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Gadolinium – Evaluation of study results in biological material

Assessment Values in Biological Material – Translation of the German version from 2021

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated the background concentration of gadolinium [7440-54-2] in occupationally not exposed persons of the general population without gadolinium application for magnetic resonance imaging (MRI). Available publications are described in detail.

In total, only few publications on the background exposure to gadolinium could be found, some of which used different analytical methods and different sample matrices (urine, blood, serum). Gadolinium concentrations from background exposure were extremely low, often barely measurable and found only just above the respective detection limit. The number of samples in each study is small. All publications reported values below 300 ng/l blood/urine (many significantly below), but there are significant differences in the observed concentrations.

According to the limited number of publications determining background levels of gadolinium, the small sample sizes involved and the heterogeneous data situation, no biological reference value (BAR) was derived.

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BAR (2020)	**not established**
MAK value	–
CAS number	7440-54-2
Molar mass	157.25 g/mol (IFA 2021)
Melting point	1313 °C (IFA 2021)
Boiling point	3273 °C (IFA 2021)
Density at 25 °C	7.886 g/cm^3 (IFA 2021)

Gadolinium is a silvery-white to grey-white shining metal, belongs to the group of lanthanides and thus belongs to the rare earth metals. Seven stable isotopes are known of gadolinium: ^{152}Gd (0.20% relative abundance (ra)), ^{154}Gd (2.18% ra), ^{155}Gd (14.80% ra), ^{156}Gd (20.47% ra), ^{157}Gd (15.65% ra), ^{158}Gd (24.84% ra), ^{160}Gd (21.86% ra) (Thermo Fisher Scientific 1995). No physiological function in the human organism is known for gadolinium. Because of its paramagnetic properties, gadolinium is used in the form of gadolinium(III) compounds as a contrast agent in magnetic resonance imaging (MRI). Except for biomonitoring in the course of MRI examinations, no systematic data on background exposure in the general population have been collected so far.

1 Metabolism and Toxicokinetics

1.1 Absorption and distribution

With regard to background exposure, the literature has so far only reported on the possibility of gadolinium uptake from contaminated drinking water. However, the concentrations observed there are many times lower than after MRI examinations with contrast media containing gadolinium and are thus usually below the detection limit, i. e. they are not measurable. It is therefore unlikely that they contribute to gadolinium retention in the body (Lord et al. 2018).

1.2 Elimination

Gadolinium is excreted mainly in the urine. Corresponding elimination kinetics are available after contrast medium administration (Alwasiyah et al. 2019; Künnemeyer et al. 2009). Pharmacokinetic studies have estimated that up to 100% of an intravenously administered contrast agent containing gadolinium is excreted in the urine after about 72 hours (Staks et al. 1994).

2 Critical Toxicity

Free gadolinium ions are considered very toxic. They are incorporated mainly in the liver and the skeleton and can remain there for years (Lord et al. 2018). A risk assessment for contrast media containing gadolinium was published by the European Medicines Agency in 2017 (PRAC 2017). Since the ionic radii of calcium and gadolinium ions are almost identical, gadolinium ions are accordingly distributed in the organism in a similar way to calcium ions. As a result, gadolinium is toxic to all cell and organ systems in which calcium plays an important physiological role. Gadolinium impairs the contractility of the myocardium and inhibits the coagulation system. Intravenously injected solutions of free gadolinium ions are acutely toxic. Among other things, the smooth and striated muscles and the function of the mitochondria are affected by the toxicity of the ionic gadolinium. In contrast, gadolinium in complexed form, as it is present in the approved contrast media, has generally been considered to be well tolerated. Currently, its tolerability

is under discussion, mainly because of deposits in the brain (see Section "Contrast agents"), so that an evaluation procedure was initiated by the European Commission in 2016 (PRAC 2017).

Contrast agents

Intravenously administered gadolinium(III) compounds, such as gadopentetate dimeglumine, serve as contrast agents in magnetic resonance imaging examinations. Ion complexing agents with a high complexation constant, such as the chelates DTPA (diethylenetriaminepentaacetic acid) and DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, with gadolinium = gadoic acid) are used for this purpose. Due to the seven unpaired electrons in the f-shell, gadolinium has strong paramagnetic properties, which significantly improves imaging of magnetic structures in an MRI examination. However, gadolinium can be deposited in the brain. That is why the German Nuclear Medicine Association (BDN) advises that gadolinium should only be used as a contrast medium for absolutely necessary examinations.

