

Renal Effects of Uranium in Drinking Water

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Animal studies and small studies in humans have shown that uranium is nephrotoxic. However, more information about its renal effects in humans following chronic exposure through drinking water is required. We measured uranium concentrations in drinking water and urine in 325 persons who had used drilled wells for drinking water. We measured urine and serum concentrations of calcium, phosphate, glucose, albumin, creatinine, and β -2-microglobulin to evaluate possible renal effects. The median uranium concentration in drinking water was 28 $\mu\text{g/L}$ (interquartile range 6–135, max. 1,920 $\mu\text{g/L}$) and in urine 13 ng/mmol creatinine (2–75), resulting in the median daily uranium intake of 39 μg (7–224). Uranium concentration in urine was statistically significantly associated with increased fractional excretion of calcium and phosphate. Increase of uranium in urine by 1 $\mu\text{g/mmol}$ creatinine increased fractional excretion of calcium by 1.5% [95% confidence interval (CI), 0.6–2.3], phosphate by 13% (1.4–25), and glucose excretion by 0.7 $\mu\text{mol/min}$ (–0.4–1.8). Uranium concentrations in drinking water and daily intake of uranium were statistically significantly associated with calcium fractional excretion, but not with phosphate or glucose excretion. Uranium exposure was not associated with creatinine clearance or urinary albumin, which reflect glomerular function. In conclusion, uranium exposure is weakly associated with altered proximal tubulus function without a clear threshold, which suggests that even low uranium concentrations in drinking water can cause nephrotoxic effects. Despite chronic intake of water with high uranium concentration, we observed no effect on glomerular function. The clinical and public health relevance of the findings are not easily established, but our results suggest that the safe concentration of uranium in drinking water may be within the range of the proposed guideline values of 2–30 $\mu\text{g/L}$. **Key words:** drinking water, glomerular function, renal tubular function, uranium, uranium toxicity. *Environ Health Perspect* 110:337–342 (2002). [Online 1 March 2002] <http://ehpnet1.niehs.nih.gov/docs/2002/110p337-342kurttio/abstract.html>

Uranium occurs naturally in the earth's crust and surface and groundwaters. If the bedrock consists mainly of uranium-rich granitoids and granites and contains soft, slightly alkaline bicarbonate waters, uranium is highly soluble under oxidizing conditions at a wide pH range. These conditions occur widely in Finland (1), and consequently, exceptionally high uranium concentrations (up to 12,000 $\mu\text{g/L}$) are found in wells drilled in bedrock (2,3).

Animal studies, as well as studies of occupationally exposed persons, have shown that the major health effect of uranium is chemical kidney toxicity, rather than a radiation hazard (4–7). Both functional and histologic damage to the proximal tubulus has been demonstrated (8–13). Little is known about the effects of long-term environmental uranium exposure in humans. Only two small studies with 50–100 study persons have been published on the kidney toxicity of natural uranium from drinking water. They have shown an association of uranium exposure with increased urinary glucose, alkaline phosphatase, and β -2-microglobulin excretion (14), as well as increased urinary albumin levels (15).

The World Health Organization (WHO) (7) has proposed a guideline value of 2 $\mu\text{g/L}$

for uranium in drinking water, based on animal experiments in the absence of human data. Risk assessment and establishment of exposure limits for uranium in drinking water is of considerable importance in areas with granite rock, such as in Finland, where approximately one-seventh of the population uses drinking water with uranium concentration above 2 $\mu\text{g/L}$ (16).

The aim of the present study was to evaluate possible kidney effects of chronic exposure to uranium through drinking water. Our sample size was larger than in earlier studies, with a wide range of uranium concentration in drinking water and well-characterized uranium exposure.

Materials and Methods

Study population. The source population was based on the drinking water database of STUK-Radiation and Nuclear Safety Authority, with radioactivity measurements of more than 5,000 drilled wells (Table 1). The study was limited to 28 municipalities in southern Finland, where uranium concentrations are highest and uranium measurements have been made most extensively.

Sample-size calculations indicated that a study population of 300 would provide adequate statistical power ($\alpha = 0.05$ one-sided,

$1 - \beta = 0.9$) to detect a 20% increase in β -2-microglobulin excretion and creatinine clearance.

The first questionnaire was mailed to 798 households, with questions about the use of the drilled well, possible water purification equipment, and medical history, as well as the person's willingness to participate in the study (Table 1). Based on the first questionnaire, we selected 436 persons, restricted to those older than 15 years of age, with a maximum of two persons per household where a well had been used for drinking water for at least 1 year.

