituents have been described as emerging pollutants originating from pharmaceuticals and personal care products (PPCPs), which found their way into the environment through human and animal excretion (urine and feces) disposal in wastewater. The disposal of pharmaceuticals in water ultimately results in micro contamination of the environment from nanogram-per-liter (ng/L) to microgram-per-liter ($\mu\text{g/L}$), which only became detectable by the recent improvements in instrumental methods (Ahuja, 2019; Cuong et al., 2011; Bell et al., 2011). Despite much progress and innovation in wastewater treatment technologies, pharmaceuticals continue to be detected in surface water and ultimately in our drinking water and beverages. The concentration of pharmaceuticals in surface water ranges from several to over a hundred ng/dm^3 (Brünjes and Hofmann, 2020; Szymonik et al., 2017). Emission of Gd compounds from contrast-enhanced MRI imaging has been the principal source of anthropogenic Gd anomalies in surface water. The GBCAs administered during magnetic resonance imaging (MRI) end up directly in coastal seawaters primarily through excretion from the patient's urine or hospital sewage disposals. Ideally, approximately 91 minutes is required to excrete GBCAS from a patient with healthy kidney function; however, it may take longer for a patient suffering from renal impairment. Increased Gd concentrations in water from rural areas with no MRI facilities have been attributed to many outpatients receiving MRI scans and returning home to release the Gd through their renal route (Atinkpahoun et al., 2020). The increasing Gd concentrations found in water systems and drinking water are of profound interest to both experts, policy makers, and the general public (Brünjes & Hofmann, 2020).

Unfortunately, conventional and advanced wastewater treatment plants' treated water is still rich in highly stable Gd due to lack of / incomplete removal (Steinberg et al., 2020; Rogowska et al., 2018; Cyris et al., 2013). A detailed study conducted by Lena Telgmann and co-researchers in 2012 has shown that approximately ninety percent of Gd are retained post-conventional wastewater treatment (Telgmann et al., 2012; Rogowska et al., 2018; Elizalde-González et al., 2017). Worse still, while city water treatments are not tailored to remove GBCAS, it is pertinent to note that specific GBCAS are susceptible to degradation during the treatment processes of chemical coagulation (using FeCl_3 and $\text{Al}_2(\text{SO}_4)_3$, which forms an acidic microenvironment). Other processes that can cause GBCAS degradation include chlorination and U.V-photolysis. (Kulaksiz and Bau, 2011a; Brünjes and Hofmann, 2020; Lee et al., 2014). Transmetallation of GBCAS involves the substitution of Gd^{3+} from GBCA complexes by other substituents metal ions such as Iron (Fe^{3+}), zinc (Zn^{2+}), and copper (Cu^{2+}) due to their similar and, in some cases, higher thermodynamic stability, which increases the toxicity of GBCAs by releasing toxic-free Gd^{3+} (Lee et al., 2014). It has been shown that Gd^{3+} can be partially moved from chelates by competing with other metals such as magnesium and calcium when waste effluents mix up with seawater. In addition, there is evidence that zinc, calcium, and iron can partially displace Gd^{3+} of its medical chelating agents in vivo in spite of very high stability constants. Consequently, the environmental chemistry of Gd^{3+} can be determined by the abundance of inorganic and organic ligand substitutes, which also determines its bio-availability and toxicity. (Steinberg et al., 2020; Tovar-Sanchez et al., 2018; Port et al., 2008a).

GBCAs are unintentionally destabilized during conventional or advanced water treatment yielding to rapid transmetallation of GBCAS into free toxic Gd. Consequently, there is an urgent need to recover the controversial anomaly Gd during the water and wastewater treatment process to prevent the inadvertent consumption of Gd through drinking water, beverages, and other processed or raw foods.

The long environmental half-lives and high stability of the GBCAs administered during MRI examinations leave the sewage treatment process almost unchanged (Kulaksiz and Bau, 2011a; McDonald et al., 2018; Thomsen, 2017; Kulaksiz, 2012; Kulaksiz and Bau, 2011b). The previous assumptions concerning the stability of GBCAs no longer hold. Recent reports show that they degrade, and their degraded products (Gd^{3+}) are severe threats to aquatic organisms and human beings (Brünjes and Hofmann, 2020; Ebrahimi and Barbieri, 2019). Admittedly, their degradation processes and potential health impacts remain the subject of scientific debate because of the limited number of in-depth studies. Similarly, at present, the amount of anthropogenic Gd detected in tap and surface water is relatively small, ranging from 100 to 1100 ng L⁻¹, which makes some opines that the ingestion and retention of such a low quantity of gadolinium as observed in brains seems more of a curiosity than a health concern. (Fox-Rawlings and Zuckerman, 2019; Garcia et al., 2017). However, the latter author admitted that the long-term sequestration of any toxic metal, even in an inert state, in a sensitive structure such as the brain, is perturbing. They also feared that there could be a point in its lifespan where pathological or other processes could release gadolinium and pose a risk for the local deposition concentration of gadolinium to reach either pathological levels or directly cause harm to human organs (e.g., vascular emboli). In the same vein, the potential harm of continual exposure to low levels of Gd contaminated water, particularly at critical developmental stages and for the more sensitive populace such as pregnant women and their fetuses, remained unknown (Fox-Rawlings and Zuckerman, 2019; Sherry et al., 2009). It is, however, known that fetuses and children are yet to fully develop a blood-encephalic barrier necessary to protect the passage of toxic chemicals from blood to neural tissue. Therefore, this vulnerable group of people cannot be considered safe even at the reported low-level concentration coupled with the unanimously predicted increasing deposition of Gd in the hydrosphere