Evaluation procedure according to Article 31 of Directive 2001/83/EC at the request of the European Commission

For contrast media containing gadolinium, an evaluation procedure was initiated on 18 March 2016, for which expert opinions were obtained and evaluated. On 15 December 2017, the Federal Institute for Drugs and Medical Devices implemented the corresponding implementing decision of the European Commission C (2017) 7941 of 23 November 2017 and transferred it into national legislation (BfArM 2020). The European risk assessment procedure according to Article 31 of the Directives 2001/83/EC on contrast media containing gadolinium is thus legally binding in conjunction with the opinion of the Committee for Medicinal Products for Human Use (CHMP) of 21 July 2017 (EMA/457616/2017). In summary, with this decision, the European Commission determined that the marketing authorisation for some of the intravenously administered linear contrast media was withdrawn in the EU. In addition, the field of application of the linear contrast agent gadobenic acid is to be restricted to liver imaging.

3 Exposure and Effects

Gadolinium concentrations from background exposure have been hardly ever recorded (see Section 6) and, if measurable, are extremely low and only just above the respective detection limit.

4 Selection of the Indicators

Gadolinium in urine is chosen as the indicator of background exposure.

5 Analytical Methods

For the detection of gadolinium in very low concentrations from background exposure, inductively coupled plasma mass spectrometry (ICP-MS) is available for analysis. Only at higher concentrations total reflection x-ray fluorescence (TXRF) or inductively coupled plasma optical emission spectrometry (ICP-OES) can be used (Telgmann et al. 2011, 2013). When measuring background concentrations with ICP-MS, it should be noted that all gadolinium isotopes exhibit pronounced polyatomic interferences, which can lead to falsely elevated values without appropriate corrective measures. The more abundant gadolinium isotopes are particularly strongly interfered by $[LaO]^+$ (99.67%, interference on ^{155}Gd), $[CeO]^+$ (88.27%, interference on ^{156}Gd), $[PrO]^+$ (99.76%, interference on ^{157}Gd) and $[ArSn]^+$ (24.12%)/$[NdO]^+$ (27.03%)/$[CeO]^+$ (11.04%, interference on ^{158}Gd) (Thermo Fisher Scientific 1995). Suitable measures to eliminate the interferences are, for example, temporal differentiation of the measurement of interference and gadolinium signal by means of electrothermal evaporation (ETV) as sample feed to the ICP-MS, spectral resolution of interference and

gadolinium signal by means of high-resolution ICP sector field-MS (ICP-sf-MS) or by means of collision or reaction cells (ICP-cc-MS, ICP-DRC-MS).

6 Background Exposure to Gadolinium in the General Population

Currently, there is no systematically collected reference value for gadolinium in the non-occupationally exposed general population. Therefore, the literature on background exposure to gadolinium in the general population was reviewed to examine the possibility of deriving a biological reference value (BAR). In this context, gadolinium levels in blood or urine after the administration of contrast media containing gadolinium during MRI examinations were not considered, as they cannot be regarded as background exposure.

Allain et al. (1990) used the then novel ICP-MS technology in their study. Corrective measures (see Section 5) were not yet available in 1990. Their recovery rates after addition of 5 µg gadolinium/l were 92.3% (4.63 µg/l) in plasma and 101.4% (5.07 µg/l) in urine. The authors analysed all determined lanthanides, including gadolinium, and found gadolinium levels in plasma and urine below the then achievable limit of detection (LOD) of 0.3 µg/l (Allain et al. 1990).

Buseth et al. (1998) used ETV-ICP-qMS to determine endogenous concentrations of lanthanides including gadolinium. Blood samples were taken from two collectives: (1) Americans (men ≥18 years and women (not able to give birth due to surgery or menopause) < 114 kg) and (2) Swedes (healthy men, 18 to 45 years, 66 to 90 kg). The mean value of the American collective for gadolinium was 293 ng/l, the median 162 ng/l (range 112 to 889 ng/l). The mean value in the Swedish group for gadolinium was 92 ng/l, the median 78 ng/l (range 71 to 176 ng/l).

Inagaki and Haraguchi published data on rare earths in serum after sample enrichment with a chelating resin followed by ICP-MS measurement (Inagaki and Haraguchi 2000). Serum gadolinium was determined in blood samples from five students. The recovery rate for the lanthanides was 93 ± 1.2%. In the reference material NIES-4 (target value: 46.5 ± 1.0 ng gadolinium/l), 41.0 ± 3.7 ng gadolinium/l were determined. In the serum, a mean value of 7.2 ± 1.4 ng gadolinium/l was obtained.