The second questionnaire (Table 1) was used to collect information on residential history and use of well water, daily consumption of water from the drilled well, and liquids from other sources, as well as smoking history, education, occupation, and use of analgesics, other drugs, and herbal products. In addition, we obtained information on kidney, cardiovascular, and liver diseases and diabetes, as well as exposures to heavy metals at work or during leisure time. Seventy-eight percent of the persons who received the second questionnaire consented to participation in the study. The nonrespondents were slightly older (mean age 56 years vs. 48 years of respondents). Parental consent was required for children younger than 18 years of age. The study protocol was approved by the National Public Health Institute Standing Committee on Ethics (project number 8/030399).

We restricted the study area to municipalities with at least one well in the original high-uranium group. Persons with diabetes mellitus ($n = 4$) or chronic use of methotrexate ($n = 1$) or sodium aurothiomalate ($n = 1$), pregnant women ($n = 4$), and households with effective equipment for removing uranium from well water ($n = 4$) were excluded.

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Table 1. Selection of the study population.

Original uranium concentration group ^a	Number of persons who replied to the first questionnaire	Number of persons to whom the second questionnaire was sent	Number of persons who attended the study	Final study population after exclusions
Low (< 10 µg/L)	398	150	113	108
Medium (10–100 µg/L)	363	150	121	116
High (> 100 µg/L)	347	136	105	101
Total	1,108	436	339	325

^aTo obtain a wide range of exposure levels, the wells were divided primarily into three groups based on the uranium concentrations calculated from gross alpha analyses (33) (low, $n = 300$; medium, $n = 300$; and high, $n = 198$).

Table 2. Analytical methods used in the study.

Analysis	Method	Detection limit
Uranium in water	ICP-MS (Elan 6000; Perkin Elmer, Bodenseewerk, GmbH, Toronto, Canada)	0.0004 µg/L
Uranium in urine		0.002 µg/L
Serum creatinine	Jaffe method (Konelab 60i analyzer and reagents; Konelab Co., Espoo, Finland)	19 µmol/L
Urine creatinine	Clinical Chemistry automatic analyzer (Konelab Co.)	0.4 mmol/L
Serum calcium	Colored complex with Arsenazo III (Konelab 60i analyzer and reagents; Konelab Co.)	0.5 mmol/L
Urine calcium	Atomic absorption spectrophotometry (EFOX 5053; Eppendorf, Hamburg, Germany)	0.1 mmol/L
Serum phosphate	Colored complex with ammonium molybdate (Konelab 60i analyzer; Konelab Co.)	0.1 mmol/L
Urine phosphate		2.0 mmol/L
Serum albumin	Bromocresol purple method (Konelab 60i analyzer; Konelab Co.)	5 g/L
Urine albumin	Immunological method (Beckman Immunochemistry Systems Micro Albumin; Beckman Instruments Inc., Galway, Ireland) using a Beckman Array Protein analyzer (Beckman Instruments Inc., San Diego, CA, USA)	2 mg/L
Serum glucose	Hexokinase method (Konelab 60i analyzer; Konelab Co.)	0.5 mmol/L
Urine glucose		1 mmol/L
Serum β-2-microglobulin	Immunoturbidimetric method (Tina-quant β-2-microglobulin; Roche Diagnostics GmbH, Mannheim, Germany)	0.2 mg/L
Urine β-2-microglobulin	with a Hitachi model 717 automatic analyzer (Hitachi Ltd., Tokyo, Japan)	0.1 mg/L

The final study population (Table 1) consisted of 325 persons with 194 wells in 24 municipalities. The wells had been used as the main source of drinking water for 13 years on average (range 1–34 years).

The mean age of the persons in the final study population was 52 years (range 15–82 years). Fifty percent of the persons were women ($n = 163$). Fifty-six percent had never smoked cigarettes, cigars, or pipes; 29% were ex-smokers; and 15% were current smokers. Thirty-eight persons reported exposure to heavy metals, but the exposure periods had been short; therefore, this exposure was considered insignificant.

Sample collection and preparation. The water, urine, and nonfasting blood samples were collected between 14 September and 1 December 1999. The samples were collected at a time when the study persons had consumed water from the drilled well during the previous week. Samples were not taken unless at least 1 week had elapsed since an acute infection. The study persons collected water samples for uranium analyses in a plastic bottle in the evening. Overnight urine samples were collected in plastic bottles and the collection times recorded (median 11 hr, range 7–17 hr).

