Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 15 April 2020 | doi:10.4414/smw.2020.20207
Cite this as: Swiss Med Wkly. 2020;150:w20207

Uranium exposure of the Swiss population based on 24-hour urinary excretion

Jenny-Burri Judith[a], Blanc Annabelle[a], Aubert Rafael[a], Haldimann Max[a], Zürcher Ursina[a], Burnier Michel[b], Paccaud Fred[c], Bochud Murielle[c], Dudler Vincent[a]

[a] Federal Food Safety and Veterinary Office (FSVO), Risk Assessment Division, Bern, Switzerland
[b] Service of Nephrology and Hypertension, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[c] Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland

Summary

AIM OF THE STUDY: Important regional differences in uranium exposure exist because of varying uranium concentrations in soil, water and food. Comprehensive data on the exposure of the general population to uranium is, however, scarce. Based on the 24-hour urinary excretion, the uranium exposure of the adult Swiss population was assessed in relation to age, sex, place of residence, body mass index (BMI), smoking habit and type of drinking water, as well as risk factors in relation to kidney impairment and indicators of a possible renal dysfunction.

METHODS: Uranium was quantified in 24-hour urine from a nationwide population-based sample (n = 1393). The ratio $^{238}U/^{233}U$ was measured for isotope dilution calibration with a sector field inductively coupled plasma mass spectrometer (HR-ICP-MS).

RESULTS: Overall median and 95th percentile were 15 and 67 ng/24 h, respectively. The place of residence significantly influenced urinary uranium excretion. However, most of the highest urinary uranium excretion levels could not be associated to areas known for their elevated uranium concentrations in the drinking water. Sources other than the local drinking water (e.g., bottled water) might be important, too. Gender as well as albumin excretion also had a significant effect on uranium excretion. The latter was, however, strongly dependent on the presence of diabetes mellitus. No association was found for age, BMI, smoking habit or the other examined kidney related variables.

CONCLUSIONS: On the basis of uranium exposure, assessed via 24-hour urinary uranium excretion, and current knowledge of the toxicity of naturally occurring uranium, a substantial corresponding health risk for the general adult population is unlikely. However, as long as no specific sensitive biomarker for the biological impact of low-dose chronic uranium exposure has been identified and validated, assessing subtle health impact of such exposure will remain difficult.

Correspondence:
Judith Jenny-Burri, Federal Food Safety and Veterinary Office (FSVO),, Schwarzenburgstrasse 155,, CH-3003 Bern, judith.jenny-burri[at]blv.admin.ch

Keywords: *urinary uranium, excretion, Switzerland, 24-hour urine, renal dysfunction, drinking water*

Introduction

The radioactive element uranium (U) is ubiquitous and exists in the form of various compounds. It is redistributed in the environment by either natural processes or human activities. Erosion or leaching from natural deposits, as well as volcanic eruptions, can occur naturally, whereas mining and processing of uranium ores or phosphate rocks and the combustion of coal and other fuels, as well as the use of uranium containing phosphate fertilizers, are man-made [1–5]. The accumulation or mobility in soil and aqueous media depends on uranium concentration and oxidation state, as well as the properties of the environmental matrix such as pH, soil redox potential (Eh) and the presence of inorganic or organic ligands. Under oxidising conditions, the most prevalent species in nature is the uranyl ion (UO_2^{2+}) [2, 6]. The presence of naturally occurring uranium in partly very high concentrations in Swiss soils has been documented before, especially in some alpine regions [7–10].

Uptake of uranium in plants depends on the bioavailable concentration in the soil or irrigation water, as well as the plant species. Leafy vegetables and herbs show higher uranium amounts than tubers, fruits or grains [11, 12]. Two other factors, namely the time of harvesting and food preparation, influence uranium concentration in food. Firstly, uranium contents of plants are highest in early spring and decrease over the course of the season [11] and secondly, washing and peeling of vegetables can reduce the uranium content considerably [4]. Animal-based food products contribute in general less to the uranium intake than plant-based foods, as biomagnification within the food chain is considered poor [11, 13].

Because of its wide distribution, uranium is present in water, air, food and animal feed [1, 2]. For people who are not occupationally exposed, food and drinking water are the principal sources of uranium intake [1, 2, 14]. A daily dietary uranium intake through food of between 1 and 4 µg/day was estimated by the World Health Organiza-

tion (WHO) [5]. The corresponding intake estimates for Switzerland of 3.7 µg/day by Stalder et al. [9] and 1.5 µg/day by Bosshard et al. [7] fall within this range. The contribution of drinking water to the dietary uranium intake is considered low [5] or at equal to that of food [1]. However, uranium exposure from drinking water becomes important where local water sources contain elevated uranium concentrations [2, 5, 15]. The same also applies to bottled water [2, 7, 16].

Up to 80% of the tolerable daily intake (TDI) of uranium is allocated to drinking water if significant amounts of uranium are present. The corresponding provisional guideline value of 30 µg/l uranium for drinking water was derived from a TDI of 60 µg [5], based on an epidemiological study from Kurttio et al. [17]. For a naturally occurring element such as uranium, the hitherto controversial history of guideline values is unique [18].

Uranium is considered nonessential for both animals and humans, as neither biological nor physiological functions are known [2, 5]. Even though all uranium isotopes are radioactive, the chemical toxicity of uranium in food and drinking water is of greater concern than the radiotoxicity because of its low specific activity [1, 19].

After oral exposure, the major portion of ingested uranium passes via the intestine [20]. Human gastrointestinal absorption is generally low and depends on the solubility of the uranium species [2, 21]. Uptakes in a range between 1 and 2% have been suggested for adults [22–26]. However, absorption rates can go up to 6% [11, 25].