Despite the emerging concerns about its toxicity, increasing Gd deposit in water from magnetic resonance imaging (MRI) examinations and radiology practices are expected (Thomsen, 2011; Thomsen et al., 2007; Rogosnitzky and Branch, 2016). This projection is reinforced by the current improvement in medical facilities worldwide due to the sudden health complications arising from the COVID-19 Pandemic, which probably includes installing MRI facilities either as a new supply or replacing old ones. Similarly, the number of MRI examinations performed in the USA within fifteen years (2000-2015) was more than doubled, while in Turkey, where MRI prescriptions are considered overuse, the number of MRI examinations has tripled within an interval of eight years (2008-2015; OECD, 2017). Therefore, except if the more rational use of MRI (for only essential diagnostic tests) is promoted and sustained, higher anthropogenic Gd concentrations in water resources are likely to occur as a result of an increase in applications (Brünjes and Hofmann, 2020; Caravan et al., 1999; Ebrahimi and Barbieri, 2019).

Many researchers have reported and restricted high positive Gd (Gd_{ant}) anomalies in the REE model in surface waters to the highly populated and industrialized areas with a sophisticated medical system. A typical example is a case reported for the highly populated Lorraine's northern region in France, where most contrast-enhanced MRIs are carried out (Parant et al., 2018). However, some of the publications reviewed in this paper have reported anomaly gadolinium in river water, seawater, groundwater, and tap water in developed cities and less populated locations without developed health facilities, as presented in Table 3. The number of MRI examinations per million population between 2017 and 2019 in selected countries as reported by the Organization of Economic Co-operation and Development (OECD) (OECD, 2020) are presented in Table 3. The number of MRI applications expectedly contributed to the discharge of Gd in water and the number of affected localities. Japan, Germany, the U.S., Korea, Finland, Italy, France, Australia, and Belgium have the highest number of MRI examinations in descending order expectedly; they all reported anomaly Gd in their water systems. Curiously, other countries with a relatively higher number of MRI examinations per capita have not reported any Gd case in their aquatic systems. In contrast, those with fewer MRI applications showed positive results for anomaly Gd. Thus, while anomaly Gd in the aquatic system may be directly related to the increased number of MRI devices in use, other factors such as patient migration and non-point source contamination through water tributaries could also play a significant role in its ecological distribution.

Several researchers have reported positive Gd abnormalities in several countries; hence, the problem cannot be categorized as a localized phenomenon or restricted to highly industrialized countries only (Braun et al., 2018; Kulaksiz and Bau, 2011a). For example, the value of anthropogenic Gd concentrations in wastewater effluents observed in southeast Queensland ranged from 0.1 to 1.5 nmol/kg anthropogenic Gd. However, a far greater value of 7 nmol/kg was reported in Berlin, Germany. The latter value indicates a 2000 times higher concentration than the natural concentration of Gd in the environment (Gd_{Natural}), while the former value indicates a 10–100 times more than the Natural Gd (Michael G. Lawrence, 2010), and Table 2 summarizes the

geographies' spread of anomaly Gd in aquatic systems and sediments reported within the last two decades from all the six regions and across different localities except the Middle East. The positive anomalies spread of Gd in the aquatic space are anthropogenic and are more likely to be attributable to magnetic resonance imaging (MRI) (Bau & Dulski, 1996)

Table 2.

