REVIEW ARTICLE

Diet Controls Uranium Intake and Aggravates Health Hazards

Authors
Silvia H, Haneklaus[1], Heike Windmann[2], Miyuki Maekawa[1], Liankai Zhang[3] and Ewald Schnug[1]

Affiliations
[1]Institute for Crop and Soil Science, Julius Kühn-Institute, Bundesallee 69, D-38116 Braunschweig, Germany
[2]Specialist Surgery for Internal Medicine, Rosentorstrasse 13, D-38640 Goslar, Germany
[3]Institute of Karst Geology (CAGS), Chinese Academy of Sciences (CAS), Guilin 541004, P.R. China

Correspondence
Silvia H, Haneklaus
Email: silvia.haneklaus@julius-kuehn.de

Abstract

Uranium (U) is ubiquitously abundant in the environment. Significant amounts of U are applied on agricultural soils with mineral phosphorus fertilizers; thus, entering the food chain. The daily intake of U with solid food varies only slightly. It is lowest with a mixed standard diet (1.3 µg/day U) and highest with a vegan diet (2.0 µg/day U). It is the U content of tap and mineral water which determines the total U intake (1.7 – 7.1 µg/day U). Next to U speciation and amount of U entering the human body, an oversupply with phosphorus, and a critical supply with calcium and iron may amplify negative health effects. Kidneys are the prime target of a high P intake and U toxicity. The additional daily phosphorus intake by food phosphates peaked to 1000 mg/day in the last 20 years. This may add on an average 1.2 µg/day U and worst case 11 µg/day U to the solid diet. Toxicological studies suggest that damages of kidneys can be expected when the U content is as low as 0.1-0.4 µg/g U. The study provides a comprehensive overview of potential health hazards caused by dietary uranium intake in relation to nutritional habits.

Keywords: Calcium (Ca), drinking water, food phosphates, iron (Fe), phosphorus (P), uranium (U)

1. Introduction

Uranium (U) and phosphorus (P) are two elements which occur together in the animate and inanimate world. Phosphate rock is the basic material for the processing of mineral P fertilizers. P is essential for all living organisms and mineral P fertilization being vital for food security on a global scale. U has been extracted from phosphate rock until the late 1990s before it became unprofitable. Nowadays, 7-22 g/ha*yr U enter the food chain by different mineral P fertilizers if applied at a rate that replaces the mean P off-take of 22 kg/ha*yr P[1]. An intake of U by natural food products is inevitable, however, the U uptake by crop plants is limited in general. U is highly mobile in agricultural soils and discharged to water bodies by run-off and leaching. The provisional guideline value for U in drinking water is 30 µg/L[2], in the U.S.A. EPA[3] set a limit value of 20 µg/L U. In Germany, for the preparation of infant food a limit value of 2 µg/L and an action value of 20 µg/L in drinking water has been adopted[4,5]. The U content of bottled mineral water worldwide has been compiled by Knolle[6]. Schnug et al.[7] calculated a mean U intake of 2.5 µg/day by solid food. With a vegan and a carnivore dietary style the corresponding values are 1 and 4 µg/day U.

U poses a radiological risk and is a heavy metal poison that concentrates in bone, principally targeting lung and kidneys[8]. The incorporation of U into bones poses in particular a radiological risk as the retention time is about 200 days[89]. In comparison, kidneys and liver have a high blood circulation so that the chemical toxicity prevails.

The dangers arising from the biochemical toxicity of U are generally considered to overweigh the risks from its radioactivity[10]. At this point it is important to note that it is the aim of this contribution to outline potential health hazards caused by the dietary intake of U. The impact of U on miners and Gulf War veterans exposed to dust or depleted U deserve separate attention; one effect of U in these humans was, however, chromosome damage[11,12].