Once ingested and intestinally absorbed, uranium appears in the bloodstream and subsequently accumulates mainly in the kidney, the liver and bone. The former is the primary target organ for uranium chemical toxicity, whereas the latter represents the major long-term repository for uranium within the body [4, 19, 23]. Besides nephrotoxicity, other health outcomes such as reproductive and developmental alterations, diminished bone growth, DNA damage, neurotoxicity and oestrogenic effects are documented, though mainly from animal studies [1, 19]. Furthermore, uranium can both cross the blood-brain barrier as well as the placenta and is excreted in breast milk [4]. Despite these findings, no clear no-effect concentration could be derived from human studies as yet [5], and no specific sensitive biomarker is currently available for the characterisation of effects caused by low-dose chronic uranium exposure [1].

Significant associations between uranium exposure and cancer are still under discussion as both negative [1, 27–29] and possible positive findings are reported [30, 31]. So far, uranium has not been classified as a carcinogen for humans because of inadequate evidence [23].

Urinary elimination of incorporated uranium takes place in stages; about two-thirds are cleared within 24 hours, whereas the remainder is excreted from various tissues at different rates over several days, month or years [6, 24]. The amount of uranium absorbed from the diet can be approximated to the urinary uranium excretion on the assumptions that the contribution from inhaled uranium and from endogenous secretion of uranium into the gastrointestinal tract are negligible, and that the person is in uranium balance [24, 26]. Day-to-day fluctuation of uranium excretion can however be remarkable [32, 33]. For non-exposed subjects, a urine uranium concentration up to 60 ng/l has been suggested as a typical background burden [14].

This study aimed at assessing uranium exposure of the general Swiss adult population through measurement of 24-hour urinary uranium excretion.

Materials and methods

Urine sample collection and interview

A 24-hour urinary collection and an interview were conducted between 2010 and 2011 in 11 centres from nine cantons (Basel, Fribourg, Geneva, Lucerne, St Gallen, Ticino, Valais, Vaud and Zurich) as part of the nationwide salt intake survey. The collective covered the three main linguistic regions (German, French and Italian) and was balanced for gender and age (15–91 years of age). All regional ethics committees approved the study and all participants gave written consent before sampling. Further information on sample collection is given by Chappuis et al. [34].

Urinary albumin, calcium, sodium, potassium, urea and creatinine, as well as serum creatinine were analysed by the Laboratoire de Chimie Clinique of the Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne, Switzerland). The types of assays were immunoturbidimetry (albumin), O-Cresolphtalein (calcium), indirect potentiometry ISE (sodium, potassium), urease-GLDH (urea), and Jaffé kinetic compensated method (creatinine) from Roche Diagnostics (Rotkreuz, Switzerland) [34].

Frozen urine aliquots of 40 ml were brought to the laboratory of the Federal Food Safety and Veterinary Office and stored at −20°C until uranium analysis.

During the interview, participants were asked, among other things, about the type of water consumed. For the first question “What kind of water do you drink?” a choice of six responses was given: (1) exclusively tap water, (2) mainly tap water, (3) exclusively water from bottles, (4) mainly water from bottles, (5) sometimes one, sometimes the other and (6) I do not drink water.

For the second question, “Usually, before taking water from the tap (to prepare coffee or tea…) do you let water flow for some seconds or minutes?” a choice of yes or no was given [34].

Reagents and standards

A ^{233}U spike solution at a concentration of 980 ng/l in 1% HNO_3 Suprapure (Merck, Darmstadt, Germany) was prepared daily from an enriched certified isotope reference material (activity concentration of 36.0 ± 0.5 kBq/g corresponding to 100.9 ± 1.5 mg/kg in HNO_3 6%, CERCA Framatome, Laboratoire Etalons d’Activité, Pierrelatte Cedex, France).

Two aqueous uranium solutions at concentrations of 10 and 1.0 ng/l in 1% HNO_3 (from a stock solution of 10.07 mg/l, Certipur Merck) as well as certified urine (NIST-2670a Urine Low Level, NIST Gaithersburg, MD, USA) and two selected urine samples were used for method validation and quality assurance (trending).

High-purity water (18.3 MΩ cm, ELGA LabWater, Marlow, UK) was used for all dilutions.

Sample preparation

Urine samples were thawed overnight at 4°C, equilibrated for 2 hours to ambient temperature, and homogenised before pipetting. Aliquots of 0.3 ml of each sample were frozen again at −20°C. For final dilution, the aliquots were thawed and equilibrated to ambient temperature for 1 hour. Lastly, 0.1 ml of ^{233}U spike solution and 2.7 ml HNO_3 1% were added to a final volume of 3.1 ml. Preparation of reference and quality control samples was similar.

The samples were then either measured directly or stored at 4°C until analysis within 3 days. Exceptionally, the final solutions were frozen at −20°C until the day of analysis. All freezing and cooling cycles were checked beforehand for sample stability.

Analysis

Isotope dilution was the calibration method of choice. The ratio $^{238}U/^{233}U$ was measured after the addition of a defined amount of ^{233}U to each sample. With the simplified formula for non-natural tracer isotopes, according to Adriaens et al. [35], uranium urine contents were calculated.

The two isotopes were analysed by means of a sector field inductively coupled plasma mass spectrometer (HR-ICP-MS) (Element 2, Finnigan-MAT, Bremen, Germany). A Cinnabar cyclonic spray-chamber, a SeaSpray nebuliser (both from Glass Expansion, West Melbourne, VIC, Australia) and an autosampler (ASX-260 from CETAC, Omaha, NE, USA) completed the setting.