Anthropogenic Gds in water from various geographic regions and MRI Examinations per million population within the review period.

| Country | Region | MRI/mill. | Locality | Water source | Ref. |
|-----------|---------|-----------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Australia | Oceania | 14.78 | Moreton Bay, Mackay, Central Queensland, Brisbane River plume, Southeast Queensland | Wastewater, Rivers | (Catherine et al., 2020), (Michael G. Lawrence, 2010); (Michael Glen Lawrence & Bariel, 2010),(Rapp, 2018), (Michael G. Lawrence et al., 2009) |
| Brazil | America | N/A | Paranao, Brasilia, Atibaia River and Anhumas Creek, Bahia, Salvador | Lake, River, Atlantic Coast Waters | (Pedreira et al., 2018);(Amorim et al., 2019),(de Campos & Enzweiler, 2016) |
| Turkey | Asia | 11.24 | Ankara, | Stream | (Alkan et al., 2020) |
| Germany | Europe | 34.71 | Halle, Rhine River, Berlin, Essen, Munich, Dresden, Karlsruhe and Düsseldorf, Berlin, North Sea | River, Surface water, Wastewater, Seawater, Tap water, soft drinks, and Groundwater | (Kulaksiz & Bau, 2011a);(Tepe et al., 2014); (Kulaksiz, 2012),(Merschel & Bau, 2015),(K. Schmidt et al., 2019), |
| Finland | Europe | 28.82 | Northern Finland | Sediment | (Hölttä, P., Nenonen, K. & Eerola, 2017) |
| China | Asia | N/A | Jinzhong, Yangtze, Sunhuajing, Pearl, Haihe River, Huaihe River, and Liaohe river. Redang Island | Streams, River water, Coastal water Stream Sediments | (J. Zhang et al., 2019) |

| | | | | | |
|----------------|---------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| S / Korea | Asia | 30.8 | Shihwa, Han | Lake and Stream | (I. Kim et al., 2020a), (Song et al., 2017), (Casey, 2017), (I. Kim et al., 2020b), |
| Kazakhstan | Asia | N/A | Aral Sea (SAS), Syr Darya River | Sea and River | (Rzymiski et al., 2019) |
| Malaysia | Asia | N/A | Linggi | River and Lake | (Elias et al., 2019) |
| USA | America | 40.44 | San Francisco, Erie, Ohio, Pennsylvania, Beaver, Allegheny, Mississippi, Monongahela, Juniata, Susquehanna, Boulder Creek, Colorado, Boulder Creek Watershed, North Carolina | Stream, Surface-water, wastewater plant effluents | (Zabrecky et al., 2021), (Verplanck et al., 2005), (Verplanck et al., 2005) (Johannesson et al., 2000), (Verplanck et al., 2010), (Bau et al., 2006), (Rogosnitzky & Branch, 2016) |
| Benin | Africa | N/A | Cotonou, | Wastewaters, well water | (Atinkpahoun et al., 2020) |
| France | Europe | 15.43 | Hérault, Garonne, Bordeaux, Lorraine, Moselle, Southern France | Wastewaters, Surface Waters, rivers, Marine waters | (M. Rabiet et al., 2009); (Parant et al., 2018) |
| Japan | Asia | 55.21 | Nagoya, Hokkaido, Tokyo, Japanese Ara, Tama, and Tone river-estuaries, Osaka Bay area | Seawater, River water, treated effluent. | (Ridley, 2020), (Inoue et al., 2020) (Zhu et al., 2004), (Bau et al., 2006), (Rapp, 2018), |
| Italy | Europe | 28.73 | Trento and Bolzano/Bozen | River Waters | (Peter Möller et al., 2003) |
| The U.K. | Europe | N/A | England, River Thames, Danube river, Rhine- Meuse Delta | Rivers and Tap water | (Kulaksiz & Bau, 2011a) |
| Belgium | Europe | 11.61 | Dommel in northern Belgium | Surface water, Groundwater | (Klaver et al., 2014); (Petelet-Giraud et al., 2009) |
| Netherlands | Europe | 13.06 | Dommel southern Netherlands | Surface water, Groundwater | (Petelet-Giraud et al., 2009) |
| Czech Republic | Europe | 10.35 | Prague, Eastern Bohemia region | Surface water, River, Sewage effluents | (P. Möller et al., 2002); (Bendakovská et al., 2016) |
| Switzerland | Europe | N/A | across Switzerland | Groundwaters. wastewater treatment effluents | (Kaegi et al., 2021) |

N/A= Not available

From the above Table 2, it can be observed that almost all known water sources, including surface waters (rivers, ocean, seawater, and stream), municipal water supplies, Groundwater, and steams, across the globe are reportedly contaminated with Gd anomaly. The list reported in this review is by no means exhaustive because the detection of Gd in the aquatic and sediment systems is ongoing research. The risk associated with each identified water source varies considerably, and different priority attention and treatment techniques may be required. Most of the reported Gd anomaly incidence is found in the river and surface water that are highly dynamic reservoirs of various wastewater effluents. However, considering the natural hydrological cycle, there is no gainsaying that there could be a knock-on-effect from one source to another as the water moves through different tributaries resulting in point and non-point sources of water pollution (Ahuja, 2019; Wu et al., 2019; Council, 1999; Sullivan et al., 2005; Sasakova et al., 2018). Gd in the municipal tap and well water in identified locations in the U.K., Benin, and Germany indicates the precariousness of the potential exposure of people living in these communities to drinking Gd contaminated water at least at low concentrations.