The study persons brought the samples to the laboratory in the morning, and we measured urine volume (median 800 mL, range 210–2,600 mL). The urine samples for calcium and phosphate analyses were conserved with hydrochloric acid. During the same visit, we collected a spot urine

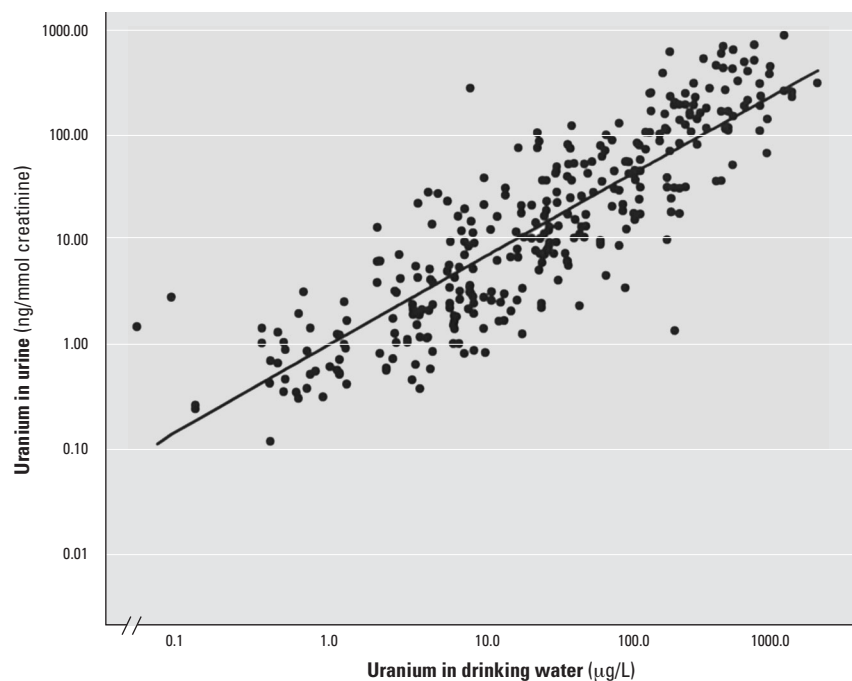


Figure 1. Correlations of the uranium concentration in drinking water and in urine [$\log(y) = 0.01 + 0.80 \log(x)$; Pearson correlation = 0.85].

sample for analyses of β-2-microglobulin (conserved with sodium bicarbonate) and drew blood samples to obtain serum for clinical chemistry. In addition, we measured supine blood pressure, body weight, and height according to standard procedures. The water and overnight urine samples for uranium analyses were conserved with nitric acid. Water, serum, and overnight and spot

urine samples were stored frozen at -20°C until analysis.

Uranium exposure assessment. Uranium in drinking water and urine were analyzed blind with inductively coupled plasma mass spectrometry (ICP-MS) in the laboratory of Consulting Engineers Paavo Ristola Laboratory, Hollola, Finland (Table 2). Urine samples were diluted 1:5 with 2%

Table 3. Uranium exposure from drinking water and measured kidney function parameters among the study population ($n = 325$).

Parameter	Mean	Median	Percentile		Range
			25th	75th	
Uranium in drinking water ($\mu\text{g/L}$)	131	28	6.2	135	0.001–1,920
Uranium in urine ($\mu\text{g/L}$)	424	78	17	413	1–5,650
Uranium in urine (ng/mmol creatinine)	73	13	2.5	75	0.1–955
Daily intake of uranium from drinking water (μg)	235	39	7.5	224	0.0006–4,128
Daily intake of uranium from drinking water ($\mu\text{g}/\text{kg}$ body weight)	3.2	0.6	0.1	3.2	0.00007–52
Cumulative intake of uranium from drinking water (mg)	1,360	129	24	887	0.001–33,100
Intake of drilled-well water (L/day) ^a	1.7	1.6	1.2	2.0	0.3–5.6
Total fluid intake (L/day) ^a	2.7	2.6	2.1	3.2	1.0–6.7
Duration of the use of drilled well (years)	13	11	6	20	1.3–34
Calcium fractional excretion (%) ^b	1.6	1.3	0.8	2.0	0.08–10
Phosphate fractional excretion (%) ^c	27	24	19	33	3.6–177
Glucose excretion ($\mu\text{mol}/\text{min}$) ^d	0.9	0.7	0.5	0.9	0.1–21
Creatinine clearance (mL/min) ^e	103	100	83	116	20–239
Urinary albumin ($\mu\text{g}/\text{min}$) ^f	3.3	1.7	1.1	2.6	0.3–92
β -2-Microglobulin concentration in urine (mg/L)	0.12	0.05	0.05	0.13	0.05–6.0