Accuracy of the analysis method was verified beforehand with independent measurements of the NIST-2670a standard with the certified value of 102.0 ± 2.3 ng/l. Method performance over all measurement series (trending) resulted in mean concentrations ± standard deviation (SD) of 105 ± 3 ng/l (n = 28) for the same certified NIST-2670a, 469 ± 52 ng/l (n = 29) for a high-level real urine sample and 10 ± 1 ng/l (n = 30) for a uranium standard solution. The corresponding RSD for between-run precisions were at 2.9% for the NIST standard, 11.1% for the high-level urine and 7.4% for the uranium standard solution. With the analysis of 1% HNO_3 as blank solution, a limit of detection (LOD, mean + 3 SD) of 5 ng/l was calculated for the undiluted urine samples.

Statistical analysis

Systat (version 13.00.05, Systat Software Inc., San Jose, CA, USA) was the software used for statistical evaluation.

Samples were excluded from statistical analysis if they were replicates, incomplete according to Reinivuo et al. [36], or with missing information. For samples below the LOD, LOD/2 was used for the calculations.

A total of 1393 samples remained with complete data. Uranium concentration was normalised for 24-hour excretion by means of the 24-hour urine volume. Within the results section, median excretions were compared as data did not follow a normal distribution. For the same reason, data were naturally log-transformed prior to the multivariate analysis by means of a general linear model (GLM). Independent explanatory variables for the GLM model were chosen according to different criteria. Participant characteristics were complemented with known risk factors for kidney impairment as well as indicators of a possible renal dysfunction [6, 37–39]. A two-sided p-value <0.05 was considered significant for all statistical tests.

Results

From the 1393 participants, 1009 (72%) had a urine uranium concentration above the LOD of 5 ng/l and up to 459 ng/l, 384 samples were below LOD. The 24-hour urine volume ranged between 321 and 7500 ml with a median of 1881 ml.

Urinary uranium excretion depicted a positively skewed distribution with an excretion median of 15 ng/24 h and the corresponding 25th, 75th and 95th percentiles of 7, 31 and 67 ng/24 h. A compilation of the uranium excretion medians of different subgroups is shown in table 1. The most marked range in uranium excretion was found among the cantons of sampling, with the highest values for Valais and Geneva. The overall median urinary uranium concentration was 8 ng/l. When the suggested background burden by UBA [14] was taken into account, n = 36 or 2.6% of the participants from the current collective showed a uranium concentration >60 ng/l.

By means of GLM analysis, association between independent explanatory variables and naturally log-transformed urinary uranium excretion, the response variable, were studied. An overview of all variables is given in table 2. A squared multiple correlation (R^2) of 0.541 defined the overall fit of the resulting model. The model residuals followed normal distribution as verified through a Shapiro-Francia test (data not shown).

The output comprised statistically significant p-values for the variables place of residence (p <0.0001), gender (p = 0.024), naturally log-transformed urinary albumin excretion (p = 0.013) as well as the type of water consumed (p = 0.001; tap water, water from bottles, both).

For participants with an exclusive tap water consumption, the median uranium excretion was 11 ng/2 4 h. The highest median uranium excretion of 18 ng/24 h was found within the group of participants with an exclusive consumption of bottled water.

No significant association was detected in relation to any other explanatory variables within the GLM model (table 2). However, the variables naturally log-transformed urinary calcium excretion, naturally log-transformed urinary creatinine excretion, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and BMI showed p-values oscillating around the significance level in dependence of the selection of explanatory variables.

Exclusion of the highest uranium value of 591 ng/24 h did not have any influence on the overall results or on the conclusions of this work. The second highest uranium excretion was 1.6 times lower at 364 ng/24 h.

Discussion

The assessment of low level uranium exposure is important as population-based studies including mostly non-occupationally exposed participants are still scarce. This is to our knowledge the first study analysing uranium in 1393 24-hour urine samples on a nationwide level, stratified for gender and age.

A relevant health risk, attributable to uranium exposure, is assumed unlikely for the general Swiss adult population. Even for participants with uranium excretion values above the 95th percentile, a health impact is still rather improbable as only mild effects from subclinical toxicity were observed in other international studies with considerably higher urinary uranium excretions [17, 29].

Increased urinary uranium values from individual study participants were expected beforehand as some Swiss uranium "problem" areas, explained by elevated uranium concentrations in the drinking water, have already been described [9, 10].

The highest uranium excretion values among the cantons of sampling were found in Valais, followed by Geneva.

Table 1: Urinary uranium levels (24-hour sampling) of subgroups of the collective under study.

