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Are the increasing amounts of gadolinium in surface and tap water dangerous?

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Since its introduction in the early 1980s, magnetic resonance imaging (MRI) has become an indispensable modality for diagnostic imaging. Gadolinium (Gd)-based contrast media have been used in MRI since 1988 and are now administered in 33–50% of examinations. Six of the nine available agents are excreted only via the kidneys and the remaining three agents are also excreted via the hepatocytes into the biliary system (range, 4–50%) so a major proportion of all agents reaches the sewage. Because of their high stability, none of the agents are removed in waste water treatment plants (WWTP) to a significant extent so they are transferred to surface water with the clear water discharge from the WWTP. Teglmann et al. showed that less than 10% of Gd-based contrast media may be removed during current water treatment (1). The contrast media which remain in the water are described as anthropogenic pollutants, meaning that they occur as a result of human activity. The anthropogenic Gd is also transported into groundwater both by natural and by induced bank filtration[a] (2). Twenty years ago, Bau and Dulski (3) described the anthropogenic Gd anomaly in our water and its correlation with the administration of Gd contrast agents, and showed that the amounts of Gd were enriched, i.e. greater in amount relative to the other rare earth elements.

Gadolinium

Because of its paramagnetic properties, Gd^{3+} decreases the T1 relaxation time of protons causing improved signal-to-noise ratio and so enhancing the MRI signals. Gd^{3+} has better paramagnetic properties than all the other paramagnetic elements, e.g. manganese, dysprosium, iron, and copper (4). The ionic radius of Gd^{3+} is very similar to that of Ca^{++}, making Gd^{3+} a strong inhibitor of Ca^{++} activated enzymes as well as those physiological processes that depend on Ca^{2+} (e.g. contraction of smooth, skeletal and cardiac muscle, transmission of nerve impulses, blood coagulation). Gd also inhibits the reticuloendothelial system, and $GdCl_2$ accumulates in the Kupffer cells and kills them by inhibiting their phagocytic capacity (5). A human being would not survive 0.1 mmol kg^{-1} free Gd (e.g. $GdCl_2$) injected into circulation. Because free Gd is toxic, the Gd^{3+} in the contrast agents is bound to polyaminocarboxylic acid chelating agents.

Gadolinium-based contrast media

Gd^{3+}-based contrast media are classified by the chemical structure of the ligand to which the Gd^{3+} is bound. The ligands are either linear or cyclic and may be ionic, with a charge in solution, or non-ionic. The osmolality of the contrast agents is in the range of 600–2000 mosmol kg^{-1} and all have low viscosity. Their stability depends on their kinetic, thermodynamic, and conditional stability (6). The contrast agents with cyclic ligands, in which Gd^{3+} is caged ion a pre-organized cavity, are more stable than those with linear ligands.

By September 2009, Gd-DTPA had been administered an estimated 100 million times worldwide and recently 200 million administrations were reached. Increasing numbers of patients are being scanned because of the increasing number of MRI scanners worldwide, so the use of Gd-based contrast agents continues to grow. In the year 2005 alone—the last full year before the link between Gd and nephrogenic systemic fibrosis was shown—more than 20 million Gd-based contrast-enhanced procedures were performed worldwide (7). An estimated 22–66 tons of Gd is used each year, with each enhanced examination using 1.1–1.3 g of Gd^{3+}. This is a sizable fraction of the annual total world Gd production (~400 tons) (2). There is therefore a large and continuously increasing amount of Gd^{3+} entering the environment. Gd^{3+} is present in higher amounts than other rare earth elements in densely populated areas with developed healthcare.

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Emission of gadolinium

Gd in the environment comes from a variety of different sources, with by far the greatest amount coming from radiology departments. In 2000, Kümmerer and Helmers (8) found that the annual Gd emission from Freiburg University Hospital, which offers all medical services including using Gd^{3+}-based contrast media in MRI, was between 2.1 and 4.2 kg per year, yielding a theoretical concentration of 8.5–30.1 μg L^{-1} in the hospital's effluent. The estimated annual emission by German hospitals, based on the number of MRI scanners in Germany, was in the range of 484–1160 kg. Since then, these figures will have increased. This has been documented in San Francisco Bay, where the anthropogenic Gd concentrations have increased from 8.27 to 112 pmol kg^{-1} over the past two decades (9).