^aFrom a questionnaire covering fluid intake (from drinks and soups) at home and elsewhere. ^b(Urine calcium $\times$ serum creatinine)/(serum calcium $\times$ urine creatinine) $\times$ 100. ^c(Urine phosphate $\times$ serum creatinine)/(serum phosphate $\times$ urine creatinine) $\times$ 100. ^d(Urine glucose $\times$ urine volume)/urine collection time. ^e[(Urine creatinine $\times$ urine volume)/serum creatinine] $\div$ urine collection time $\times$ (1.73/body surface). ^f(Urine albumin $\times$ urine volume)/urine collection time.

Table 4. Association of uranium exposure in kidney function indicators, blood pressure, and diuresis.

	Uranium in urine ($\mu\text{g}/\text{mmol}$ creatinine)		Uranium in drinking water (mg/L)		Daily intake of uranium (mg)	
	<i>b</i>	(95%CI)	<i>b</i>	(95%CI)	<i>b</i>	(95%CI)
Calcium fractional excretion (%)	1.5	(0.6–2.3)	0.5	(0.06–1.0)	0.4	(0.2–0.7)
Phosphate fractional excretion (%)	13	(1.4–25)	4.5	(–2.3–11)	3.1	(–0.5–6.7)
Glucose excretion ($\mu\text{mol}/\text{min}$)	0.7	(–0.4–1.8)	0.2	(–0.4–0.8)	0.2	(–0.1–0.5)
Creatinine clearance (mL/min)	–7.6	(–33–18)	1.7	(–13–16)	0.8	(–6.8–8.4)
Urinary albumin ($\mu\text{g}/\text{min}$)	–2.1	(–8.8–4.6)	0.1	(–3.7–3.9)	0.2	(–1.8–2.2)
β -2-Microglobulin in urine (< 0.1 ; 0.1 – 0.39 ; ≥ 4 ng/L)	–107	(–523–309)	–82	(–318–153)	–49	(–175–76)
Systolic blood pressure (mmHg) ^a	6.8	(–5.7–19)	7.4	(0.3–14)	4.1	(0.3–7.9)
Diastolic blood pressure (mmHg) ^a	8.5	(1.4–15)	5.0	(0.9–9.0)	3.0	(0.8–5.1)
Diuresis ($\mu\text{L}/\text{min}$) ^a	599	(129–1,070)	61	(–211–332)	71	(–73–217)

Values shown are the increase of outcome variables (*b*), which is associated with an increase of exposure variables by one unit, and 95% CI ($n = 325$). Uranium exposure is a continuous variable adjusted for age, sex, and body mass index, except where indicated.

^aAdjusted for age, sex, body mass index, and smoking.

HNO_3 before analyses. Water samples were diluted with 2% HNO_3 if uranium in water exceeded 500 $\mu\text{g/L}$.

For quality assurance, split water ($n = 38$) and urine samples ($n = 20$) were analyzed. The coefficient of variation for water samples was 3.0% (regression coefficient = 0.98) and for urine samples 16% (regression coefficient = 0.99). In addition, 15 water samples were analyzed blind by ICP–MS in another laboratory (Nuclear Research Center, Negev, Beer-Sheva, Israel, by Zeev Karpas); these samples were also analyzed for uranium isotopes ^{238}U and ^{234}U by radiochemical and alpha-spectrometric methods (2) at STUK–Radiation and Nuclear Safety Authority. The results in different laboratories were comparable between the ICP–MS measurements (regression coefficient = 0.91) and between the ICP–MS and the radiochemical analyses (regression coefficient = 0.96).

We used four measures of uranium exposure: uranium concentration in drinking water (micrograms per liter), uranium concentration in urine (nanograms per liter or nanograms per millimole creatinine), daily intake of uranium from drinking water

(volume used $\times$ concentration, micrograms), and cumulative intake from drinking water (daily intake $\times$ duration of the water consumption, milligrams). The exposure variables were highly correlated with each other (R^2 from 0.54 to 0.92) (Figure 1). Only the uranium concentrations in drinking water and in urine (per creatinine) and daily intake related to the outcome variables are shown. The exposure variables were analyzed both as continuous and categorical variables. We chose the cut points of the uranium concentration in drinking water based on the present or suggested guideline values for drinking water, and the cut points for uranium in urine and daily intake were approximate quintiles.