	All				Men			Women		
	n	Median (ng/l)	Median (ng/24 h)	Range (ng/24 h)	n	Median (ng/l)	Median (ng/24 h)	n	Median (ng/l)	Median (ng/24 h)
Whole collective	1393	8	15	1–591	688	9	15	705	8	14
Canton of sampling										
Basel	185	8	17	2–164	92	9	15	93	8	18
Fribourg	84	4	7	2–255	36	4	9	48	4	7
Geneva	113	16	29	4–145	56	16	29	57	15	28
Lucerne	182	9	14	2–181	89	10	18	93	8	13
St Gallen	154	8	17	3–278	67	7	11	87	8	20
Ticino	158	8	10	2–132	82	9	12	76	7	9
Valais	97	23	39	6–591	50	25	41	47	22	34
Vaud	164	9	14	1–364	83	9	16	81	8	13
Zurich	256	5	9	2–132	133	5	10	123	5	8
Age strata from recruitment (years)										
15–29	332	9	14	1–591	156	11	18	176	8	12
30–44	320	8	17	2–134	143	9	18	177	8	14
45–59	340	8	14	2–364	174	9	14	166	7	15
≥60	401	8	14	2–256	215	8	13	186	9	16
BMI*										
<18.5 (underweight)	44	6	11	3–145	12	16	20	32	6	8
18.5–24.9 (normal range)	694	8	14	1–244	291	9	14	403	8	14
25.0–29.9 (preobese)	456	8	15	2–591	270	9	14	186	7	15
≥30 (obese)	199	11	19	2–255	115	10	17	84	11	21
Smoking habit										
Smokers	246	9	16	2–214	131	10	17	115	9	15
Ex-smokers	380	8	17	2–364	215	9	17	165	7	17
Never-smokers	767	8	14	1–591	342	8	14	425	8	14
Diabetes mellitus therapy (self-reported)										
Yes	44	9	13	3–255	31	11	15	13	5	10
No	1349	8	15	1–591	657	9	15	692	8	15
Hypertension (average blood pressure ≥140/90 mm Hg or on treatment)										
Yes	351	8	14	2–256	223	8	13	128	8	15
No	1042	8	15	1–591	465	9	17	577	8	14
Use of nonsteroidal anti-inflammatory drugs (NSAIDs)										
Yes	66	8	16	2–256	30	8	16	36	7	16
No	1327	8	15	1–591	658	9	15	669	8	14
Type of water consumed										
Exclusively tap water	271	6	11	1–189	120	6	10	151	6	14
Mainly tap water	486	8	14	2–591	224	9	16	262	7	14
Exclusively water from bottles	82	10	18	3–255	52	13	20	30	9	18
Mainly water from bottles	182	10	17	2–278	119	9	15	63	11	18
Sometimes one, sometimes the other†	372	9	17	2–244	173	12	18	199	8	15
Running tap water before consumption										
Yes	973	8	15	1–364	489	9	16	484	8	14
No	420	9	15	2–591	199	9	14	221	8	15

* Body mass index (BMI), classification according to the WHO † Including 11 participants who responded with "I do not drink water"

This order is reflected in the uranium concentrations in drinking water measured by Stalder et al. [9].

On the individual level, the compilation of the places of residence of participants with a uranium excretion above the 95th percentile (n = 70) and uranium hot spots from the above mentioned drinking water study did reveal that 70% of these participants live not in such an area, but rather in other communes all over the country. The other 30% do live in the canton of Valais, including 13 participants who live in the uranium hot spot cities Martigny or Sion. Further analysis of all participants living in one of those two cities (n = 28) shows that the range of their urinary uranium excretion is very broad, from below LOD to the maximum value of this study. Hence, based on the place of residence, no prediction can be made about the individual uranium exposure of a person.

Consumed water, likely representing the major source of uranium for the non-occupationally exposed individuals, can either be tap or bottled water [14, 39, 40]. Higher uranium concentrations in bottled water than in tap water have already been detected in Switzerland [2, 7], as well as in the neighbouring countries France [41] and Germany [16]. The observed association of 24-hour urinary uranium excretion with the type of water consumed highlights the importance of bottled water as a uranium source in Switzerland (table 2).

Whether or not the tap water was rinsed prior to consumption had no effect on urinary uranium excretion, as the uranium comes from the water itself and is not a component of water pipes.

Spot urines are usually preferred for population-based studies because of the cumbersome sampling of 24-hour urine. However, for the assessment of excreted elements, 24-hour urine is most appropriate as further adjustments by creatinine excretion or the like are unnecessary. Such corrections are sensitive to bias, especially in population-wide collectives, due to demographic differences [42–44]. The willingness of people to participate and to collect a 24-hour urine sample was at the same time the biggest challenge and limitation of this study. Young people in particular were very difficult to recruit. Replicates of urine collections would have been a further gain of information; this was however not part of the current study.

Comparability with population-based studies from other countries is, apart from the use of spot urines, further limited by number. A median of 4.9 ng/l or 4.6 ng/g creatinine was reported in France (n = 1991, 18–74 years of

Table 2: Independent explanatory variables of the general linear model (GLM) influencing the response variable naturally log-transformed uranium excretion in urine (µg/24 h).

GLM model predictors		Estimates of effects (β_i)	Analysis of variance (ANOVA)		
			d.f.	F-ratio	p-value
Place of residence		Range −2.069 to 2.974	534	1.761	0.000
Gender			1	5.113	0.024
	Male	0			
	Female	0.093			
Age		−0.002	1	1.029	0.311
BMI		0.010	1	1.582	0.209
Smoking habit			2	0.174	0.840
	Never-smokers	0			
	Ex-smokers	0.000			
	Smokers	0.023			
Diabetes mellitus therapy (self-reported)			1	0.062	0.804
	No	0			
	Yes	−0.021			
Hypertension (average blood pressure ≥ 140/90 mm Hg or on treatment)			1	0.014	0.906
	No	0			
	Yes	−0.005			
Use of nonsteroidal anti-inflammatory drugs (NSAID)			1	3.097	0.079
	No	0			
	Yes	0.114			
(ln) Creatinine excretion (mmol/24 h)		0.271	1	2.102	0.147
(ln) Albumin excretion (mg/24 h)		0.080	1	6.189	0.013
(ln) Calcium excretion (mmol/24 h)		0.091	1	3.310	0.069
(ln) Sodium excretion (mmol/24 h)		−0.010	1	0.013	0.908
(ln) Potassium excretion (mmol/24 h)		−0.137	1	1.690	0.194
(ln) Urea excretion (mmol/24 h)		0.098	1	0.456	0.500
Type of water consumed			4	4.501	0.001
	Exclusively tap water	−0.260			
	Mainly tap water	0			
	Exclusively water from bottles	0.182			
	Mainly water from bottles	0.087			
	Sometimes one, sometimes the other*	0.030			
Running tap water before consumption			1	0.714	0.398
	Yes	0			
	No	0.027			

