Detection of Gadolinium

Contrast Agents in Surface Water and Plants

For years an increased concentration of gadolinium has been observed in the environment. This can be traced back to its use in medicine, as gadolinium has been used for about 25 years in hospitals as a contrast agent for magnetic resonance imaging (MRI).

Toxic to Humans
In order to protect patients from the toxic effects of the free gadolinium ion, the metal is bound and administered as a highly stable, less toxic polyaminocarboxylate-chelate complex [1] Fig. 1 shows some typical Gd-based contrast agents. The toxic effect of free gadolinium is based on the fact that gadolinium is a competitor of calcium and can therefore block cellular processes in the organism [2].

Most of the administered gadolinium complex is excreted by the patient a few hours after the examination without any serious side effects [3]. Because of this, these contrast agents are considered to be harmless. However, it has been known for some time that in rare cases the intake of gadolinium-based contrast agents may cause NSF (Nephrogenic Systemic Fibrosis). NSF is a disorder with symptoms such as irreversible hardening of the skin and organs, which may be fatal [4]. This primarily applies to patients suffering from kidney damage. It is suspected that through the intake of preparations containing iron, the transmetallation process in the body is accentuated and toxic gadolinium is released. In case of renal failure, excretion of the contrast agent is delayed, so that a longer retention of the complex in the organism could lead to increased transmetallation and decomposition of the gadolinium chelate [5, 6].

Toxic to the Environment
As the gadolinium-based contrast agent is not collected in hospitals after excretion and there is no adequate purification of the waste water by the sewage treatment plants, Gd-based contrast agents can be detected in rivers and lakes, in some cases in the range of μg l\(^{-1}\). An increased concentration of gadolinium in surface water was first recorded by Bau and Dulksi in 1996 [7] and was described as a gadolinium
It can be found everywhere where gadolinium-based contrast agents are used in hospitals and clinics [8 - 14].

It is estimated that annually, 1,100 kg of gadolinium complexes are released into the environment in Germany [10,15]. In a baseline study it could be demonstrated by means of measurements in a sewage treatment plant, that only about 10 % of the contrast agent is decomposed or retained during the sewage treatment process, while the remainder enters the surface water unchanged. Little is known about the quantity of this input and the whereabouts of the contrast agent in the environment.

**Analysis**

The determination of the concentration of an element does not present a challenge to analysis; however this is not the case with the analysis of the species of bound gadolinium in the various contrast agents. Due to the very low concentrations of Gd compounds in environmental samples, mass spectroscopy with inductively coupled plasma (ICP-MS) is a suitable choice for analysis. This method is characterized by the very low detection limits (sub-ng/l), which are necessary for this investigation. The especially large linear dynamic measurement range and simple preparation of the samples as well as calibration by means of liquid standards are other convincing features. As in the plasma (5,000 - 10,000 K) of ICP-MS information about the species is completely lost due to atomization and ionization of the compounds, leaving only information about the elements, high performance liquid chromatography (HPLC) is used for the analysis of the species. Among the various HPLC methods in particular hydrophilic interaction chromatography (HILIC) has proved to be effective for these investigations due to its high separation performance. In this case, ICP-MS is used as a highly sensitive HPLC gadolinium detector. With the aid of HILIC, above all hydrophilic, polar species such as Gd-based contrast agents can be separated, for which the usual Reverse-Phase (RP-
HPLC has proved to be inadequate [17 - 19]. However, a disadvantage of HILIC with ICP-MS is the high input of organic solvents, which may cause the formation of carbon and carbon deposits due to the combustion of the solvent in ICP-MS. Because of this, in spite of a low flow rate of only 150 μl min\(^{-1}\) in HPLC, oxygen must be added as an ancillary gas in order to burn the excess carbon.

**Gd in Surface Water**

The section of the Teltow Canal near to Stahnsdorf was selected as a suitable model system for a surface water, as the waste water from Berlin is discharged into this canal and the quantities of water are well recorded. For the analysis, samples of the surface water were taken over a distance of 5 kilometers downstream of the inlet point of a sewage treatment plant in Stahnsdorf. Over this distance there are no further inflows into the canal. The sewage treatment plant accepts the waste water from several clinics, so that a high input of Gd contrast agents could be expected. This was confirmed by means of concentration measurements using ICP-MS. The Gd input at the sewage treatment plant discharge point was approx. 990 ng l\(^{-1}\) on the date of sampling. Within the first kilometer, the Gd concentration reduced rapidly and then remained constant at 99 ± 16 ng l\(^{-1}\) over the further course of 4 km. Mathematically this reduction in concentration can be explained simply by the dilution of the water from the sewage treatment plant by the water in the Teltow Canal. Figure 3 shows a typical HPLC-ICP-MS chromatogram from the surface water of the Teltow Canal. In this sample, the two contrast agents Dotarem and Gadovist (see Fig. 1) were detected.

**Bioaccumulation**

The very high concentrations of gadolinium measured in the Teltow Canal and the gadolinium-based contrast agents which were identified in this inevitably give rise to the question as to whether the contrast agent can enter the foodchain or can be taken in by plants, fish or other organisms, or possibly can even be accumulated. To investigate this question an examination using the model of cress plants (Lepidium sativum) was carried out to determine whether gadolini um-based contrast agents can be absorbed via the root system. For this, the irrigation water of the plants was dosed with various contrast agents for several days (3 and 5). Subsequently the plants were decomposed and the gadolinium concentration was determined using ICP-MS (plasma mass spectrometry). With this it could be confirmed that there is absorption of contrast agents by plants and that the root system does not block the intake. The concentrations which were found in the leaves corresponded to the concentration in the irrigation water. Interestingly, the concentration in the roots and stems of the plants was considerably lower (Factor 5 - 10). The same plants were also subjected to a gentle aqueous extraction process in which the species of
contrast agent are retained. With the aid of the HPLC-ICP-MS method described above, all of the contrast agents used could be found in the extracts. This means that the plants completely absorb the contrast agents (without metabolisation or decomposition).

Summary
These investigations of environmental samples provide a first insight, which is intended to show how easily these contrast agents can enter the food chain. However, essential questions with regard to the whereabouts, decomposition or deposition, transport and input or accumulation in the biosphere still remain unanswered. In our opinion there is a need for action and with the highly sensitive HPLC-ICP-MS we have the necessary tool to pursue these questions.

Literature

Further literature is available from the authors.

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