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A roadmap towards pollution prevention and sustainable development of Gadolinium

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Graphical abstract

An average of 11% of GBCA is disposed of and lost after each MRI exam.

Gadolinium (Gd) is widely used in medical, industrial and household applications such as radar technologies, compact discs, and microwaves. Gd^{3+} ion is hydrophilic and induces Magnetic Resonance Imaging (MRI) contrast. For medical application, Gd^{3+} must be chelated by different organic ligands such as polyaminocarboxylic acid derived from either linear (open chain) or macrocyclic compounds. The linear Gadolinium-Based Contrast Agents (GBCA) complexes, thermodynamically less stable and inert, have been banned from the EU market to avoid toxic effects of free Gd^{3+}.

GBCA degrade in water, and photochemically [1]. Furthermore, as for lanthanides and other heavy metals such as yttrium (Y^{3+}), GBCA can be dissociated in the presence of other ions such as iron (Fe^{3+}), zinc (Zn^{2+}), copper (Cu^{2+}), over a long time period [2]. High concentrations of calcium and magnesium can also transmetalize some linear GBCAs in seawater due to the isosteric effect between the cations.

Several studies have shown the evidence of GBCAs' environmental pollution and Gd^{3+} toxicity both in aquatic organisms and humans [3,4].

This short communication provides a roadmap using recent quantitative data on GBCAs' consumption, medical use and waste, towards environmental pollution mitigation and sustainable development.

Consumption of Gadolinium in medicine

World consumption of gadolinium oxide is estimated at approximately 1000 tons per year. REEs, heavy metals and in particular metals such as Gd^{3+} are difficult to remove from the environment. To date, there is no evidence or technology for Gd removal and recycling. This heightens its dose accumulation and impact on ecosystem.

GBCAs are used in MRI examinations to improve visualization of a target structure or organ.

Increased GBCAs consumption is associated with increased number of MRIs performed [5], but the annual quantity of gadolinium per machine remained unchanged (estimated at 2.7 kg per MRI in 2018) [6].

MRI-related GBCAs consumption and waste

Gd bioavailability, long-term bioaccumulation and stability in the environment or in biological systems should be further explored. This warrants a comprehensive analysis of GBCAs use and waste in medicine. To reach this objective, we conducted a 1-year (2019-2020) observational study in 7 centers of heterogeneous sizes and practices (Singapore (Republic of Singapore), Brest, Strasbourg, Lyon, Lille, Dijon, (France), Boston (USA)). The following data relevant to MRI use of GBCAs were collected: Gd^{3+} chelates name, amount of injected and unused GBCAs. Given the known GBCA concentration for each dose, we were able to calculate the amount of gadolinium used (i.e. adjusted according to patient's weight). Quantitative variables were described in means and 95 % confidence interval (CI). Statistical analyzes were conducted using STATA software (15.1, Statacorp). This research was conducted in accordance with the current regulatory and ethical frameworks as well as the Helsinki Declaration and its revisions. A compliance notice with Patient Data Protection Regulation for non-interventional study was obtained from the institutional review board at each center.

A total of 18 MRI machines were recorded for all 7 centers. Data were obtained from 60,886 contrast-enhanced MRI examinations (Table 1): 12.92 % from USA, 78.77 % from France (Brest 14.69 %, Dijon 18.38 %, Lille 15.22%, Lyon 6.76 % Strasbourg 23.72 %), 8.31% from Republic of Singapore) (Figure 1). A mean wasted GBCA of 11.71% [95 % CI: 11.58; 11.82] was reported for a mean wasted GBCA dose of 1.78 mL [95 % CI: 1.76; 1.80] per MRI examination. This yielded a total mean wasted Gd. oxide of 5.41 kg [95 % CI: 5.35; 5.47] per center per year.