* Including 11 participants who responded with “I do not drink water”

age, ENNS, survey years 2006–2007) [41]. The Centers for Disease Control and Prevention (CDC) reported a urinary uranium concentration median of 5 ng/l for the US population (n = 1715, 20 years of age and older, NHANES, survey years 2011–2012). The same median was found in the subsequent survey from 2013–2014 (n = 1811) [45]. In Canada, median urinary uranium concentrations of both survey cycles 1 and 2 were below the respective LOD of 9 ng/l (n = 3474, 20–79 years of age, survey years 2007–2009) and 10 ng/l (n = 3635, 20–79 years of age, survey years 2009–2011) [46, 47]. A further study was carried out in Finland (n = 951, 18–66 years of age, overnight urine samples), where 73% of the collective showed a uranium concentration below the LOD of 10 ng/l [15]. In Germany, samples from a student collective aged between 20 and 29 years are collected annually for the Federal Environmental Specimen Bank. For the 24-hour urine, an overall uranium median of 6.1 ng/l was obtained for the survey years 2001–2009 (n = 3840), as well as 5.9 ng/l for the survey year 2011 (n = 424) [48].

Different explanatory variables were evaluated for the statistical GLM model. The estimated glomerular filtration rate (eGFR), which represents an overall index of kidney function [49, 50] was not considered as a model variable in order to prevent the reduction of the collective size by the participants who refused a blood withdrawal. The exclusion of the eGFR as an independent explanatory variable did, however, not alter the output of the GLM model and the variable itself was not statistically significant (data not shown).

The difference in urinary uranium excretion between men and women was small but statistically significant within the GLM model (p = 0.024). No difference in urinary uranium excretion between genders was found in several other studies [41, 51–53]. Higher levels in men than women were observed in Germany at each repetition of the human biomonitoring studies (Humanprobenbank) [48], but only for the 24-hour urine samples. No gender difference was detected when whole blood or plasma samples of the same collectives were analysed. On the contrary, Berglund et al. [54] reported higher uranium excretion in women than in men in a rural population from Bangladesh.

Urinary uranium excretion was not associated with age in the present study. Other authors have reported mixed findings on the influence of age on uranium excretion. While some studies reported a positive association [33, 41], others were in line with our results [52, 53].

The smoking habit of the participants did not significantly affect the uranium excretion of the current study. In literature, a difference between smokers and non-smokers was both confirmed [41, 55] and not found [56].

Finally, a significant relation between uranium excretion and albumin excretion was revealed. Data analysis by means of a two-sample t-test on naturally log-transformed uranium excretion between participants with normal and elevated albuminuria did not, however, allow a better understanding of this relation (p = 0.949) (elevated albumin excretion ≥30 mg/24 h [57], n = 70). Furthermore, as an increased albumin excretion could also be caused by diabetic nephropathy [58], the GLM model was recalculated after exclusion of all participants with ongoing diabetes mellitus therapy (n = 44). The overall result of the GLM model remained thereby unchanged, but the p-value of the albumin excretion was now only marginally significant (p = 0.045). Hence, diabetes mellitus seems to affect albumin excretion to a greater extent than uranium exposure.

Findings reported in previous studies on correlations between uranium exposure and albuminuria or other kidney function parameters are inconsistent [17, 37, 39, 56, 59].

In conclusion, based on the measured data, a substantial health risk attributable to uranium exposure is, at the current knowledge, unlikely for the general adult population, despite the presence of naturally occurring uranium in Swiss soils and water. Nonetheless, the assessment of possible health impacts through uranium such as renal dysfunction remains difficult, as the current biomarkers are not specific for the effects caused by chronic uranium exposure. Future advancement in analytics might discover specific biomarkers with the potential to reveal underlying yet unknown mechanisms on chronic low-dose uranium contamination. Appropriate measures will be necessary if they prove to be harmful to health.

Acknowledgements

The authors express their sincere gratitude to the Swiss Survey on Salt Group, namely E Battegay, I Binet, A Chappuis, D Conen, P Erne, L Gabutti, A Gallino, N Glatz, P Greminger, I Guessous, D Hayoz, P Meier, F Muggli, A Péchère-Bertschi, PM Suter and A von Eckardstein, for their key participation in data collection.

Financial disclosure

The Swiss Survey on Salt study (SSS) was funded by the Swiss Federal Office of Public Health and was institutionally supported by the CHUV. An additional contribution has been received from the Swiss Society of Hypertension.

Potential competing interests

The authors declare they have no actual or potential conflict of interest relevant to this article.

References

1 ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological profile for Uranium. U.S. Department of Health and Human Services, Division of Toxicology and Human Health Sciences, Atlanta, GA. 2013. [Cited 2019 July 22.] Available from: https://www.atsdr.cdc.gov/toxprofiles/TP.asp?id=440&tid=77

2 EFSA (European Food Safety Authority). Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from German Federal Institute for Risk Assessment (BfR) on uranium in foodstuffs, in particular mineral water. EFSA J. 2009;1018:1–59. [Cited 2019 July 22.] Available from: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2009.1018

3 Bigalke M, Ulrich A, Rehmus A, Keller A. Accumulation of cadmium and uranium in arable soils in Switzerland. Environ Pollut. 2017;221:85–93. doi: http://dx.doi.org/10.1016/j.envpol.2016.11.035. PubMed.