Gadolinium may also come from automobile catalysts (8) and the Gd concentration decreases with increasing distance from the road. At the end of the 1990s, up to 3400 kg of Gd was emitted from this source in Germany. Some of the Gd emitted by cars may then pass with the street runoff into the sewers and may cause an increase of Gd in sewage sludge. The Gd emitted by cars will very likely have different toxicity and response to treatment processes to that from Gd-based contrast media, because different types of Gd are involved. Additives to glass are another source of gadolinium in the environment (10). Manufacturers of phosphors and of garnets for microwave application are also main users of Gd, but it seems unlikely that the Gd used for these purposes ends up at WWTPs.

Waste water treatment plants

High concentrations of Gd are detected in hospital effluents and later, in the effluent of WWTPs. This indicates that the Gd-based contrast media administered during MRI examinations go through the sewage treatment process largely unchanged because of their high stability and water solubility. Little is known about the chemical behavior of Gd contrast agents in relation to degradation and to the generation of transformation products either in the environment or during the process of water treatment.

Verplanck et al. (11) made a detailed study of the behavior of Gd through a large metropolitan WWTP in the USA and showed that Gd-based contrast media remained in the dissolved phase rather than transferring into the sludge. This behavior was not observed in so-called advanced water treatment plants that use reserve osmosis membranes which remove 99.85% of anthropogenic Gd (12).

Möller and Dulski (13,14) studied transmetallation of Gd-DTPA with other rare earth elements and with copper and yttrium in suspension experiments with clay minerals. Among the findings were an increase of rare earth elements-DTPA and a decrease in Gd-DTPA in solution, indicating that Gd had been replaced by other rare earth elements. It was estimated that about 10% of the Gd-DTPA undergoes transmetallation into rare earth elements-DTPA per year, suggesting environmental equilibrium would only be reached after 70 years.

Advanced oxidation processes are a potential additional step in the treatment of waste water which aim to decrease the input of xenobiotics (synthetic chemicals) into the environment using reactions with hydroxyl radicals. They may involve UV irradiation (15,16). The effect of sunlight, and UV radiation in particular, on Gd-based contrast agents has recently been studied. In 2013, Cyris et al. (17) measured the reaction rate constants for Gd chelates like Gd-DTPA in waste water with ozone and hydroxyl radicals. There was very little reactivity with the ozone but reactions with hydroxyl radicals took place. The contrast agents Gd-DTPA, Gd-DOTA, and Gd-BT-DO3A generally had high stability towards UV radiation. However, using hydrophilic interaction liquid chromatography with inductively coupled plasma mass spectrometry (HILIC-ICP-MS), degradation of Gd-BOPTA and the formation of Gd-containing transformation products were detected. This can be explained by the aromatic side chain of the molecule absorbing UV radiation. However, the experimentally applied UV irradiation cannot be considered to accurately simulate environmental conditions, or conditions in waste water treatment or drinking water purification (18).

It can be concluded that currently most of the Gd input entering WWTPs is not removed from the aqueous phase during sewage treatment, but in large part enters the environment, leading to a very high load of anthropogenic Gd in surface water. Measurements indicate that about 90% of the Gd input enters the environment in the sewage treatment effluent, with only 10% being removed during sewage treatment (1).

Lakes and rivers

Bau and Dulski (3) already showed in 1996 that rivers draining densely populated and industrialized areas in Central Europe and North America were characterized by pronounced positive Gd anomalies. Geologists use the term 'anomaly' to indicate a deviation from normal levels. Gadolinium is a rare earth element (REE). The concentration of REE (or the 14 lanthanide elements) in surface waters and sediments, when normalized on an element-by-element basis to one of several rock standards and plotted versus atomic number, yield curves that reveal partitioning between different sediment fractions and sources of those fractions (19). Rivers in thinly populated non-industrialized areas in Värmland

and Dalarna (central Sweden) and Hokkaido (Japan) did not show anomalies. While passing through Prague, the Gd load of the Vltava river increases from 4.5 to 19.2 nmol/m^3 because of the effluent from the central sewage treatment plant (20). The positive Gd anomaly appeared to be a potential tracer of wastewater even in rural watersheds (21). Very high levels of Gd have been found in the surface waters of Berlin, indicating anthropogenic enrichment of Gd by a factor of nearly 103 compared to the geogenic background level which arises from normal geological processes. Anthropogenic Gd increases as the rivers Havel and Spree go downstream in Berlin (20). Rare earth element patterns with distinct Gd anomalies have been reported from three Japanese river estuaries (22) and the concentrations of rare earth elements measured in water samples from the Atibaia River and its tributary Anhumas Creek in Brazil showed excess dissolved Gd (23). However, other rivers in urban areas, such as the Chao Phraya, which runs through the densely populated Bangkok Metropolitan area in Thailand, do not show anomalously high Gd concentrations (24).