Technologies for GBCAs Remediation in water

It is evident from the preceding that anomaly Gd contamination in water systems is a global threat that requires urgent appropriate actions regardless of the prevailing controversies. This position was also collaborated by (Ebrahimi & Barbieri, 2019). Therefore, a search for an effective treatment for removing anomaly gadolinium in water is critical to protect abiotic and biotic elements in the ecosystems due to its high toxicity (Rogowska et al., 2018; Gwenzi et al., 2018). Literature has reported several techniques employed to recover free metallic Gd and GBCAs from different aqueous solutions. However, most of the works reported removing free Gd using different techniques rather than GBCAs, which is the most sought (El-Sofany, 2008; Li et al., 2015; Zheng et al., 2019). Separation of GBCAs from wastewater had received lesser attention probably because it is relatively easier to separate the free Gd from an aqueous solution than the complex GBCAs, which is more challenging to treat by conventional technique. Indeed, the dissociation constant, thermodynamics, and kinetic stability among GBCAs types (linear and macrocyclic) limit their separability behaviors (Rogowska et al., 2018; Runge, 2018). The different remediation techniques for GBCAs within the last two decades are presented in Table 3.

Table 3. Remediation Techniques for GBCAS in aqueous solutions.

| Method | Medium | Target metal | Brand Name | Chelate type | Charge at pH 7 | Efficiency | Ref. |
|--------------------|------------------|--------------|-------------------------------|--------------|----------------|---------------|------------------------------------|
| Adsorption | Aqueous solution | GBCAs | Dotarem, Magnevist, Primovist | Macrocyclic | Cationic | 70 - 90 % | (Elizalde-González et al., 2017) |
| | | | | Linear | Cationic | | |
| | | | | linear | Cationic | | |
| Ozonation | Wastewater | GBCAs | Gadovist, Omniscan, Magnevist | Macrocyclic | Neutral | Insignificant | (Cyris et al., 2013) |
| | | | | Linear | Neutral | | |
| | | | | Linear | Cationic | | |
| Biological Filters | Freshwater | GBCAs | Omniscan, Dotarem | Linear | Neutral | Insignificant | (Braun et al., 2018) |
| | | | | Macrocyclic | Cationic | | |
| Membrane | Wastewater | GBCAs | N/S | N/S | N/S | 99.85 % | (Michael G. Lawrence et al., 2010) |

N/S = Not-specified

The reverse osmosis separation technique activated carbon adsorption process, biological filters, and Ozonation are popular techniques reportedly applied to remediate GBCAs in an aqueous solution with widely varying efficiencies. The adsorption process is a simple design, low cost, and effective method for treating and removing inorganic and organic contaminants in water and wastewater. Gadolinium chelates removal in wastewater and drinking water through activated carbon adsorption is generally considered ineffective due to its low absorption capacity (Cyris, 2013). However, Elizalde-González et al. (Elizalde-González et al., 2017) achieved an adsorption capacity of 70 - 90 % for selected GBCAs using three different optimized carbon samples (commercial activated carbon, activated carbon obtained from guava seeds, activated carbon obtained from avocado). The highest removal was achieved with the commercial carbon sample, followed closely by the Avocado carbon. According to the authors, the pH, and the number of functional groups on the carbon, specifically, the phenolic functional groups, played a significant role in the removal efficiency. Unfortunately, its efficiency was dramatically reduced when model urine was treated, an observation attributed to the competing urine components, limiting the adsorption capacity. The limitation in the adsorption techniques is that its efficiency varies with Sorbent's types and the aqueous solutions' characteristic nature. Most of the sorbents are only effective for removing free Gd rather than the GBCAs except for the limited success reported by Elizalde-González et al. The observed limitation is attributable to the problem of fouling caused by other molecules present in the urine. Fouling is a common problem in the adsorption process that causes a significant decrease in the adsorption capacities of Sorbent; therefore, further research is required to tackle this gap.