For the following syringe or vial volumes of 5 mL, 7.5 mL, 10 mL, 15 mL, and 20 mL, the percentage of wasted GBCAs were 10.12 %, 14.65 %, 5.98 % and 13.38 %, respectively. Mean injected GBCA dose was 12.71 mL [95 % CI: 12.68; 12.74]. GBCAs used were ARTIREM (0.04 %) and DOTAREM (52.93 %) (Gadoteric Acid, Guerbet), EOVIST (0.98 %) (Gadoxetic acid, Bayer), GADOVIST (17.07%) (Gadobutrol, Bayer), MULTIHANCE (0.48%) (Gadobenic acid, Bracco), PROHANCE (20.13 %) (Gadoteridol, Bracco), CLARISCAN (8.37 %) (Gadoteric Acid, GE Healthcare), OMNISCAN (1 dose, < 0.01 %) (Gadodiamide, GE Healthcare) [7].

Fate of unused medical GBCAs: from syringes to solid waste incineration plant

(Figure 1)

GBCA dosage is adjusted according to patient's weight before injection. The syringes containing the unused GBCAs are then put into a medical waste bin and later transported to the municipal solid waste incineration plants for disposal to smoke and ash residues (i.e. 5.41 kg of Gd per center per year, as estimated). Some of the latter are transformed into construction materials such as clinker. The speciation of Gd derived from GBCAs after combustion of the waste, as well as the behavior of this element in the resulting clinkers, are unknown. In any case, treated in this way gadolinium is irretrievably lost, and it is difficult to imagine an economically tenable industrial protocol that would allow to treat the produced clinkers, and to recover this element.

Fate of injected GBCAs: from urine to wastewater treatment plant

(Figure 1)

Following their excretion, these contrast agents are known to be eliminated from the patient's body by the urinary route, with a previously reported urinary elimination of > 95 % of injected GBCA in 72 hours [8]. However, more recent studies suggested a longer urinary elimination of > 1 month post-GBCA injection [9,10], at concentrations ranging from 350 mg (Gd)/L (or 2.23 mmol/L) on day 1 after injection to 7 µg (Gd)/L (or 4.45×10^{-5} mmol/L) by progressive decrease until day 39 after injection.

Most of the GBCAs injected is eliminated in urine into urban sewer system and transported to urban wastewater treatment plant (WWTP).

Annual Gd discharge from a German University Hospital was estimated at 2.1 to 4.2 kg per machine, with a mean 1.2 g of Gd. element delivered at each GBCA injection and a theoretical concentration of 8.5 to 30.1 µg/L in hospital effluent [11]. This gives a total of 481 to 1160 kg annual MRI-related Gd effluent from German hospitals to WWTP. To date, GBCAs are not regarded as toxic or hazardous requiring customized and specific treatments in WWTP.

The presence of these gadolinium-containing compounds in WWTP is significantly correlated with the high Gd concentrations reported in the water sources adjacent to WWTP. The anthropogenic Gd (Gd_{ant}) measured in wastewater during the various treatments in wastewater treatment plants is of the order of a few hundred ng/L [12] but can reach a few hundred μg/L. Several studies have shown that the share of Gd_{ant} found in the dissolved phase in WWTP represented 90 % to 97 % [2] of the total Gd measured in these aqueous fractions.

Health and urban stakeholders need to acknowledge GBCAs as toxic compounds to be treated with pollution-remediation processes and monitoring-quality control measures comparable to those used for radioactive elements [13], or organics (e.g. pesticides).

In a perspective of sustainable development

Anomalous levels of Gd can be observed in different ecosystems [14]. Medical GBCA plays an important role in the rise of Gd environmental pollution (i.e. impacts of its unsustainable packaging, preparation, use, and waste management). Such pollution seems to be a threat to biodiversity. Moreover, there is evidence of REE bioaccumulation in mining districts and correlation between REE exposures and residents' – miners' adverse health outcomes [15]. Taken altogether, the stakeholders involved in the life cycle of Gd should be watchful and take active part at reducing its environmental and human impacts. This should be in the footsteps of a roadmap towards producing Gd (recover and reuse) in a sustainable way, by mitigating its consumption and waste production while increasing its economic efficiency **(Figure 2).**