4 Keith LS, Faroon OM, Fowler BA. Uranium. In: Nordberg GF, Fowler BA, Nordberg M, Friberg LT, editors. Handbook on the Toxicology of Metals. 3rd ed. Cambridge, MA: Academic Press; 2007. Chapter 45. p. 881–903. https://www.elsevier.com/books/handbook-on-the-toxicology-of-metals/nordberg/978-0-12-369413-3

5 WHO. (World Health Organization). Uranium in drinking-water, Background document for development of WHO guidelines for drinking-water quality. 2012. [Cited 2019 July 22.] Available from: https://www.who.int/water_sanitation_health/water-quality/guidelines/chemicals/background_uranium.pdf?ua=1.

6 Taylor DM, Taylor SK. Environmental uranium and human health. Rev Environ Health. 1997;12(3):147–57. doi: http://dx.doi.org/10.1515/REVEH.1997.12.3.147. PubMed.

7 Bosshard E, Zimmerli B, Schlatter C. Uranium in the diet: Risk assessment of its nephro- and radiotoxicity. Chemosphere. 1992;24(3):309–22. doi: http://dx.doi.org/10.1016/0045-6535(92)90299-7.

8 Regenspurg S, Margot-Roquier C, Harfouche M, Froidevaux P, Steinmann P, Junier P, et al. Speciation of naturally-accumulated uranium in

