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Announcement by the German Federal Environment Agency

Uranium and Human Biomonitoring

Opinion of the Human Biomonitoring Commission of the German Federal Environment Agency

Contents

Introduction

The importance of uranium in terms of environmental medicine has become a subject of increasing scientific and public interest. Knowledge about the exposure of humans to uranium as a basis for the assessment of possible health risks from such exposure has markedly increased in recent years owing to improved analytical methods for its detection in the context of human biomonitoring. Likewise, an improved basis has been developed for the identification of the general exposure to uranium and for the evaluation of possible environment-specific routes of chronic exposure. In accordance with its terms of reference, the Commission is therefore primarily concerned with the chemical and toxicological properties of uranium with regard to the current state of knowledge about the general exposure situation in order to identify and evaluate the background exposure in Germany.

Occurrence and properties

Uranium is a natural element of almost ubiquitous occurrence in different mineral compounds in soils and rock formations. Its proportion in the soil of 1 - 10 mg/kg, on an average approximately 3 mg/kg, exceeds those of gold, mercury and silver. High uranium concentrations may occur particularly in regions with granite rock underground. Uranium is an important natural resource and therefore subject to intensive mining. In 1989, uranium ore extraction in the Western world amounted to 34 000 tons. Up to 1990, the former German Democratic Republic was the third largest producer of uranium ore in the world. Uranium is radioactive by nature, and with an activity of 25.4 becquerels (Bq)/mg (number of decays per s and mg), it is rated as a weakly radioactive substance. Uranium consists of the three principal isotopes, ^{238}U (99.3 %), ^{235}U (0.7%) and ^{234}U (0.005%). All three isotopes are alpha emitters, with radiation from ^{238}U and ^{235}U being considerably weaker than that from ^{234}U.

Uses

As a nuclear fuel, enriched uranium is used which is obtained by increasing the rate of the isotope, ^{235}U, from 0.7 % to ca. 3 % in an enrichment process. During this isotope enrichment process, depleted uranium (DU) is obtained in which the rate of the ^{238}U isotope of 99.8 % has furthermore shifted in favour of this most abundant isotope. Due to the low proportions of ^{235}U and above all, ^{234}U, depleted uranium has no more than about 60 % of the activity of natural uranium.

Because of its material properties, above all, however, because of its markedly higher density as compared to lead, depleted uranium is used for civil and military purposes irrespective of its radioactivity. It is used as a counterweight in airplanes and racing yachts, as a shielding material for purposes of radiation protection, as an additive for catalysts and certain types of steel, and to a minor extent, also for the production of X-ray tubes and photoelectric cells. Its military uses include the armouring of vehicles and the production of anti-tank ammunition. The projectiles have a high penetration power owing to the physical properties of uranium. They are considered as conventional weapons and are used without any restriction.

Exposure of humans

Since uranium is found almost everywhere in the earth's crust in the form of more than 200 minerals, corresponding concentrations of uranium are also contained in foods of vegetal and animal origin and in groundwater, surface and drinking waters. Solubility, mobility and availability of uranium-containing compounds in abiotic and biotic systems are very complex and depend, to a high extent, on the respective uranium species present [1]. Additional contamination of arable soils is caused by the use of phosphate-containing fertilizers due to the relatively high uranium levels in phosphate ores (30 - 200 mg/kg). Such anthropogenic influence has not only resulted in a relative increase of uranium levels but also in a largely uniform distribution of the contamination of arable soils, in addition to the inhomogenous natural distribution. Concentrations of 1–15 µg/kg fresh weight have been detected in vegetables, cereal products and some fish species, thus making a noteworthy contribution to uranium ingestion [2]. Above all, however, mineral waters originating from regions with elevated levels of natural radioactivity (Erzgebirge, Vogtland, Fichtelgebirge, Upper Palatinate Forest, Bavarian Forest and Black Forest) may exhibit considerable levels of uranium, in addition to other radionuclides. Uranium concentrations detected in samples of mineral waters covered a wide range, from about 0.08 ng/L up to 40 µg/L [3]. Recent studies on uranium concentrations in mineral waters in Germany have revealed levels up to 10 µg/L [4, 5]. Therefore, regular consumption of such mineral waters may constitute the main contribution to uranium exposure. In the German Environmental Survey of 1990/92, uranium levels ranging from <0.1 to 48.4 µg/L were detected in drinking water samples collected at the waterworks which supplied the test persons with water. The mean uranium level in drinking water was 0.30 µg/L. The 95th percentile was 4.7 µg/L and the 98th percentile was 7.3 µg/L [6].