In 2001, Rodushkin et al. (2001) published studies on gadolinium analyses in urine and blood of 12 subjects (six males, six females, 5 to 61 years) using double-focus ICP-sf-MS. ICP-sf-MS was used to avoid spectral interference on lanthanoid isotopes. The LOD for gadolinium was 0.4 to 1.7 ng/l. The concentration ranges determined for gadolinium were < 0.6 to 1 ng/l urine, 1.3 to 10.2 ng/l whole blood and < 0.6 to 4.9 ng/l serum.

Zhu et al. (2010) examined the concentrations of gadolinium in organs of 68 deceased Chinese without documented previous diseases. In addition, whole blood from ten test persons was examined. In addition to 59 other elements, gadolinium was analysed using ICP-qMS. Table 1 shows the results of the investigations on gadolinium concentrations.

Tab. 1 Gadolinium concentrations in tissues and blood (Zhu et al. 2010)

Tissue	Gadolinium in blood [ng/l] or tissue [ng/kg]	
	Median	Range
Blood	56	8–290
Liver	456	59–2670
Lung	2240	300–15 700
Kidney	190	40–700
Heart	120	40–360
Spleen	190	60–750
Muscle	335	59–2090
Rib	2220	310–5130
Pancreas	170	80–480

Tab. 1 *(continued)*

Tissue	Gadolinium in blood [ng/l] or tissue [ng/kg]	
	Median	Range
Stomach	566	90–1450
Adipose tissue	240	120–840
Testis	150	60–260
Colon	177	110–480
Small intestine	326	120–980
Thyroid	639	88–2360
Skin	370	200–820
Thymus	645	110–915
Adrenal	380	90–1450

A working group from China published two studies in which, in addition to urine from factory workers at a cerium lanthanum oxide factory, urine from administrative employees was also examined as unexposed controls (Li et al. 2016, 2017). The mean value of the gadolinium concentrations from eight urine samples from unexposed persons (n = 8) was 12 ± 6 ng/l urine (95% confidence interval was 7 to 16 ng/l urine). In the follow-up study from 2017, in addition to 16 urine samples from exposed persons, seven urine samples from unexposed persons were examined and related to creatinine. The mean value of the urine samples from unexposed persons was determined to be 19 ng gadolinium/g creatinine, the median 16 ng/g creatinine.

Alwasiyah et al. (2019) analysed urine samples from thirteen patients receiving gadolinium-containing contrast agents for the first time before an MRI examination and the gadolinium excretion kinetics afterwards. The measurements before the MRI examination yielded a mean gadolinium concentration in the urine of 300 ± 300 ng/g creatinine.

For better comparability, Table 2 summarises the results from the above publications.

Tab. 2 Gadolinium in blood and urine of occupationally non-exposed persons

Collective	Urine		Blood	Serum/plasma	References
	[ng/l]	[ng/g creatinine]	[ng/l]	[ng/l]	
France (n = 28)	< 300		–	< 300	Allain et al. 1990
USA (n = 30)	–	–	293	–	Buseth et al. 1998
Sweden (n = 12)	–	–	92	–	
Japan (n = 5)	–	–	–	7.2 ± 1.4	Inagaki and Haraguchi 2000
Sweden (n = 12)	< 0.6–1		1.3–10.2	< 0.6–4.9	Rodushkin et al. 2001
China (n = 10)	–	–	56	–	Zhu et al. 2010
China (n = 8)	12 ± 6		–	–	Li et al. 2016
China (n = 7)		19	–	–	Li et al. 2017
USA (n = 13)		300 ± 300	–	–	Alwasiyah et al. 2019

7 Evaluation

In the studies on background exposure to gadolinium in blood and urine, the number of samples was small in each case (see Table 2). All publications reported values of less than 300 ng gadolinium/l; the values varied widely. The improved analytical methods since 2000 should be taken into account here.

Due to the heterogeneous data situation, no BAR could be derived.