Due to its solubility and chemical reactivity, the ozonation technique is strongly reactive and selective in water pollution control. The technique effectively inactivates micro-organisms and decomposes organic pollutants in water and wastewater treatment (Wei et al., 2017). Therefore, Cyris et al. determined the reactions of gadolinium chelates with ozone for Magnevist, Omiscan, and Gadovist chelates and obtained rate constants values of 4.8 ± 0.88 , 46 ± 2.5 , and $24 \pm 1.5 \text{ M}^{-1}\text{s}^{-1}$, respectively. The values obtained for each chelate test show that the ozonation degradation of Gd chelates in wastewater is both slow and ineffective, and the techniques concluded to be unsuccessful (Cyris et al., 2013). Braun et al. (Braun et al., 2018) also attempted to use aquatic plants as biological filters to remove common GBCA- s (Omniscan and Dotarem) from water. Unfortunately, the test results strangely showed that none of the four investigated macrophytes (*Elodea nuttallii*, *Lemna gibba*, *Ceratophyllum*

demersum, E., and Canadensis) had a remarkable impact on Gd removal even though biofilters have been effectively used to treat domestic and industrial wastewater to remove contaminants (Mulay & Rajasekhara Reddy, 2019). Curiously, the four investigated macrophytes show high bioaccumulation removal activity for other heavy metals like Pb, Ni, Mn, Cr, and Cd, indicating the peculiar separation behaviors of GBCAs.

The membrane separation is a favorite water treatment technology for removing pollutants from water and wastewater streams for re-use through a selectively permeable barrier. The barrier is usually a thin sheet of material separating substances based on their chemical and physical characteristics under a driving force (Brose et al., 2002; Ezugbe and Rathilal, 2020). The membrane technology's aims to produce high mechanical strength materials and an excellent and high degree of selectivity of the desired permeate, which comes in different modules including; Membrane filtration that is pressure-driven processes (microfiltration, ultrafiltration, nanofiltration, and reverse osmosis), Pressure and thermal Driven Processes (Membrane distillation), Non-pressure driven process (Forward Osmosis, Liquid membrane) and Non-pressure electricity-driven processes electro dialysis (Shen, 2016; Khanzada et al., 2020; Ezugbe and Rathilal, 2020; Wenten, 2015; Iritani and Katagiri, 2016; Mulder, 1991). The reverse osmosis has been demonstrated to be an effective technique to remove stable anthropogenic GBCAs contaminants from wastewater, preferably when employed at the last treatment stage (Brünjes and Hofmann, 2020; Thomsen, 2017; Schmidt et al., 2019). For instance, 99.85 % GBCAs removal efficiency was achieved with reverse osmosis in a state-of-the-art water treatment plant (Michael G. Lawrence et al., 2010). Thus, Reverse Osmosis is the only recognized technique among all the reported tested techniques that have proven efficient in removing the GBCAS. Unfortunately, it is a very costly option, primarily due to the high pressure required for its operation (Ezugbe and Rathilal, 2020; Crini and Lichtfouse, 2019; Ezugbe and Rathilal, 2020). The high cost of the reverse osmosis limits its practical inclusion in every treatment plant where it is required. Similarly, Jiang et al. opined that technological innovation and development of new components in the future are required to circumvent the identified limitations of reverse osmosis (Jiang et al., 2018). Hence further research is required to explore effective optional techniques to treat the anomaly Gd in water using a more affordable technique.

5. Perspective

It is pertinent to note that up to date, only a handful of research has reported the removal of GBCAs in the wastewater treatment process in the last two decades. Most research in this area focused on removing free Gd rather than the GBCAs, the pharmaceutical form of the anomaly Gd in water. Therefore, people probably ingest a minute quantity and concentration of dechelated Gd via drinking contaminated municipal tap, domestic well water, beverages, or consuming contaminated food ingredients (meat, seafood, and vegetables) unwittingly. The several studies that reported low-level gadolinium concentration in the brain tissues and bones of patients who had never received any GBCA reinforced this possibility (Fox-Rawlings & Zuckerman, 2019). The increasing spread of anomaly Gd across the continents suggests that it is crucial to investigate the probable presence of anomaly Gd in new localities that are not yet investigated, especially those with a relatively high MRI examination per capita. A sporadic increase in the concentration of Gd in Berlin within just three years suggests an imminent danger as similar trends could be discovered in other locations where anthropogenic Gd are previously detected at lower concentrations or where they were earlier non-existent (Tepe et al., 2014). Hence, it is strongly recommended that communities where anomaly Gd is yet to be investigated or previously reported to be free of Gd should be monitored. The observed precarious Gd spreads and the gloomy future projections call for appropriate authorities to protect groundwater and surface water from impending Gd pollution disasters. In the same vein, it is needful to examine the possible presence of Gd in the tissues of people with no previous record of GBCAs administration particularly, those living in localities with highly exposed drinking water sources. Such information from volunteers is required to form part of the much-sought data about the environmental fate of Gd in different ecosystems and its possible bioaccumulation in the human body through contaminated water.