Kidney function assessment. We selected excretion of glucose, calcium, phosphate, and β -2-microglobulin as indicators of effects on proximal tubulus, and creatinine clearance and urinary albumin as indicators for glomerular function. These outcome measures were chosen based on previous results on uranium toxicity and suitability for kidney function monitoring in a large study population. Because the fractional excretion (formula shown in Table 3 footnote) is

independent of the urinary volume or collection time (eliminating one source of uncertainty), we used fractional excretion of calcium and phosphate as the main outcome measure in the final analyses. Urinary glucose and albumin were used as clinically relevant measures of kidney dysfunction. The kidney function parameters were measured at the Department of Clinical Chemistry of Kuopio University Hospital according to certified laboratory procedures (Table 2).

Because 65% of β -2-microglobulin concentrations in urine were below the detection limit of the assay, we analyzed the variable as a trichotomous variable.

Statistical analyses. For the all parameters determined, the observations below the detection limits were recorded as half of the detection limit.

The crude and adjusted (by age, sex, and body mass index) analyses were performed using generalized linear models assuming normal distribution of the outcome and an identity link function ($y = a + bx$; a = baseline, b = regression coefficient, y = kidney function, x = uranium exposure) in SAS version 6.12 PROC GENMOD (SAS Institute

Inc., Cary, NC, USA). An adjustment for duration of uranium exposure, education, occupation, use of analgesics, or smoking (never, ex-smoker, or current smoker) did not change the effect of uranium exposure to kidney functions and were therefore not used as covariates. The results of univariate analyses were similar to those from multivariate analyses, and only adjusted results are shown.

We also conducted an analysis using a log transformation, but the results remained essentially unchanged. There was no obvious skewness for residuals across predicted values for any of the main outcome measures (i.e., showing no substantial departure from normality). No systematic variation in residuals was observed in relation to exposure variables, suggesting that the effect of uranium was adequately described by a linear exposure term. To estimate the shape of the dose–response curve, we also conducted analyses separately for those above and below median exposure. These analyses were conducted for calcium and phosphate fractional excretions as end points.

Results

The uranium concentration in water varied from 0.001 to 1,920 µg/L, and 30% of the concentrations exceeded 100 µg/L. The median daily intake of uranium from drinking water was 39 µg (Table 3).

An increase in the daily intake of uranium from drinking water by 1 µg was associated with an increase of 0.21 ng of uranium in urine/mmol creatinine (95% confidence interval (CI), 0.19–0.24) (Figure 1). The median of the ratio of uranium in urine (micrograms per liter)/uranium in water (micrograms per liter) was 3×10^{-4} (25th and 75th percentiles 2×10^{-4} and 7×10^{-4}). The ratio was not associated with the exposure levels (daily intake, $p = 0.6$), age ($p = 0.5$), or sex ($p = 0.3$).

Uranium exposure (uranium in urine, uranium in drinking water, and uranium intake) was statistically significantly associated with increased fractional excretion of calcium ($p = 0.0006$, 0.03, and 0.001 for continuous exposure variables, respectively) (Table 4; Figure 2). Phosphate fractional

excretion was statistically significantly ($p = 0.03$) associated with uranium concentration in urine, but not with uranium in drinking water ($p = 0.2$) or uranium intake ($p = 0.09$) (Table 4). The tendency of uranium exposure to increase glucose excretion was not statistically significant. An increase of uranium in urine by 1 µg/mmol creatinine was associated with an increase of fractional excretion of calcium by 1.5% (95% CI, 0.6–2.3), phosphate by 13% (1.4–25), and glucose excretion by 0.7 µmol/min (−0.4–1.8) (Table 4). We observed a statistically significant increase in phosphate fractional excretion for drinking water uranium concentration > 300 µg/L relative to < 2 µg/L (Table 5). Similarly, the study persons with the highest uranium excretion and intake had elevated calcium and phosphate fractional excretion compared with the lowest exposure groups (Tables 6 and 7). We observed no association between uranium exposure and creatinine clearance, urinary albumin, or concentration of β-2-microglobulin in urine (Table 4).

Uranium exposure was associated with increased systolic and diastolic blood pressures and diuresis (urine volume/time) when continuous exposure variables were used (Table 4), but the association was statistically significant only between diuresis and the highest categoric exposure group (uranium in urine) compared with the lowest exposure group (Table 7).