U has three common isotopes, U-238, U-235 and U-234. With a specific activity of about 14 MBq/kg U has been considered to be a low cancer risk[13]. The weighted energy dose is called ‘equivalent dose’ to a tissue and given in Sv (Sievert). The equivalent dose takes the type of radiation (α, β, ɣ) into account. Fertilizer-derived U that shows up in drinking water would statistically increase the annually added effective dose by 7 µSv for infants and 3 µSv for adults[14]. Schmitz-Feuerhake and Bertrell[14] concluded that the radiological health risk of U entering the food chain by fertilization is only minor.

The uranyl ion exhibited anomalous genotoxic effects at low concentrations causing genomic and genetic damage in cell cultures at concentrations where there are no significant alpha emissions[15,16] and caused cancer in laboratory animals[17]. U caused anomalous inflammation in lung, kidney, brain and other living tissue in rats and produced neurological effects in mice[18]. Thiebault et al.[19] showed that U caused DNA damage and apoptosis in a concentration-dependent manner in rat kidneys. The molecular and cellular mechanisms responsible for the genotoxicity of U concentrate on vertebrates such as fish[20].

Neither the radiological, nor the chemical risk assessment of U delivered a satisfactory explanation for the occurrence of cancer. Busby and Schnug[13] suggested that the so-called photoelectric effect multiplies the radiation of U. This means that U, e.g. bound to the DNA, absorbs ɣ-radiation from the environment resulting in the emission of α- and additional β-radiation so that the total radioactivity multiplies. DNA saturated with U would absorb >55,000 times more of the surrounding ɣ-radiation than the DNA itself. The photoelectric effect has been described in radiation therapy of cancer employing gold nano-particles[21]. Further damage may result from the bystander and low dose effect (Bishop 2005, citing Busby and Schnug[13]). Radiated cells signal to neighboring cells, which did not receive direct radiation and thus enhance damages. A detailed description of these effects is provided by Busby and Schnug[13].

Not only the dietary style, but also dietary habits changed significantly during the past decades. The result is an increased serum phosphate level, which was determined twice

as often in socially weaker strata where people consumed preferably processed and convenience food products. For patients with a mild to moderate kidney insufficiency the risk of hyperphosphatemia was increased up to 2.7-fold in the lowest income group[22]. Kidneys are a target organ of high P intake; regulatory mechanisms result in the de-mineralization of bones and excretion of Ca (nephrocalcinosis)[23]. Several reviews highlight the impact of high P intake on health hazards[24,25]. The reason for an increased P intake is the use of food phosphates in processed food products. Their use is regulated in Europe in EU regulation No 231/2012 for maximum quantities of phosphates added during food processing[26]. However, it is not so much the higher U intake by processed food products as combination toxicological aspects of a concomitant over-proportional P intake that poses a yet neglected risk of health hazards[9].

2. Potential health hazards of dietary uranium intake

U is taken up with solid food and water. In surface water the U-species U(V), UO_2^+ und U(VI) can be found, which bind to complexes with sulfate, carbonate and hydroxyl-ions and phosphates. In plants U can be found as U(VI) in phosphate complexes irrespective of the U speciation in soils[27]. Thus U ingested with solid food is less soluble and will be less absorbed in the human body as for instance soluble compounds in drinking water. About 0.2% of hardly soluble U species are absorbed in the human body[28], while it is 2.0% of the diet[29]. This stresses the significance of the U intake by water as an integral part of nutritional intervention.