From their 3rd edition onwards, the WHO Guidelines for drinking water quality [6] have given a health-based guideline value of 15 µg/L U, while in 2003, this value had already been raised from 2 µg/L to a provisional value of 9 µg/L [7]. Irrespective of this value, the TDI (tolerable daily intake) for uranium given by WHO has remained unchanged at 0.6 µg/kg body weight and day since 1998. Only the allocation of the daily total intake in 2 L drinking water per person was raised from an initial 10 % [8, 9] to 50 % [7] and to a current share of 80 % [6]. Such relatively high allocation corresponds to the realistic view that the total oral uranium exposure of humans, if any, outside of conflict areas is predominantly determined by drinking water consumption.

For a limitation of radioactivity, the German Drinking Water Regulations 2001 [10] have only derived limit values for the total dose of tritium.

Numerous data are available on the daily uranium intake, with the majority of levels being in a range between ca. 1 and 1.5 µg uranium per day [11]. Higher intake levels of 13 – 18 µg per day have been reported from uranium mining regions [12].

The level of exposure to uranium that can be identified in the context of human biomonitoring is primarily determined by the uranium levels found in food and drinking water and thus, the oral intake of uranium-containing compounds. In contrast to this, inhalation of airborne particles containing uranium is insignificant for the general population. Typical uranium concentrations in atmospheric air in non-contaminated environments are as low as 0.04 ng/m³ on average [13]. However, in cases of occupational exposure or industrial accidents, other exposure scenarios and routes of incorporation may contribute to the uranium body burden. Thus, the distribution mechanisms governing the introduction of depleted uranium from industrial sources into the environment are different from those of uranium from natural sources. This applies to the type of the uranium species involved (as a rule, this will be metallic uranium) and also to the local and regional distribution of concentrations or the routes of incorporation. For example, when DU ammunition is used, parts of the depleted uranium are transformed into an aerosol at the moment of the impact. The major part of such aerosol undergoes immediate combustion to uranium oxides. The particles formed in this process have a diameter of less than 10 µm. As airborne particles, they may become inhaled directly or after having been whirled up again by the wind and may become deposited in the lower areas of the respiratory tract. Depleted uranium was released during the use of DU ammunition in conflict regions (in the Balkans, in the Persian Gulf) and after airplane crashes (Amsterdam, Netherlands 1992 and Stansted, Great Britain 2000) [14]. The Human Biomonitoring Commission of the Federal Environment Agency feels that special exposure scenarios have to be expected in such situations.

However, the Commission's terms of reference include above all the identification and evaluation of the exposure of the general population to environmental pollutants, which does not necessarily include specific exposure scenarios or the evaluation of an exposure to radiation that may arise from such scenarios.

Biokinetics of uranium

The systemic availability of uranium after oral intake is very low. Depending on the type and solubility of the corresponding uranium compound, only about 0.2 – 2 %, at best 6 % [15] are absorbed from the gastrointestinal tract and thus become systemically available. The rest is not absorbed and is excreted in faeces after a few days. Depending on the particle size, inhalation of uranium-containing particles may be followed by a long-term corpuscular deposition in the lung tissue without absorption, resulting in a local exposure of the lung tissue to elevated radiation doses. Thus, a number of occupational studies performed in uranium miners revealed an elevated risk of lung cancer. However, this was essentially attributed to the impact of radon decay products rather than that of the weak alpha emitter, uranium. The risks of other radiation-induced cancers, including that of leukaemia, have been rated much lower for this kind of exposure than that of lung cancer [7]. In contrast, the inhalation of uranium-containing particles is a negligible risk in persons without occupational exposure.

The distribution and elimination processes of uranium and the associated organotropy of chemical toxicity are independent of the isotope composition. Clearance of systemically available uranium is a two-phase elimination process, i.e. a major part (ca. 70 %) is excreted in urine within 24 hours, the rest with a markedly longer half-life after having undergone a variety of distribution processes [16]. Chronic intake will result in an approximate balance so that renal excretion of uranium essentially corresponds to the quantity absorbed per unit of time. The renal excretion of uranium correlates to a high degree with uranium concentrations in drinking water [17, 18], while the age of test persons has no influence. Likewise, it is of no importance over which period such water has been consumed, even if uranium levels exceeded the levels of the drinking water standard. However, after long-term elevated intake of uranium in drinking water, higher uranium levels in urine could be detected even after a period as long as 10 months after termination of the elevated exposure [18].