In dose–response analyses, risk estimates tended to be slightly higher for the subgroup with uranium levels below the median than for those above the median, whether calcium or phosphate fractional excretion was used as the end point and for both water and urinary uranium concentrations. A squared uranium exposure term was not statistically significant and had a negative regression coefficient.

Discussion

The study showed an association between increased uranium exposure through drinking water and tubular function, but not between uranium exposure and indicators of glomerular injury (i.e., creatinine clearance and urinary albumin). Even though the

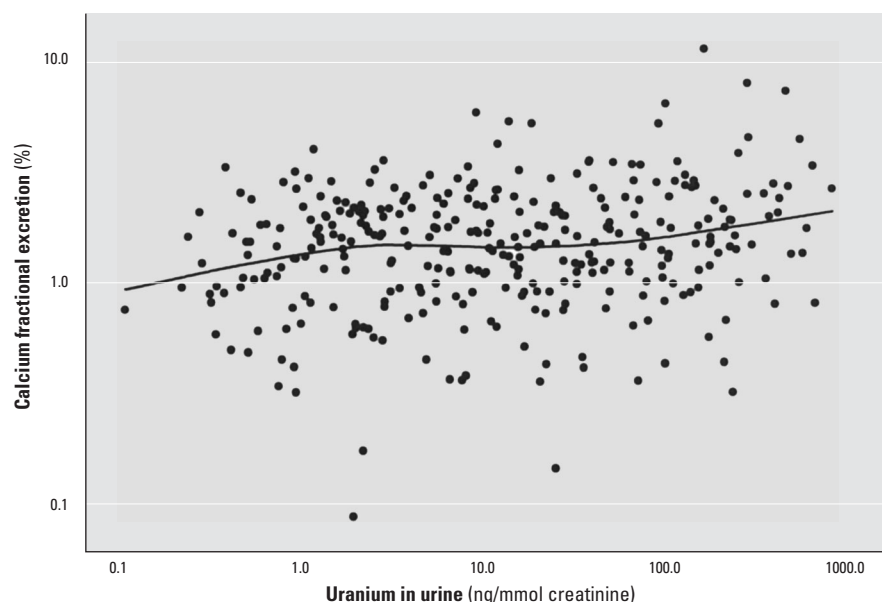


Figure 2. Uranium concentration in urine and fractional excretion of calcium crude values. The line represents the smoothed running means.

Table 5. Kidney function indicators for uranium in water.

Uranium in water (µg/L)	0.001–1.9	2–9	10–19	20–99	100–299	300–1,920
<i>n</i>	37	82	25	83	55	43
Calcium fractional excretion (%)						
Mean	1.5	1.3	1.4	1.5	1.8	2.0
<i>b</i>	Ref	−0.19 (−0.61–0.23)	−0.11 (−0.67–0.46)	−0.04 (−0.46–0.38)	0.23 (−0.22–0.69)	0.38 (−0.10–0.87)
Phosphate fractional excretion (%)						
Mean	23	27	28	26	28	32
<i>b</i>	Ref	4.6 (−1.2–10)	5.5 (−2.3–13)	2.9 (−2.9–8.7)	5.1 (−1.2–11)	9.0 (2.4–16)
Glucose excretion (µmol/min)						
Mean	0.8	0.7	0.8	1.0	0.8	1.0
<i>b</i>	Ref	0.01 (−0.51–0.53)	0.05 (−0.65–0.74)	0.23 (−0.28–0.75)	0.09 (−0.47–0.64)	0.29 (−0.30–0.89)

Values shown are the increase of outcome variables (*b*) compared with the lowest exposure strata (Ref), 95% CI, and means of unadjusted outcome variables in each exposure strata (*n* = 325). Uranium exposure is a categorized variable adjusted for age, sex, and body mass index.

effects were of modest magnitude, they occurred without a clear threshold.

The results are consistent with previous findings, suggesting that uranium in drinking water affects kidney tubular function (14,15). In our study, uranium concentrations were higher than in the earlier studies. In the study by Zamora et al. (14) of persons using water containing < 1 µg/L uranium ($n = 20$) or between 2 and 780 µg/L ($n = 30$), the daily intake of uranium was 0.3–570 µg. Increased urinary glucose, β -2-microglobulin, and alkaline phosphatase were associated with daily uranium intake, but most values remained within the normal range. Indicators for glomerular injury (urinary creatinine and total protein) were not associated with uranium intake. In another study, the uranium concentrations in water were between < 0.1 and 50 µg/L ($n = 100$), and slightly increased levels of urinary albumin were associated with cumulative intake of uranium from drinking water (15). Other biochemical parameters in urine were not evaluated.