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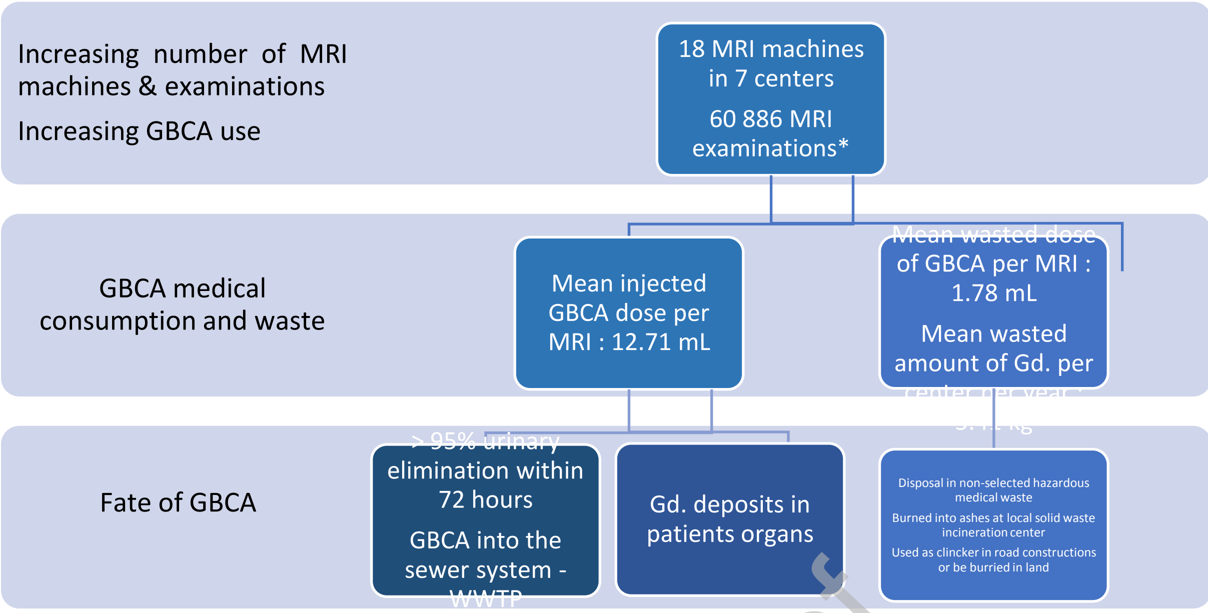

Figure 1. Current challenges in Magnetic Resonance Imaging (MRI) – Gadolinium (Gd)-Based Contrast Agent (GBCA) use and waste management: towards pollution remediation in the environment and water resources.

WWTP: waste water treatment plant. *according to our one year-study : MRI examinations: 12.92 % from USA, 78.77 % from France (Brest 14.69 %, Dijon 18.38 %, Lille 15.22 %, Lyon 6.76 % Strasbourg 23.72%), 8.31 % from Republic of Singapore.