However, the data listed in Table 2 can be used for guidance.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

References

Allain P, Berre S, Premel-Cabic A, Mauras Y, Delaporte T (1990) Concentrations of rare earth elements in plasma and urine of healthy subjects determined by inductively coupled plasma mass spectrometry. Clin Chem 36(11): 2011–2012. DOI: https://doi.org/10.1093/clinchem/36.11.2011b

Alwasiyah D, Murphy C, Jannetto P, Hogg M, Beuhler MC (2019) Urinary gadolinium levels after contrast-enhanced MRI in individuals with normal renal function: a pilot study. J Med Toxicol 15(2): 121–127. DOI: https://doi.org/10.1007/s13181-018-0693-1

BfArM (Federal Institute for Drugs and Medical Devices) (2020) Contrast agents containing gadolinium: deposits in the brain and other tissues. https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/EN/RV_STP/g-l/gadolinium-kernspin-neu.html, accessed 01 Jul 2021

Buseth E, Wibetoe G, Martinsen I (1998) Determination of endogenous concentrations of the lanthanides in body fluids and tissues using electrothermal vaporization inductively coupled plasma mass spectrometry. J Anal At Spectrom 13(9): 1039–1049. DOI: https://doi.org/10.1039/A801612G

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (2021) Gadolinium. GESTIS substance database. https://gestis-database.dguv.de/data?name=007640, accessed 07 Jul 2021

Inagaki K, Haraguchi H (2000) Determination of rare earth elements in human blood serum by inductively coupled plasma mass spectrometry after chelating resin preconcentration. Analyst 125(1): 191–196. DOI: https://doi.org/10.1039/a907781b

Künnemeyer J, Terborg L, Nowak S, Brauckmann C, Telgmann L, Albert A, Tokmak F, Krämer BK, Günsel A, Wiesmüller GA, Karst U (2009) Quantification and excretion kinetics of a magnetic resonance imaging contrast agent by capillary electrophoresis-mass spectrometry. Electrophoresis 30(10): 1766–1773. DOI: https://doi.org/10.1002/elps.200800831

Li Y, Yu H, Zheng S, Miao Y, Yin S, Li P, Bian Y (2016) Direct quantification of rare earth elements concentrations in urine of workers manufacturing cerium, lanthanum oxide ultrafine and nanoparticles by a developed and validated ICP-MS. Int J Environ Res Public Health. DOI: https://doi.org/10.3390/ijerph13030350

Li Y, Yu H, Li P, Bian Y (2017) Assessment the exposure level of rare earth elements in workers producing cerium, lanthanum oxide ultrafine and nanoparticles. Biol Trace Elem Res 175(2): 298–305. DOI: https://doi.org/10.1007/s12011-016-0795-z

Lord ML, McNeill FE, Gräfe JL, Noseworthy MD, Chettle DR (2018) Self-identified gadolinium toxicity: comparison of gadolinium in bone and urine to healthy gadolinium-based contrast agent exposed volunteers. Physiol Meas 39(11): 115008. DOI: https://doi.org/10.1088/1361-6579/aaedc6

PRAC (Pharmacovigilance Risk Assessment Committee) (2017) Gadolinium containing contrast agents. European Medicines Agency, Amsterdam. https://www.ema.europa.eu/en/documents/referral/gadolinium-article-31-referral-assessment-report_en.pdf, accessed 08 Jul 2021

Rodushkin I, Ödman F, Olofsson R, Burman E, Axelsson MD (2001) Multi-element analysis of body fluids by double-focusing ICP-MS. Recent Res Dev Pure Appl Chem 5: 51–66

Staks T, Schuhmann-Giampieri G, Frenzel T, Weinmann HJ, Lange L, Platzek J (1994) Pharmacokinetics, dose proportionality, and tolerability of gadobutrol after single intravenous injection in healthy volunteers. Invest Radiol 29(7): 709–715. DOI: https://doi.org/10.1097/00004424-199407000-00008

Telgmann L, Holtkamp M, Künnemeyer J, Gelhard C, Hartmann M, Klose A, Sperling M, Karst U (2011) Simple and rapid quantification of gadolinium in urine and blood plasma samples by means of total reflection X-ray fluorescence (TXRF). Metallomics 3(10): 1035–1040. DOI: https://doi.org/10.1039/c1mt00054c

Telgmann L, Sperling M, Karst U (2013) Determination of gadolinium-based MRI contrast agents in biological and environmental samples: a review. Anal Chim Acta 764: 1–16. DOI: https://doi.org/10.1016/j.aca.2012.12.007

Thermo Fisher Scientific (1995) ICP-MS Interference Table. Thermo Fisher Scientific, Waltham, MA

Zhu H, Wang N, Zhang Y, Wu Q, Chen R, Gao J, Chang P, Liu Q, Fan T, Li J, Wang J, Wang J (2010) Element contents in organs and tissues of Chinese adult men. Health Phys 98(1): 61–73. DOI: https://doi.org/10.1097/HP.0b013e3181bad921