We did not find an association between uranium exposure and excretion of β -2-microglobulin in urine. The results are consistent with the previous studies (14,15)

in that β -2-microglobulin and albumin rarely exceeded the normal range.

Our findings are supported by experimental findings on toxicity of uranium in laboratory animals. Very high doses of uranium (10–25 mg/kg body weight) cause an acute renal failure (8,9,17,18), and lower exposure levels induce morphologic and functional changes in kidneys (10,12,19). The primary target is the proximal convoluted tubule, and the damage at higher doses is irreversible (8–10). Histologic changes are paralleled by glucosuria, aminoaciduria, proteinuria, polyuria, and increased excretion of enzymes such as alkaline phosphatase and lactate dehydrogenase (5,10,12,17,20,21) as indicators of altered function of proximal tubules and cell damage, respectively.

In this study, the changes in tubular function were associated more closely with urinary uranium concentration than daily intake or uranium concentration in water. Uranium concentration in groundwater may vary over time, and therefore a spot sampling does not necessarily represent long-term uranium exposure. Additionally, self-reported estimates of drinking water consumption were required for calculating the daily

intake, which adds uncertainty. Urinary uranium concentration is independent of these sources of uncertainty. Furthermore, it also encompasses individual variation in uranium kinetics within the body, which further increases its validity as an indicator of uranium concentration in the kidney.

Renal effects of uranium were not associated with the duration of well-water use or with cumulative uranium intake. These findings suggest that short-term exposure is most relevant for kidney effects of uranium, and effects are not likely to be cumulative. This is also supported by kinetic studies (4–6).

In our study population, drinking water is the predominant source of uranium, especially among those with elevated uranium concentrations in well water. We had no data on dietary intake of uranium, but the average daily intake of uranium in food in other countries has been reported to be 1–2 µg/day (22,23). We had no information on uranium in previous drinking water sources. However, the findings were independent of duration of residence in the dwelling, suggesting that this is not likely to affect the results. We analyzed only uranium from the water samples. To confound the results,

Table 6. Kidney function indicators for daily intake of uranium.

Daily intake of U (µg) <i>n</i>	0.0006–4.9 60	5–19 68	20–99 81	100–299 51	300–4,128 65
Calcium fractional excretion (%)					
Mean	1.4	1.3	1.4	1.8	1.9
<i>b</i>	Ref	−0.08 (−0.46–0.30)	−0.05 (−0.41–0.31)	0.37 (−0.03–0.78)	0.45 (0.07–0.83)
Phosphate fractional excretion (%)					
Mean	25	26	26	28	31
<i>b</i>	Ref	2.0 (−3.3–7.2)	0.93 (−4.1–6.0)	2.8 (−2.9–8.5)	5.9 (0.56–11.2)
Glucose excretion (µmol/min)					
Mean	0.7	0.7	0.8	1.2	1.0
<i>b</i>	Ref	0.02 (−0.45–0.48)	0.02 (−0.42–0.46)	0.51 (−0.01–1.01)	0.23 (−0.24–0.70)

Values shown are the increase of outcome variables (*b*) compared with the lowest exposure strata (Ref), 95% CI, and means of unadjusted outcome variables in each exposure strata ($n = 325$). Uranium exposure is a categorized variable adjusted for age, sex, and body mass index.

Table 7. Kidney function indicators, blood pressure, and diuresis for uranium in urine.

U in urine (ng/mmol creatinine) <i>n</i>	0.1–1.9 68	2–9 80	10–19 37	20–99 72	100–955 68
Calcium fractional excretion (%)					
Mean	1.3	1.4	1.7	1.5	2.0
<i>b</i>	Ref	0.05 (−0.30–0.40)	0.28 (−0.15–0.71)	0.09 (−0.27–0.45)	0.66 (0.29–1.0)
Phosphate fractional excretion (%)					
Mean	25	26	26	26	31
<i>b</i>	Ref	2.7 (−2.2–7.7)	1.9 (−4.2–7.9)	2.9 (−2.1–8.0)	7.7 (2.6–13)
Glucose excretion (µmol/min)					
Mean	0.7	0.7	1.2	0.8	1.0
<i>b</i>	Ref	0.01 (−0.42–0.44)	0.52 (−0.02–1.05)	0.07 (−0.37–0.52)	0.30 (−0.16–0.75)
Systolic blood pressure (mmHg)					
Mean	135	134	138	139	139
<i>b</i> ^a	Ref	−1.2 (−6.5–4.0)	0.3 (−6.1–6.7)	3.0 (−2.4–8.3)	1.4 (−4.1–6.9)
Diastolic blood pressure (mmHg)					
Mean	82	81	82	83	85
<i>b</i> ^a	Ref	−1.3 (−4.3–1.6)	−0.4 (−4.0–3.2)	1.1 (−1.9–4.1)	2.1 (−1.0–5.2)
Diuresis (mL/min)					
Mean	1.2	1.3	1.2	1.3	1.6
<i>b</i> ^a	Ref	0.12 (−0.07–0.32)	0.05 (−0.18–0.29)	0.11 (−0.09–0.31)	0.38 (0.18–0.58)