In both Tokyo Bay (22) and San Francisco Bay (9), positive Gd anomalies are found. Recent data show that the waters of San Francisco Bay contain substantial positive anomalies of Gd. The maximum concentrations of Gd were observed in the southern and northern areas of San Francisco Bay and were positively correlated with nutrient (i.e. nitrate and nitrite) concentrations. Although Gd constituted up to 20% of all the rare earth elements together, it was well below the threshold of toxicological effects considered likely to harm the environment (10,25).

Tap water

Analysis of drinking water from the city of Berlin by Kulakziz et al. (2) revealed a Gd anomaly. They examined samples both from the former East Berlin and the former West Berlin. In East Berlin there was very little anthropogenic Gd but in West Berlin the tap water contained large Gd anomalies. The samples from the eastern districts show a median anomaly of 1.49 while those from the western districts yield a median anomaly of 8.92, indicating that Gd concentrations in western areas are on average one order of magnitude above geogenic levels attributable to normal geological processes. The marked difference is likely to be the result of the fact that, before the reunification of Germany in 1990, filtered lake and river water was a necessity for producing enough tap water in the isolated West Berlin, but not in East Berlin, where groundwater was used, and that this has changed little over the past 20 years. Gd in drinking water has been reported from other cities: in London, both the river Thames and tap water contain anthropogenic Gd (2) and in Prague, Gd-compounds are present in low contents in some of the drinking water (20). However, Lawrence et al. (26) found no evidence of Gd in tap water or in four separate regional water supply dams in South East Queensland, Australia.

At the concentrations found in Berlin tap water, Gd toxicity should not be a problem since a person would need to drink 100 million liters of tap water to reach the dose levels given during a single contrast medium injection for MRI. With the caveat that the effects of long-term exposure to low Gd concentrations, especially in babies, infants and pregnant women, are not known, it seems unlikely that the anthropogenic Gd levels found in Berlin tap water pose a health risk to the more than 2 million people living in the western districts of Berlin (2). However, the effects of the higher Gd concentrations likely in future years because of the increasing use of Gd-based contrast media for MRI are not known. Tap water in large cities should therefore be monitored for the presence and behavior of anthropogenic Gd, which can be done relatively quickly and cheaply (2).

Food chain

The consequences of Gd accumulation in surface waters, oceans, and even drinking water have not been evaluated because there is limited knowledge about the toxicity of the various compounds to the environment. Although the Gd concentrations observed in the contaminated rivers are probably still too low to pose a severe risk to health, nothing is yet known about the possible long-term effects. The anthropogenic Gd input limits the use of the shale-normalized Gd anomaly as a natural geochemical indicator (3).

Every year tons of Gd are released into the sea and waterways. Because ''free'' lanthanide ions are very toxic in vivo, it is very important to find out whether Gd-based contrast agents are taken up by aquatic organisms and, if so, how factors such as concentration, chemical species of the Gd complexes, and exposure time influence their transport and distribution in the organism. Another important topic is how the fields irrigated by contaminated water and the animals drinking it are affected, since these could affect the human food chain. This has been studied by Lingoot et al. (27) who found that Gd-based contrast agents may reach the human food chain both from plants growing in fields which are irrigated with contaminated surface water and from animals which drink the water.

Gonzalez et al. (25) concluded that the possibility of lanthanides in the environment having additive

effects and the expected increase in their anthropogenic emission indicate the need for experimental modeling of the expected environmental concentrations under different circumstances to get a better understanding of the possible future risks. Investigations on the bioaccumulation and biochemical effects of lanthanides would also be useful to understand their ecotoxicity better.

Conclusion

In recent decades a significant amount of anthropogenic Gd has been released into the environment as a result of the widespread use of Gd-based contrast agents for MRI. Until now the concentrations of anthropogenic Gd in surface water have been rather low (in the range of 100–1100 ng L^{-1}) and the levels of anthropogenic Gd in tap water are also currently low. However, continued increases of the input from radiology practices and hospitals are likely. At present, it is not known what risks these pose for living organisms. Since Gd-based contrast agents are highly persistent in water, a monitoring system is required to document future Gd levels. In addition, better water purification using reserve osmosis membranes is needed in wastewater treatment plants so that less Gd-based contrast agents enter the environment.

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Note

a. Water filtration by passage through the bank of a river or lake, with subsequent drawing off of the water into wells.

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