Orienting studies have stated the average total uranium level in the human body to be ca. 40 – 90 µg in people without any known history of exposure [12, 19, 20, 21, 22], with somewhat more than half of the uranium amount incorporated (56 %) being deposited in the skeleton. Further overall assessments have resulted in rates of 20 % in muscle tissue, 15 % in fatty tissue, 4 % in the blood and ca. 1-2 % in the lungs, liver and kidneys [23].

The ratio of the concentrations in the organs, bone, liver and kidney has been stated to be 63/3/1, which is an indication of the prominent importance of the skeleton as a long-term accumulating organ for uranium [24].

Toxicity

In biological systems, uranium is mainly present as a carbonate or hydrogen carbonate [25, 26]. pH values below 7 will cause such compounds to dissociate resulting in a release of the biologically active uranyl cation. The kidneys are considered as the most sensitive target organ for the chemical toxicity of uranium. Similar to other heavy-metal compounds, elevated uranium concentrations lead to a reduction of glomerular filtration, of tubular secretion of organic anions and reabsorption of filtered glucose and amino acids in the proximal tubules [27]. Animal studies performed in rodents found symptoms of chronic nephrotoxicity at a uranium dosage of ca. 50 – 90 µg/kg body weight and day administered via the drinking water [28]. Taking into account common safety factors, a tolerable daily intake of no more than 30 – 40 µg uranium per day and person can be calculated from such results [29]. The same opinion is held by WHO [6] with regard to the assessment of the tolerable daily intake, which has remained unchanged at a level of 0.6 µg uranium per kg body weight per day. Such assessment is also based on the studies by GILMAN et al [30].

Nephrotoxicity of uranium in humans has recently been documented in studies from Canada [31] and Finland [17] conducted to examine the relationship between uranium concentrations in drinking water, renal excretion of uranium and sensible parameters of renal affection. Both studies included above all persons whose drinking water originated from wells with different and in some cases very high uranium concentrations due to geogenic conditions.

The results of these studies have suggested that in humans, already a daily intake of low uranium doses in drinking water will presumably lead to first signs of a tubular renal damage becoming manifest as an increase of the renal excretion of lactate dehydrogenase (LDH) (at doses of a few µg/day), of glucose (at doses of ca. 20 µg/day) or of alkaline phosphatase (at doses of ca. 200 µg/day). In addition, a minor but statistically significant increase in the excretion of β_2-microglobulin (BMG) was found. The robust parameters of glomerular affection such as increased creatinine or protein excretion remained unaffected at such intake levels (2 – 780 µg/L drinking water) [31].

The Finsh study involving 325 persons exposed to uranium levels of up to 1920 µg/L drinking water confirmed such findings on principle, however, no association with BMG excretion was seen . Excretion of calcium and phosphate showed a statistically significant correlation with uranium concentrations in urine, while uranium concentrations in drinking water and the daily uranium intake correlated with calcium excretion only, however not with phosphate excretion. The function of the proximal tubules was weakly associated with uranium exposure, but without any recognizable threshold value, so that the authors assumed that even low uranium concentrations in drinking water might cause nephrotoxic effects. The changes of the tubular function have shown a closer association with uranium concentrations in urine than e.g. with daily uranium intake levels or with concentrations in drinking water. Even short-term exposure resulted in a recognizable alteration of the renal function. Presumably, such effects are not cumulative and reversible. All recognizable signs of a tubular dysfunction became manifest within the normal physiological range. Nevertheless, the uranium-induced changes should not be ignored [17].

The German MAK (maximale Arbeitsplatzkonzentration - maximum admissible concentration at the workplace) for persons exposed in their working environments is 0.25 mg per m³ air. In the US uranium industry, this value applies to poorly soluble uranium compounds while a more stringent value of 0.05 mg/m³ applies to soluble uranium compounds. This is to ensure that a uranium concentration of 3 µg/g in the kidneys is not exceeded. Based on a reassessment of the nephrotoxic potential, however, this value should rather be fixed at 0.3 µg/g than at 3 µg/g, according to recommendations by WHO [14]. Since the exposure of the kidneys cannot be identified directly, model calculations based on exposure data are performed to obtain information on the uranium concentration in renal tissue [32].

Human biomonitoring and analytical chemistry

Since 98 % of the uranium ingested by the oral route are excreted in faeces within three or four days, a recent uranium ingestion can be identified by means of detection in stool samples. If analyses are performed to identify incorporation in the more distant past, a detection of uranium by means of renal excretion is indicated. Since variation in the daily uranium excretion may be very high [13], it is particularly recommended in this case to use 24-h urine for analysis, if possible, and to perform repeat measurements, preferably on consecutive days.