Current understanding justifies the urgent need to search for appropriate, effective, and economical technology to prevent the entering of controversial anthropogenic Gd metal into our water systems as an alternative to the high energy dependent reverse osmosis (Prathna et al., 2018). Earlier, Brünjes and Hofmann had suggested that each MRI examination should be followed by collecting the patient's urine to halt the spread of Gd contamination in drinking water. However, the sustenance of this recommendation should be a concern. Firstly, the urine collection period recommended by the authors remained indefinite for apparent reasons; it is known that differences in molecular properties significantly determine the elimination behavior of GBCA;

therefore, the elimination of each GBCA in vivo is quite different even at a very slight difference in its molecular properties and also depends on many interactive factors with the endogenous biomolecules (Aime, 2019). Moreover, considering the heterogeneity in human socio-cultural and religious perceptions, the required stakeholders' cooperation in other localities where such practice is required can hardly be assured. This can be inferred from the medical staff's initial skepticism in Germany, as revealed by the authors. Ultimately, the search for an effective and manageable treatment technique to treat this relatively new microcontaminant becomes imperative, just like other well-recognized emerging pharmaceutical contaminants.

To this end, we suggest a hybrid system that synergistically combines the dechelation of GBCAs via a commercial chemical coagulation process using ferric or aluminum salts (Lewis salts). The reaction results in an acidic microenvironment, thereby acidifying the GBCAs for easy degradation or transmetallation to release free Gd ion (Brünjes and Hofmann, 2020; Lee et al., 2014; Rabiet et al., 2014a). The coagulation process is particularly effective for the degradation of the linear GBCAs, and the degradation efficiencies of other anthropogenic organic compounds have been reported by Ballard and MacKay (2005). However, for the more prevalent and stable macrocyclic chelates, the application of the photo-Fenton process, which employs the effectiveness of hydroxyl radical reaction synergistically combined with U.V-c irradiation exposure, is recommended (Brünjes and Hofmann, 2020; Cyris, 2013; Cyris et al., 2013; Brünjes, R., Höhn, P., Hofmann, 2017; Schijf and Christy 2018). Furthermore, the photo-Fenton technique is advantageous for its low dissolved iron concentration in the effluent, multiple productions of hydroxyl radicals due to reduction of Fe^{3+} to Fe^{2+} , and photolysis of hydrogen peroxide providing an additional source of O.H. radicals (Cuerda-correa et al., 2020). In addition, Photo-Fenton treatment using sunlight compared to the alternative ozonation process could be cheaper and more effective for treating GBCAs contaminated water (Cyris, 2013; Bauer and Fallmann, 1997).

The adsorptive separation technique can then follow any or the in-situ combination of these pretreatments' techniques or the use of a target-specific modified membrane. The free Gd ions can then be effectively sorbed by several specific adsorbents or membranes, as earlier reported by several researchers (Asadollahzadeh et al., 2020; Atiba-Oyewo et al., 2019; Ojovan et al., 2019; Zheng et al., 2019; Guo et al., 2018; Perea et al., 2018; Oyewo et al., 2017; Zhang et al., 2009). This is because the released Gd ion has a higher sorption affinity for recovery in wastewater (Nassar et al., 2015; Lee et al., 2014; Brünjes and Hofmann, 2020).

The proposed hybrid technique is expected to provide a relatively economical alternative to reverse osmosis because low-pressure-driven adsorption is required. However, the possible challenges in the proposed hybrid technique include.

- i. Excess Fe or Al or/ and newly formed metal ligands as secondary pollutants during coagulation and flocculation processes.
- ii. Inability to effectively and completely degrades linear and macrocyclic chelates in a single pretreatment technique, particularly under simulated natural environment for practical industrial applications.

These possible challenges offer vast opportunities for future research in finding possible means to circumvent them.

Conclusion

Anthropogenic Gd chelates are undoubtedly emerging microcontaminants in different water resources across the continents regardless of population and number of MRI per capita. Higher trends and spreads of anomaly Gd are expected based on the increasing diagnostic requirements such as the one necessitated by the SARS – CoV-2- related heart damage. Besides, GBCAs administration is still permitted by the regulatory agencies because of the risk-benefits considerations and non-availability of a suitable substitute for the time being. Arguably, the inability to set the necessary limits to the toxic metal in the water system is due to the Gd anomaly's unknown long-term effects on the aqueous ecosystem. In our opinion, it is crucial to urgently set a precautionary limit while investigating the controversies concerning its deposition's clinical effects on human tissues. The present suggestion is per Tweedle et al.'s declaration on the intolerability of the presence of Gd ion irrespective of its source or quantity/concentration (Kanal and Tweedle, 2015; Tweedle et al., 1991).