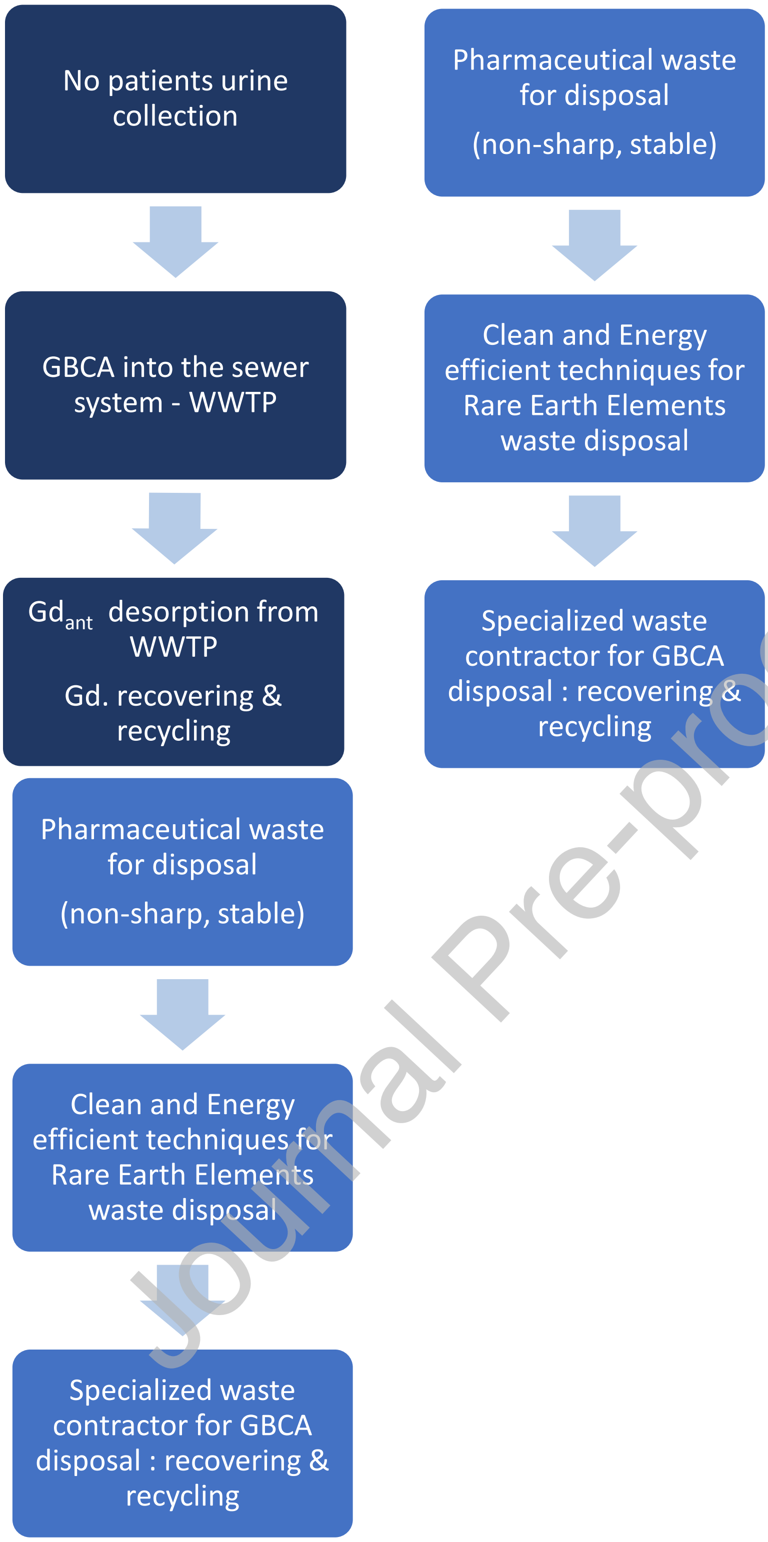

Figure 2. Steps towards GBCA pollution remediation in the environment and water resources.

GBCA: Gadolinium-Based Contrast, Agent. WWTP: waste water treatment plant. Gd_{ant}: anthropogenic Gadolinium (Gd).

Table 1. Our study's MRI - GBCA volume characteristics (injected vs. unused) per center

Center		MRI examination	Volume of GBCA : injected (mL)		Volume of GBCA: unused (mL)		Ratio of unused GBCA (%)	
Country	City	Number	Mean	95% CI (lower - upper)	Mean	95% CI (lower - upper)	Mean	95% CI (lower - upper)
France		47960	12.52	12.49 - 12.56	2.09	2.07 - 2.12	13.80	13.66 - 13.94
	Strasbourg	14440	13.22	13.15 - 13.29	2.13	2.09 - 2.17	13.91	13.65 - 14.18
	Dijon	11192	10.66	10.58 - 10.74	1.31	1.28 - 1.34	11.22	10.97 - 11.48
	Lille	9267	13.26	13.18 - 13.35	1.14	1.09 - 1.18	8.03	7.74 - 8.32
	Brest	8943	13.31	13.23 - 13.38	2.62	2.57 - 2.68	15.99	15.67 - 16.31
	Lyon	4118	11.79	11.73 - 11.84	5.09	5.00 - 5.18	28.62	28.22 - 29.02
USA	Boston	7869	15.61	15.52 - 15.70	1.00	0.97 - 1.03	6.43	6.22 - 6.63
Singapour	Singapour	5057	9.95	9.93 - 9.97	0.01	0.01 - 0.01	0.08	0.05 - 0.11