an organic-rich soil of an alpine region (Switzerland). Geochim Cosmochim Acta. 2010;74(7):2082–98. doi: http://dx.doi.org/10.1016/j.gca.2010.01.007.
9 Stalder E, Blanc A, Haldimann M, Dudler V. Occurrence of uranium in Swiss drinking water. Chemosphere. 2012;86(6):672–9. doi: http://dx.doi.org/10.1016/j.chemosphere.2011.11.022. PubMed.
10 Surbeck H, Deflorin O, Kloos O. Spatial and temporal variations in the uranium series background in Alpine groundwaters. In: Merkel BJ, Hasche-Berger A, editors. Uranium in the Environment. Berlin Heidelberg, Springer: 2006; p. 831–9. doi: http://dx.doi.org/10.1007/3-540-28367-6_86.
11 Anke M, Seeber O, Müller R, Schäfer U, Zerull J. Uranium transfer in the food chain from soil to plants, animals and man. Chemie der Erde Geochemistry. 2009;69:75–90. doi: http://dx.doi.org/10.1016/j.chemer.2007.12.001.
12 Hakonson-Hayes AC, Fresquez PR, Whicker FW. Assessing potential risks from exposure to natural uranium in well water. J Environ Radioact. 2002;59(1):29–40. doi: http://dx.doi.org/10.1016/S0265-931X(01)00034-0. PubMed.
13 Driver CJ. Ecotoxicity literature review of selected Hanford site contaminants. PNL-9394. Pacific Northwest Lab, Richland, WA, USA. 1994. [Cited 2019 July 22.] https://inis.iaea.org/search/search.aspx?orig_q=RN:25054928.
14 UBA (Umweltbundesamt). Uran und Human-Biomonitoring, Stellungnahme der Kommission Human-Biomonitoring des Umweltbundesamtes. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz. 2005;48:822–7. [Cited 2019 July 22.] Available from: https://www.umweltbundesamt.de/sites/default/files/medien/377/dokumente/uran.pdf
15 Muikku M, Puhakainen M, Heikkinen T, Ilus T. The mean concentration of uranium in drinking water, urine, and hair of the occupationally unexposed Finnish working population. Health Phys. 2009;96(6):646–54. doi: http://dx.doi.org/10.1097/01.HP.0000345026.98668.c4. PubMed.
16 Schnug E, Steckel H, Haneklaus S. Contribution of uranium in drinking waters to the daily uranium intake of humans - a case study from Northern Germany. Landbauforsch Völkenrode. 2005;55(4):227–36. Available at: https://literatur.thuenen.de/digbib_extern/bitv/zi038683.pdf. [last access 22 July 2019].
17 Kurttio P, Harmoinen A, Saha H, Salonen L, Karpas Z, Komulainen H, et al. Kidney toxicity of ingested uranium from drinking water. Am J Kidney Dis. 2006;47(6):972–82. doi: http://dx.doi.org/10.1053/j.ajkd.2006.03.002. PubMed.
18 Ansoborlo E, Lebaron-Jacobs L, Prat O. Uranium in drinking-water: a unique case of guideline value increases and discrepancies between chemical and radiochemical guidelines. Environ Int. 2015;77:1–4. doi: http://dx.doi.org/10.1016/j.envint.2014.12.011. PubMed.
19 Brugge D, Buchner V. Health effects of uranium: new research findings. Rev Environ Health. 2011;26(4):231–49. doi: http://dx.doi.org/10.1515/REVEH.2011.032. PubMed.
20 Spencer H, Osis D, Fisenne IM, Perry PM, Harley NH. Measured intake and excretion patterns of naturally occurring 234U, 238U, and calcium in humans. Radiat Res. 1990;124(1):90–5. doi: http://dx.doi.org/10.2307/3577700. PubMed.
21 Prat O, Vercouter T, Ansoborlo E, Fichet P, Perret P, Kurttio P, et al. Uranium speciation in drinking water from drilled wells in southern Finland and its potential links to health effects. Environ Sci Technol. 2009;43(10):3941–6. doi: http://dx.doi.org/10.1021/es803658e. PubMed.
22 Chen J, Lariviere D, Timmins R, Verdecchia K. Estimation of uranium GI absorption fractions for children and adults. Radiat Prot Dosimetry. 2011;144(1-4):379–83. doi: http://dx.doi.org/10.1093/rpd/ncq436. PubMed.
23 IARC (International Agency for Research on Cancer). Ionizing radiation, Part 2, some internally deposited radionuclides. IARC monographs on the evaluation of carcinogenic risks to humans, Lyon, France. 2001;Vol. 78. [Cited 2019 July 22.] Available from: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-43/.
24 Leggett RW, Harrison JD. Fractional absorption of ingested uranium in humans. Health Phys. 1995;68(4):484–98. doi: http://dx.doi.org/10.1097/00004032-199504000-00005. PubMed.
25 Limson Zamora M, Zielinski JM, Meyerhof D, Moodie G, Falcomer R, Tracy B. Uranium gastrointestinal absorption: the f1 factor in humans. Radiat Prot Dosimetry. 2003;105(1-4):55–60. doi: http://dx.doi.org/10.1093/oxfordjournals.rpd.a006301. PubMed.
26 Wrenn ME, Durbin PW, Howard B, Lipsztein J, Rundo J, Still ET, et al. Metabolism of ingested U and Ra. Health Phys. 1985;48(5):601–33. doi: http://dx.doi.org/10.1097/00004032-198505000-00004. PubMed.
27 Auvinen A, Kurttio P, Pekkanen J, Pukkala E, Ilus T, Salonen L. Uranium and other natural radionuclides in drinking water and risk of leukemia: a case-cohort study in Finland. Cancer Causes Control. 2002;13(9):825–9. doi: http://dx.doi.org/10.1023/A:1020647704999. PubMed.
28 Auvinen A, Salonen L, Pekkanen J, Pukkala E, Ilus T, Kurttio P. Radon and other natural radionuclides in drinking water and risk of stomach cancer: a case-cohort study in Finland. Int J Cancer. 2005;114(1):109–13. doi: http://dx.doi.org/10.1002/ijc.20680. PubMed.
29 Zamora ML, Zielinski JM, Moodie GB, Falcomer RAF, Hunt WC, Capello K. Uranium in drinking water: renal effects of long-term ingestion by an aboriginal community. Arch Environ Occup Health. 2009;64(4):228–41. doi: http://dx.doi.org/10.1080/19338240903241267. PubMed.
30 Radespiel-Tröger M, Meyer M. Association between drinking water uranium content and cancer risk in Bavaria, Germany. Int Arch Occup Environ Health. 2013;86(7):767–76. doi: http://dx.doi.org/10.1007/s00420-012-0806-0. PubMed.
31 Wagner SE, Burch JB, Bottai M, Puett R, Porter D, Bolick-Aldrich S, et al. Groundwater uranium and cancer incidence in South Carolina. Cancer Causes Control. 2011;22(1):41–50. doi: http://dx.doi.org/10.1007/s10552-010-9669-4. PubMed.
32 Wang YX, Pan A, Feng W, Liu C, Huang LL, Ai SH, et al. Variability and exposure classification of urinary levels of non-essential metals aluminum, antimony, barium, thallium, tungsten and uranium in healthy adult men. J Expo Sci Environ Epidemiol. 2019;29(3):424–34. doi: http://dx.doi.org/10.1038/s41370-017-0002-0. PubMed.
33 Werner E, Roth P, Wendler I, Schramel P. Renal thorium and uranium excretion in non-exposed subjects: influence of age and gender. In: Proceedings of the IRPA regional symposium on radiation protection in neighbouring countries of Central Europe. Prague, Czech Republic. 1998;Session 3:325-7. [Cited 2019 July 22.] Available from: https://inis.iaea.org/collection/NCLCollectionStore/_Public/30/031/30031550.pdf?r=1&r=1
34 Chappuis A, Bochud M, Glatz N, Vuistiner P, Paccaud F, Burnier M. Swiss survey on salt intake: Main results. Service de Néphrologie et Institut Universitaire de Médecine Sociale et Préventive. 2011;1–32. [Cited 2019 July 22.] Available from: https://serval.unil.ch/resource/serval:BIB_16AEF897B618.P001/REF
35 Adriaens AG, Kelly WR, Adams FC. Propagation of uncertainties in isotope dilution mass spectrometry using pulse counting detection. Anal Chem. 1993;65(5):660–3. doi: http://dx.doi.org/10.1021/ac00053a031.
36 Reinivuo H, Valsta LM, Laatikainen T, Tuomilehto J, Pietinen P. Sodium in the Finnish diet: II trends in dietary sodium intake and comparison between intake and 24-h excretion of sodium. Eur J Clin Nutr. 2006;60(10):1160–7. doi: http://dx.doi.org/10.1038/sj.ejcn.1602431. PubMed.
37 Kurttio P, Auvinen A, Salonen L, Saha H, Pekkanen J, Mäkeläinen I, et al. Renal effects of uranium in drinking water. Environ Health Perspect. 2002;110(4):337–42. doi: http://dx.doi.org/10.1289/ehp.02110337. PubMed.
38 Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139(2):137–47. doi: http://dx.doi.org/10.7326/0003-4819-139-2-200307150-00013. PubMed.
39 Seldén AI, Lundholm C, Edlund B, Högdahl C, Ek BM, Bergström BE, et al. Nephrotoxicity of uranium in drinking water from private drilled wells. Environ Res. 2009;109(4):486–94. doi: http://dx.doi.org/10.1016/j.envres.2009.02.002. PubMed.
40 Karpas Z, Paz-Tal O, Lorber A, Salonen L, Komulainen H, Auvinen A, et al. Urine, hair, and nails as indicators for ingestion of uranium in drinking water. Health Phys. 2005;88(3):229–42. doi: http://dx.doi.org/10.1097/01.HP.0000149883.69107.ab. PubMed.
41 Fréry N, Saoudi A, Garnier R, Zeghnoun A, Falq G. Exposition de la population française aux substances chimiques de l'environnement. Saint-Maurice: Institut de veille sanitaire. 2011;1–151. [Cited 2019 July 22.] Available from: https://www.santepubliquefrance.fr/determinants-de-sante/exposition-a-des-substances-chimiques/pesticides/documents/rapport-synthese/exposition-de-la-population-francaise-aux-substances-chimiques-de-l-environnement.-tome-1.-presentation-generale-de-l-etude.-metaux-et-metalloides
42 Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ Health Perspect. 2005;113(2):192–200. doi: http://dx.doi.org/10.1289/ehp.7337. PubMed.