Although, the reverse osmosis membrane technique, a high-pressure technique, has shown promising results for eliminating GBCAs. It is, however, a costly option available in state-of-the-earth plants; therefore, the wastewater treatment researchers and designers are required to pick up the much-desired challenge of developing an affordable and effective technique for the removal

of the ubiquitous Gd contrast agent in the water space. To this end, the proposed hybrid in-situ treatment system that degrades the complex GBCAs in the wastewater system may be considered a feasible and promising alternative treatment for the micro contaminant GBCAs. This is necessary to safeguard our aquatic foods and drinking water from gadolinium contamination. Additionally, success in this direction potentially benefits from the use of Gd as a valuable tracer of pharmaceuticals microcontaminants in wastewater because of its persistence, reliability, coupled with the fact that it is cheaper to measure accurately even at very low concentrations (Tepe et al., 2014; Lawrence and Bariel, 2010; Boester and Rude, 2020).

Declarations

Author contribution OEI: conceptualization, methodology, investigation, writing review and editing ALA: writing review and editing; funding acquisition, project management, supervision; SI: supervision; NFS: supervision. All authors have read and approved the final manuscript.

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Figures

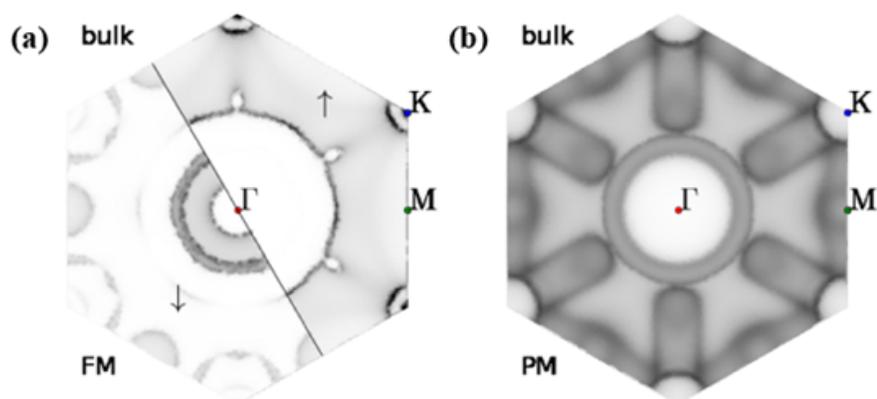


Figure 1

Electronic and magnetic properties of gadolinium metal. (a) Spin resolved spectral DOS of the ferromagnetic phase and (b) total paramagnetic phase spectral DOS. Source: (Oroszlány et al., 2015).

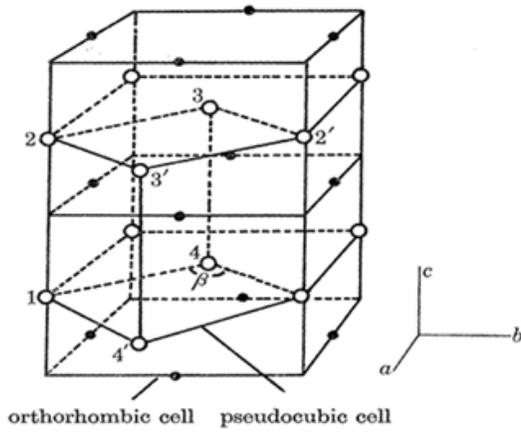


Figure 2

Structure of $GdAlO_3$ depicting the orthorhombic and pseudocubic cells (Aluminum; O_2 , gadolinium; Oxygen atoms are masked). The figure shows that the Gd ions are slightly displaced from the ideal position. Source: (Cashion et al., 1970)

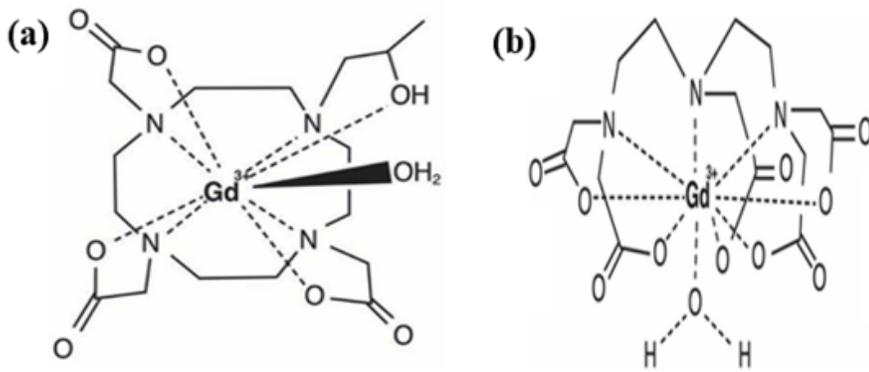


Figure 3

Gadolinium Chelates types (a) Macrocylic Gadobutrol, Gd-DO3A-butro (Gadovist). (b) Linear Gadopentetate dimeglumine, Gd-DTPA (Magnevist). Source: (Nakajima & Lamid-Ochir, 2020)