The prime targets of U toxicity are kidneys and bones[2]. Kidneys as the U concentration is highest during excretion and bones because they act as sinks for U. Typical, dose-dependent U-induced renal injury caused in animals are lesions in the outer stripes of the outer medulla[30,31]. The proximal convoluted tubules seem to be affected in particular[32]. Foulkes[33] stressed that it is not possible to define a general critical U-content for kidneys as reactions are compartment-specific; damages can be expected when the U content is as low as 0.1-0.4 µg/g U. The same author stressed that a NOAEL (no-observed-adverse-effect-level) should not exceed 0.3 µg/g U as the transferability of animal studies to humans is restricted. Vicente-Vicente et al.[34] classified a declining sensitivity against U toxicity in the order rabbit > rat > guinea pig > pig> mouse >dog > cat > human. Chandrajith et al.[35] associate the increasing number of chronic kidney disease (CKD) patients of uncertain aetiology with an increased exposure to U for which Schnug and Lindemann[36] (2006) surmise mineral waters as a potential source. Schnug et al.[37] showed that the number of patients suffering from chronic kidney failure from 1986-2004 in Austria, Germany and the U.S.A. increased by 5% and this rise coincided with an increasing consumption of mineral water, which multiplied the daily U intake. A daily U intake of 1 µg/g U results in a U concentration of 12 µg/g U in kidneys and saturation of DNA with U[13]. In a clinical study Banning and Benfer[38] found a weak, however, significant relationship between the U content in drinking water and the occurrence of tumors and liver diseases. The liver bears about 16% of the U loads in humans[39].

Currently, statistical data about the dose/effect relationship of dietary uranium intake and human health are not available as awareness of its significance has just started. Nevertheless, circumstantial evidence has been collected that dietary habits and style control the personal daily uranium intake and the associated health risks they pose. In addition, the daily supply with minerals, in particular P, is obviously causally linked to U toxicity in the human body.

2.1 Impact of the mineral nutritional status on U human toxicity

The significance of the P, calcium (Ca) and iron (Fe) status for potential U-related health effects have been paid little attention so far. The Ca level in the blood plasma influences U speciation. U can be found in the protein and

non-protein fraction of blood and is bound to erythrocytes[40]. This process is pH-dependent and declines steeply from pH 7 with the strongest binding capacity to pH 6 as carboxyl groups and lipoproteins dissociate less intensely. Uranyl-bicarbonate, $[UO_2(HCO_3)_4]^{2-}$ is the most stabile compound because of the low dissociation constant and is excreted from the plasma via kidneys. U is abundant in the inorganic part of the blood in a bicarbonate complex where it replaces Ca and/or Mg. In comparison, U can be found in the protein part of the blood as uranyl-albuminate. In the blood plasma the product of Ca*P is almost constant. Under conditions of hyperphosphatemia the Ca level is low and sensitivity against U high[41].

In the pH range of 5-7 UO_2^{2+}binds quickly to α-amylase and reduces its activity[42]. The same authors stress that Ca is crucial to counteract this effect. It is also the Ca level in the plasma that influences U speciation[43]. Interesting in this context is that U destroys intact α-helix structures of amylase, hemoglobin and blood serum albumin[42,44,45]. Computer simulation suggested that in a concentration dependent manner UO_2^{2+}-complexes are formed. UO_2 binds for example to PO_4, and promotes incorporation into bones. Thus it is fair to assume that a higher dietary P and U intake poses an additional health hazard compared to a low U intake and P intake that meets the physiological demand.

The cytotoxicity of U in liver cells was closely related to the extracelluar P concentration[46]. Liu et al.[47] showed that uranyl-nitrate is transformed into uranyl-phosphate in liver cells, which has been suggested to cause cytotoxicity[35]. Inorganic phosphate seems to actively influence metabolic cell processes[48]. An elevated phosphate level increased cell proliferation and Fra-1 and osteopontin genes were expressed stronger. *In vitro*, increasing phosphate levels were linked to tumor expressing genes and *in vivo* the same authors found in dependence on dietary P intake next to elevated P levels in the serum and osteopontin, a reduced Ca content and an about 50% higher number of skin papilloma.

U absorption increases proportionally with the amount of U ingested[49]. The U concentration in human hair is a direct, linear function of the U content in drinking water and indicator for U absorption by the human body[50]. U absorption may increase manifold under conditions of Fe deficiency, even, up to 50-fold if Fe^{3+-} is supplemented[51]. Both elements are absorbed by the same transporter (DTM1) and regulatory processes seem to be related to the redox behavior of U and P in such way that both a high external Fe supply and Fe deficiency may yield an increased U absorption[49].