43 Shelley R, Kim NS, Parsons PJ, Lee BK, Agnew J, Jaar BG, et al. Uranium associations with kidney outcomes vary by urine concentration adjustment method. J Expo Sci Environ Epidemiol. 2014;24(1):58–64. doi: http://dx.doi.org/10.1038/jes.2013.18. PubMed.

44 Weaver VM, Kotchmar DJ, Fadrowski JJ, Silbergeld EK. Challenges for environmental epidemiology research: are biomarker concentrations altered by kidney function or urine concentration adjustment? J Expo Sci Environ Epidemiol. 2016;26(1):1–8. doi: http://dx.doi.org/10.1038/jes.2015.8. PubMed.

45 CDC. (Centers for Disease Control and Prevention). Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, Volume One, Atlanta, GA. 2018. [Cited 2019 July 22.] Available from: https://www.cdc.gov/exposurereport/

46 Health Canada. Report on Human Biomonitoring of Environmental Chemicals in Canada, Results of the Canadian Health Measures Survey Cycle 1 (2007-2009). 2010. [Cited 2019 July 22.] Available from: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/report-human-biomonitoring-environmental-chemicals-canada-health-canada-2010.html

47 Health Canada. Second Report on Human Biomonitoring of Environmental Chemicals in Canada, Results of the Canadian Health Measures Survey Cycle 2 (2009-2011). 2013. [Cited 2019 July 22.] Available from:https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/second-report-human-biomonitoring-environmental-chemicals-canada-health-canada-2013.html

48 Dobler L, Eckard R, Günsel A, Langel D, Müller A, Oganowski M, et al. Umweltprobenbank des Bundes - Teilbank Humanproben und Datenbank - Jahresbericht 2010/11. Westfälische Wilhelms-Universität Münster, Münster. 2011. [Cited 2019 July 22.] Available from: https://www.umweltprobenbank.de/de/documents/publications/17723

49 KDIGO (Kidney Disease: Improving Global Outcomes). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150. [Cited 2019 July 22.] Available from: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

50 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12. doi: http://dx.doi.org/10.7326/0003-4819-150-9-200905050-00006. PubMed.

51 Hoellriegl V, Roth P, Werner E. Regional variation of urinary excretion of Uranium in non-exposed subjects. In: Osimani, C, editor. Towards harmonisation of radiation protection in Europe. European IRPA Congress 2002: Florence, Italy, 8–11 October 2002. [Cited 2019 July 22.] Available from: https://inis.iaea.org/collection/NCLCollectionStore/_Public/37/115/37115672.pdf?r=1&r=1

52 Malátová I, Bečková V, Kotík L. Urinary excretion of uranium in adult inhabitants of the Czech Republic. J Environ Radioact. 2016;152:92–6. doi: http://dx.doi.org/10.1016/j.jenvrad.2015.11.011. PubMed.

53 Orloff KG, Mistry K, Charp P, Metcalf S, Marino R, Shelly T, et al. Human exposure to uranium in groundwater. Environ Res. 2004;94(3):319–26. doi: http://dx.doi.org/10.1016/S0013-9351(03)00115-4. PubMed.

54 Berglund M, Lindberg A-L, Rahman M, Yunus M, Grandér M, Lönnerdal B, et al. Gender and age differences in mixed metal exposure and urinary excretion. Environ Res. 2011;111(8):1271–9. doi: http://dx.doi.org/10.1016/j.envres.2011.09.002. PubMed.

55 Jain RB. Effect of pregnancy on the levels of urinary metals for females aged 17-39 years old: data from National Health and Nutrition Examination Survey 2003-2010. J Toxicol Environ Health A. 2013;76(2):86–97. doi: http://dx.doi.org/10.1080/15287394.2013.738171. PubMed.

56 Mao Y, Desmeules M, Schaubel D, Bérubé D, Dyck R, Brûlé D, et al. Inorganic components of drinking water and microalbuminuria. Environ Res. 1995;71(2):135–40. doi: http://dx.doi.org/10.1006/enrs.1995.1075. PubMed.

57 de Jong PE, Curhan GC. Screening, monitoring, and treatment of albuminuria: Public health perspectives. J Am Soc Nephrol. 2006;17(8):2120–6. doi: http://dx.doi.org/10.1681/ASN.2006010097. PubMed.

58 Merker L, Ebert T, Guthoff M, Schlosser M, Hasslacher C, Wolf G. Nephropathie bei Diabetes. Diabetol Stoffwechs. 2018;13(S02):S217–20. doi: http://dx.doi.org/10.1055/a-0598-0566.

59 Zamora ML, Tracy BL, Zielinski JM, Meyerhof DP, Moss MA. Chronic ingestion of uranium in drinking water: a study of kidney bioeffects in humans. Toxicol Sci. 1998;43(1):68–77. doi: http://dx.doi.org/10.1093/toxsci/43.1.68. PubMed.