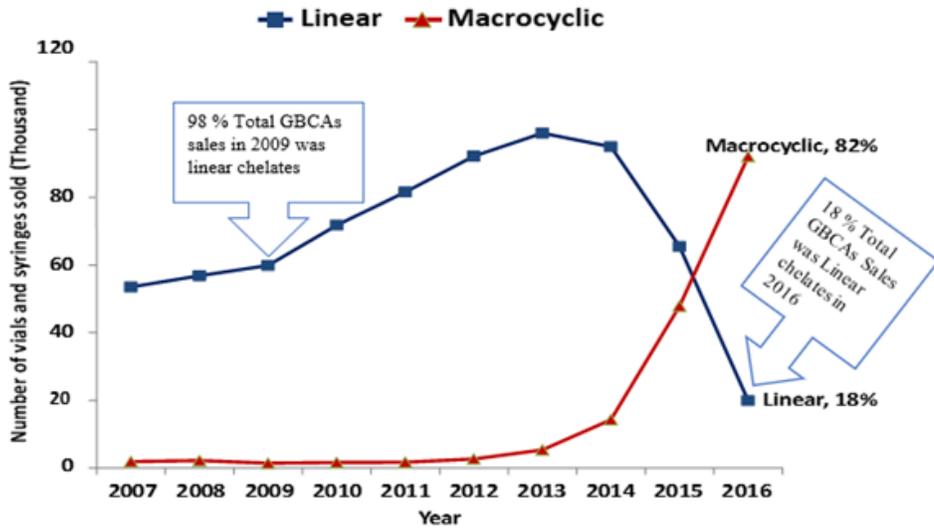


Figure 4

A ten-year Pediatric Hospital and Clinics' sales data of macrocytic and Linear GBCAs. Source: (FDA, 2018).

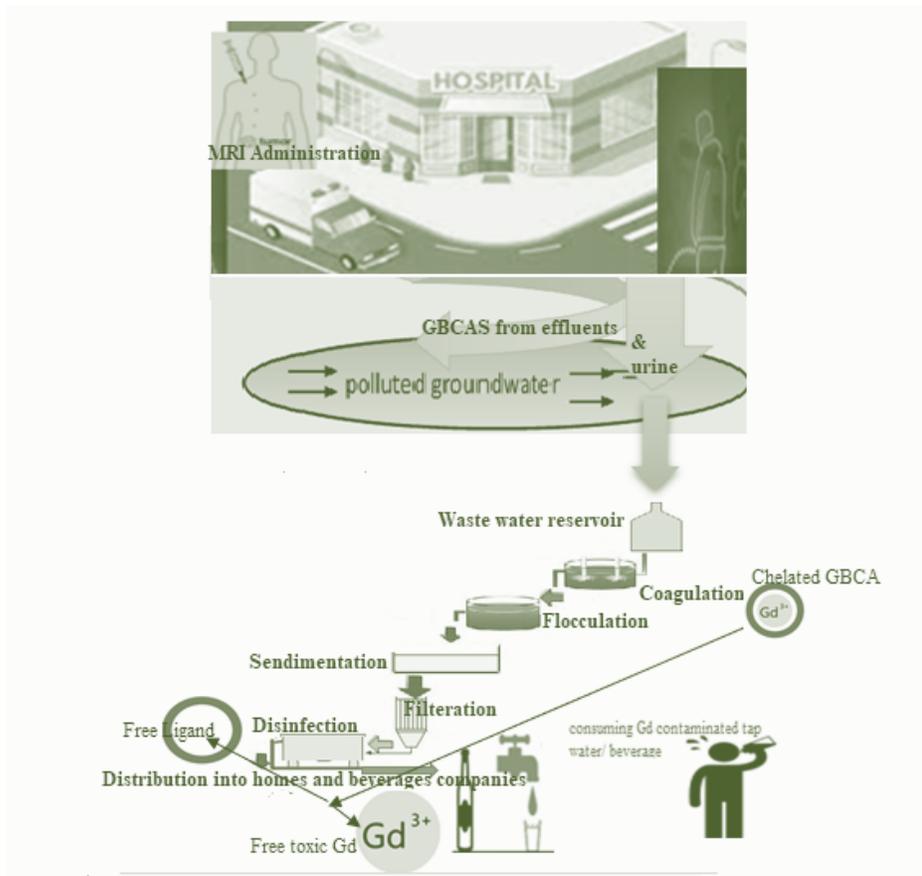


Figure 5

Pathway leading to the release of GBCAS / anthropogenic Gd into the drinking water system/beverage

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