3. Daily intake of uranium in relation to dietary style and dietary habits

Hassoun[52] developed a model in which the considerably variable food sources of human diets were assembled in affiliated categories in order to achieve a low bias from mineral intake by solid food. Her standardized mixed diet is based on an energy requirement of 2000 kcal/day[53] and follows the rules of the trophic pyramid. Hassoun[41] diversified the healthy mixed diet in three additional dietary styles: ovo-lacto vegetarian, vegan and carnivore. A standard diet supplies the smallest amount of U with solid food to the human body (1.3 µg/day U) whereas a vegan diet delivers the highest amount with 2.0 µg/day U[54]. In comparison to solid food, consumers of low and highly mineralized bottled water have the lowest (1.72 and 1.90 µg/day) and consumers of German and world bottled mineral waters the highest U intake with 6.16 and 7.08 µg/day, respectively[54]. The contribution of drinking water to the daily U intake of a tap water drinking standard diet consumer is 71.8% with a range of 56.7% for highly mineralized bottled water to 84.3% for a world bottled mineralized water consumer. The maximum reduction potential for the daily U intake through a change of water drinking and dieting habits is -67%[54]. Consumers ingest significant amounts of U with mineral and potable water while the intake by solid food is distinctly lower and shows a much smaller bandwidth[54]. The recommended upper daily P intake varies between 700 and 1250 mg[55]. In general, the P concentration of plant products is only half as

high as that of animal products[54]. The contribution of liquids to the daily P intake is negligible with <0.01% so that only a change of the dietary style may help to reduce the P intake by one third[54].

The term dietary habits reflects the consumption of natural food products versus processed and convenience foods. For the preparation of the latter food phosphates are added in varying amounts; maximum quantitative limits are defined in EU regulation No 231/2012 for the European Union[26]. For example, non-alcoholic, aromatized drinks may contain up to 700 mg/L P_2O_5 in form of phosphoric acid (E338), cheese spread 20 mg/kg and processed meat products up to 5 mg/kg P_2O_5 in form of potassium-phosphate (E340), oven-ready flour up to 20 g/kg P_2O_5 as di-magnesium-phosphate (E343). In Table 1 the descriptive statistics of 39 food phosphate samples are summarized. Variations in the total P content reflect different phosphate forms.

Table 1. Descriptive statistics of U (µg/g) in food phosphates (n=39; data extracted from Windmann[9]).

Element	Minimum	Maximum	Mean	Standard deviation
P	19780	265135	137521	68671
U	<LLD	1.90	0.257	0.379
P:U	0.08	11.03	2.031	2.100

<LLD – Lower Limit of Detection

The highest U content was 1.90 µg/g and exceeded the suggested limit value of 1.00 µg/g U[9]. Based on the data provided in Table 1 an additional dietary P intake of 1000 mg P by processed food products may add worst case up to 11 µg U to the solid diet[8]. Using the geometric instead of the arithmetic mean values which are more robust against extremes the P and U contents in the same food phosphate samples were 117,183 µg/g P and 0.14 µg/g U, respectively. This equals a daily additional U intake of 1.2 µg U[9]. These simple calculations demonstrate that potentially an excessive P intake by processed and convenience food products can be alleviated if a low-meat diet is selected.

4. Conclusions

Changes in lifestyle caused changes in the daily intake of U and P almost unnoticed as the annual consumption of mineral water and processed food has been continuously increasing during the last decades[6,56]. Phosphates are essential for the production of food and human health. And phosphates are the most significant source for the contamination of the food chain with undesired elements, especially U. Negative health effects of an increased U intake seem to be systematically amplified by an increased P intake and a reduced P intake is an integral part in chemoprevention[48]. Other mineral nutrients unfolding crosstalk with U absorption and human toxicity are Ca and Fe. Following the precautionary principle, individual health care should target on a balanced intake of minerals, especially with P, Ca and Fe and an efficient limitation of the U intake through a conscious selection of drinking water and food products.

5. References

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