Inductively coupled plasma-mass spectrometry (ICP-MS) is an efficient procedure for the detection of uranium in urine samples, which has become available recently and, in contrast to alpha spectrometry, can also be used under routine conditions [33, 34]. Presently, two different types of mass spectrometers are comercially available: quadrupole and sector-field ICP mass spectrometers. The latter have a clearly higher sensitivity than quadrupole spectrometers and allow for an approximate detection limit of 0.5 ng per L urine with the limit also being determined by the purity of the reagents used, in addition to other factors. Because such a low limit of detection can be achieved, it is possible, by means of sector-field ICP-MS, to carry out measurements in the low concentration range in persons not occupationally exposed.

Data from human biomonitoring

First data on uranium exposure of the population in Germany were obtained from extensive orienting studies in non-exposed persons. The renal excretion of uranium in about 760 people of both sexes, of different age and of different regional origin was, on average, 15 – 20 ng/day corresponding to a concentration of ca. 10 – 13 ng/L in 24-hour urine [35] (cf. Table 1). Individual daily variation of uranium excretion was found to amount to a factor of 2 or more. The reasons for this phenomenon have not yet been elucidated [35].

Corresponding studies performed in 2001 - 2003 in population groups consisting predominantly of students that included a total number of more than 1500 test persons of both sexes yielded comparable results, i.e. mean values between 6.5 and 21.0 ng/L urine and a total mean of 11.5 ng/L (cf. Table 1). Uranium concentrations detected in whole blood (WB) and blood plasma of the same population groups were 7 – 10 ng/L and 5 – 9 ng/L, respectively. These results have suggested a certain affinity (which was less pronounced than that of lead) of uranium to the corpuscular blood components [36]. Similar to other heavy metals, uranium shows a certain tendency towards accumulation that may be recognised by a possible minor age-dependent increase of uranium concentrations in urine. The mean value obtained for the daily renal excretion of uranium in persons who had had no abnormal history of exposure was ca. 15 ng in persons aged 20 years, while this level could be somewhat higher in those aged 50 years. With regard to other regional differences caused by geogenic conditions, the dependency on age plays a minor role only. No difference in the renal excretion of uranium was seen between males and females where only a low number of cases was involved [3, 37, 38], which is in line with the commonly found minor difference in excretion levels of heavy metals between males and females [36, 37].

Based on a mean daily intake of ca. 1 - 1.5 µg through food and an absorption factor of 0.02 for systemic availability after oral intake, model calculations [39, 40] have resulted in upper limits of ca. 70 ng/d being a normal range for renal excretion of uranium. The 95th percentile of renal excretion levels in population groups consisting predominantly of students was found to be between 13.1 and 62.2 ng/L [36] and corresponded to the order of magnitude of the model calculations. Above all in drinking and mineral waters, irrespective of their speciation, soluble and dissolved uranium compounds exhibit a potential nephrotoxicity for humans, which according to the Commission's opinion deserves considerable attention from the regulatory and toxicological points of view. In a technical discussion on uranium in raw water and drinking water held on 15 June 2004 with representatives of the Federal States, the Federal Environment Agency presented an assessment resulting in a tolerable daily intake of 10 µg/L of uranium in drinking water based on data obtained from animal experiments involving subchronic exposure and supported by the sparse knowledge gained so far in humans. As a corresponding threshold for measures to be taken (under the Drinking Water Regulations 2001, § 9, para 6-8, [10]) a level of 20 µg/L was stated to become valid for a regulatory period of at least 3 years. A corresponding argument has been published by KONIETZKA et al. [41].

Background level of uranium in urine: existing knowledge

Reference values for chemicals in human biological material (e. g. blood, urine) are derived from a series of measurements taken in a defined population sample and expressed as the 95th percentile following a defined statistical method [42]. Such values permit a description of the present status (so-called background exposure) in a population group without any recognizable specific exposure. If possible, the reference values are determined in a suitable reference population. At present, however, results are available only for small population groups consisting predominantly of students from the areas of Münster, Halle, Greifswald and Ulm, in addition to data collected for special reasons (see Table 1). Furthermore, these results show marked regional differences, the causes of which are not known in detail so far, so that no reference value can be derived.

Because of the relatively high number of persons included in the orienting examinations on uranium levels in urine and also due to the consistency of results obtained over three years, the Commission is of the opinion that these data represent an orienting description of the background exposure of the population to uranium, despite the reservations made above.

Based on the total of the population groups examined from 2001 to 2003 with a number of cases of n = 1518, the resulting 95th percentile was 29.0 ng/L urine. However, in some sub-populations the levels detected were higher, i.e. up to 60 ng/L (Table 1). Therefore, the Commission has recommended that a range between 30 and 60 ng uranium per litre of urine be considered as background exposure level for orientation purposes for as long as no data are available from representative population samples.