Values shown are the increase of outcome variables (*b*) compared with the lowest exposure strata (Ref), 95% CI, and means of unadjusted outcome variables in each exposure strata ($n = 325$). Uranium exposure is a categorized variable adjusted for age, sex, and body mass index, except where indicated.

^aAdjusted for age, sex, body mass index, and smoking.

other chemicals in drinking water should be associated with both uranium concentration and outcome measures. In another study we measured heavy metals, some of which are known nephrotoxic agents, in Finnish drilled wells. These preliminary results show that heavy metals other than uranium occur extremely rarely in substantial concentrations. Furthermore, none of the heavy metals are positively correlated with uranium. Therefore, other chemicals in drinking water are not likely to confound the results.

The clinical significance of the results is not easily established. We found an association between uranium exposure and tubular function (calciuria, phosphaturia, and polyuria), but no changes in glomerular function (creatinine clearance, albuminuria). Tubular dysfunction manifested within the normal physiologic range, but occurred without an apparent threshold. Excretion of calcium, phosphate, and glucose remained within normal range in most subjects, even for persons with very high and long-lasting exposure to uranium. These findings are consistent with studies of occupational exposure to uranium failing to demonstrate overt kidney disease among workers exposed to uranium (24–26). However, most occupational studies have not used sufficiently sensitive functional indicators to detect latent kidney dysfunction, and thus minor effects may have remained unobserved.

Tubular dysfunction may merely represent a manifestation of subclinical toxicity, and it is unclear if it carries a risk of development into kidney failure or overt illness. However, alterations in renal functions induced by uranium cannot be ignored, although their health significance remains to be established. They may decrease the spare capacity of kidney function or promote clinical manifestation of other harmful insults. The changes in kidney function, even in the absence of renal failure, may have subtle indirect health consequences. Increased calcium leaking into urine may lead to negative calcium balance and increase susceptibility to osteoporosis. An association between blood pressure and urinary uranium excretion may be of clinical importance to subjects with a predisposition to hypertension. Uranium elevates serum renin concentration (17,27), which may explain our finding. These findings deserve further exploration.

There is no evidence that natural uranium in drinking water would cause cancer, and chemical toxicity of natural uranium is likely to be much more important for human health than risk of cancer from radiation (4,6,28). The median annual effective dose based on the uranium intake and the average uranium isotope ratios in drilled-well waters (2) and dose conversion factors (29) was 0.02 mSv/year (maximum 2 mSv/year),

and hence remains lower than the worldwide average dose from natural sources (2.4 mSv/year) (30).

Guideline values for drinking water ranging from 2 µg/L (7) to 100 µg/L (31) have been proposed. The values are based on animal studies, with application of a safety factor to take into account the lack of human studies. Based on this report and two previous reports (14,15), the results from human studies could be used for setting guidelines. We found altered tubular function statistically significant at water uranium concentrations exceeding 300 µg/L. However, heterogeneity of exposure and of health effect (i.e., susceptibility) are possible, and this should be considered in setting the guideline values. Because our study and other human studies have shown an effect of uranium on kidney function, guideline values based on these studies are unlikely to be substantially higher than those suggested previously. Due to the lack of an obvious threshold for the nephrotoxic effect and possible heterogeneity of effect within populations, a guideline value of 100 µg/L seems too high, whereas values in the range proposed by the WHO (2 µg/L) (7) and the U.S. Environmental Protection Agency (U.S. EPA) (30 µg/L) (32) appear appropriate.

In summary, we found an association between increased uranium exposure through drinking water and excretion of several solutes in urine. The effect is consistent with reduced reabsorption in kidney tubules. The public health implications of these findings remain uncertain, but suggest that the safe concentration of uranium in drinking water may be close to the guideline values proposed by the WHO and the U.S. EPA.

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