The Commission has emphasized that the orientation range had been derived by means of statistical methods and were not based on toxicological findings. Levels exceeding this orientation range may be expected to occur for example in regions rich in uranium. In the event of levels exceeding the orientation range, no recommendations can be made with regard to measures aimed at reducing exposure, not at the least because knowledge about the sources of exposure has remained poor so far.

The issue of HBM values

In the Commission's opinion, the data available for an assessment of non-occupational uranium exposure are insufficient for deriving reliable HBM values [42]. The case-control study performed by ZAMORA et at. [31] and also the epidemiological approach by KURTTIO et al. [17] have provided confirmed indications of associations to exist between the ingestion of uranium-containing drinking water and tubular dysfunction of the kidneys. Nevertheless, neither a threshold for renal involvement could be identified nor could the health-related importance of the changes in renal function observed be clearly evaluated. This is why at present, the Commission is not in a position to derive toxicologically founded HBM values for uranium.

Conclusions

The Human Biomonitoring Commission of the Federal Environment Agency is of the opinion that a determination of the renal excretion of uranium and also the monitoring of uranium concentrations in the blood of humans are of particular importance, above all because comprehensive and representative surveys on uranium exposure of the general population are not yet available at present and regional differences have been regarded as highly probable. For an interpretation and assessment of the results of examinations preformed for special reasons, the Commission has recommended a range of 30 – 60 ng/L uranium in 24-h urine as an orientation level with regard to background exposure, for the time being as no data are available from representative samples.

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Table 1: Uranium levels in urine

Authors		Localization	Type of sample	Year	Age (years)	N	Characteristic values (statistical)			
							Range (ng/L)	Mean (ng/L)	Median (ng/L)	95th percentile
Human specimen bank (Kemper et al. 2004) [36]	D	Münster (Mü)	24-h urine	2001	17 – 64	129	1.46 – 230	10.5	5.62	22.9
				2002	19 – 53	128	1.84 – 77.1	10.3	6.57	30.0
				2003	19 – 48	132	1.51 – 27.1	7.82	6.16	18.8
Human specimen bank (Kemper et al. 2004) [36]	D	Greifswald (Gr)	24-h urine	2001	19 – 36	125	0.76 – 112	6.50	4.66	13.1
				2002	19 – 43	127	1.36 – 68.7	7.01	4.79	18.6
				2003	19 – 41	124	1.14– 91.8	8.34	4.73	24.9
Human specimen bank (Kemper et al. 2004) [36]	D	Halle/Saale (Ha/S)	24-h urine	2001	14 – 61	135	2.50 – 95.7	16.6	12.1	47.3
				2002	18 – 56	129	2.70 – 329	21.0	13.1	62.2
				2003	16 – 57	123	2.40 – 169	16.3	9.87	56.8
Human specimen bank (Kemper et al. 2004) [36]	D	Ulm (U)	24-h urine	2001	19 – 42	118	2.46 – 161	14.7	10.1	31.4
				2002	20 – 43	122	2.43 – 73.2	9.54	7.41	23.2
				2003	19 – 33	120	2.44 – 41.4	9.49	7.91	22.8
Human specimen bank (Kemper et al. 2004) [36]	D	Mü; Gr; Ha/S; U	24-h urine	2001 – 2003	14 – 64	**1518**	**0.76 – 329**	**11.5**	**7.24**	**29.0**
					16 – 64	669 (m)	1.33 – 329	13.1	8.08	36.0
					14 – 60	849 (f)	0.76 – 230	10.2	6.56	24.9
Human specimen bank (Kemper et al. 2004) [36]	D	Mü; Gr; Ha/S; U	24-h urine	2001 – 2003	20 – 29	1177	0.76 – 191	10.6	6.94	25.8
						518 (m)	1.33 – 191	12.4	7.97	29.3
						659 (f)	0.76 – 112	9.15	6.10	23.1
Roth et al. (2001) [13]	D	?	24-h urine	2000	?	43	–	17.5		
Roth et al. (2004) [35]	D	?	24-h urine	?	3 - 92	682 (m)	0.1 – 74	13.1	9.0	
						78 (f)	0.6 – 61	10.5	7.0	
Galletti et al. (2003) [43]	I	?	Urine	1999	20 – 50	38	3 – 26	10		
Caddia et al. (1998) [44]	I	?	Urine	?	26 – 58	18	4 – 27	16.1	15.1	

m = male; f = female; ? = no information available