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Environmental Uranium Exposure from Drinking Water

Keith Baker, MD
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Rocky Mountain Poison and Drug Center

PEHSU
Pediatric Environmental Health Specialty Units

Conflicts of Interest

I have no conflicts of interest to report

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Learning Objectives

1) Describe current permissible exposure limits for uranium in drinking water
2) Describe the absorption, distribution, and elimination of ingested uranium
3) Review the potential effects, if any, of ingested uranium on the renal system
4) Review the risk for development of renal or bladder malignancies after long-term exposure to uranium in drinking water
5) Describe current testing options and recommendations for patients who may have been exposure to uranium in drinking water
6) Briefly discuss possible treatment options for uranium exposure

What is uranium?

www.periodictable.com

What is uranium?

What is elemental uranium?

What is enriched uranium?

What is depleted uranium?

Uranium in drinking water

Where is it found?

What are permissible exposure limits?

What are we worried about it causing?

What do I need to do for someone who has been exposed?

www.cosmopolitan.co.uk

Why is this important?

www.6abc.com

Uranium in drinking water

Absorption

Distribution

Elimination

Journal Article #1

ACADEMIC PRESS

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Environmental Research 94 (2004) 319–326

Environmental Research

http://www.elsevier.com/locate/envres

Human exposure to uranium in groundwater☆

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Polling question #1

After prolonged exposure to uranium in drinking water ends, urine uranium concentrations are expected to:

A. Increase linearly
B. Decrease linearly
C. Increase in logarithmic fashion
D. Decrease in logarithmic fashion

Background

Elevated concentrations of naturally occurring uranium are found in ground water in parts of the United States

Nephrotoxicity and malignancy?

WHO maximum contaminant level 15 ug/L

EPA maximum contaminant level 30 ug/L

Background

Legal enforceability

Mechanism of toxicity of uranium

Research Questions

1) Does uranium concentration in urine correlate with uranium concentration in well water?

2) Does uranium in urine persist over time, and how do concentrations change?

Type of Study/Methods

Observational/Cohort

35 households

N=105 in first round, N=79 in second round

Inclusion/exclusion criteria

Water and Urine Analysis

www.nwbrhc.org

commons.wikimedia.org

Results

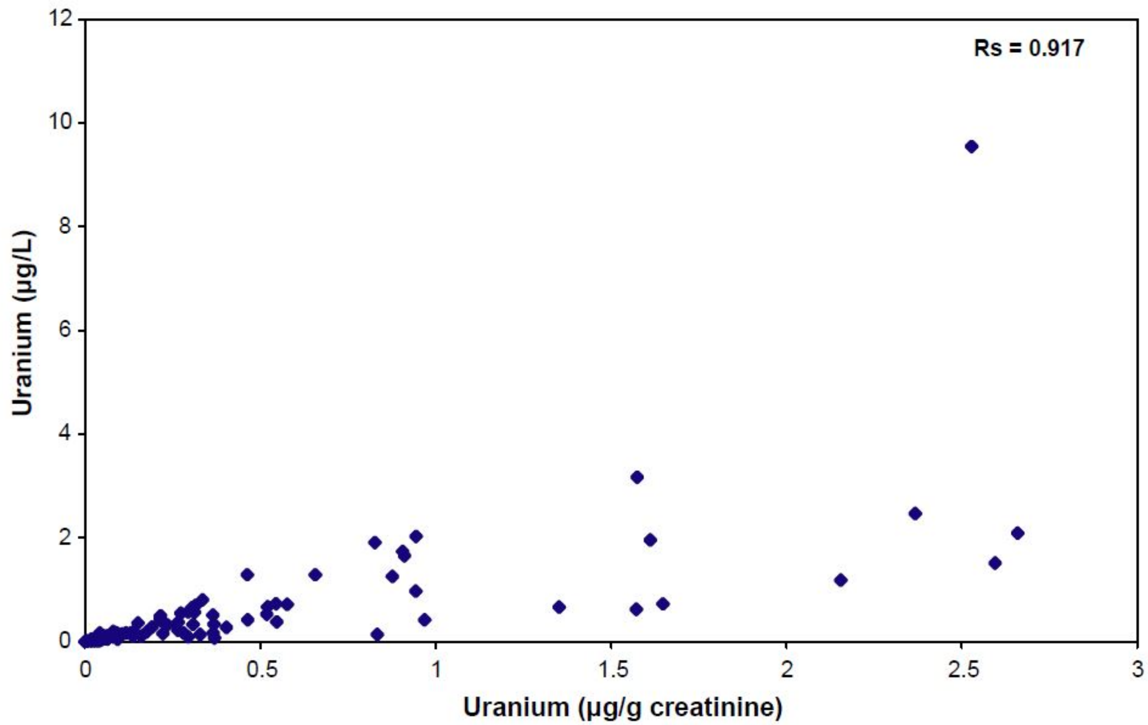

Fig. 1. Uranium concentrations in urine (µg/L vs µg/g creatinine) in sampling round 1. R_s = Spearman's rank correlation coefficient.

Results

Table 2
Summary statistics for urine uranium concentrations ($n = 79$) in two sampling rounds

	Range (μg/L)[a]	Mean (μg/L)[a]	Median (μg/L)[a]	Range (μg/g)[b]	Mean (μg/g)[b]	Median (μg/g)[b]
Round 1	ND–9.550	0.508	0.162	ND–2.659	0.481	0.215
Round 2	0.008–6.650	0.376	0.124	0.009–3.144	0.273	0.114

ND, not detected.
[a] Micrograms uranium/liter urine.
[b] Micrograms uranium/gram creatinine.

Table 1

Uranium concentrations in the general US population (NCEH, 2003)

	Percentile			
	25th	50th	75th	95th
Uranium concentration (μg/g creatinine)	<LOD	0.006	0.011	0.034

LOD, limit of detection (0.004 μg/g creatinine).

Results

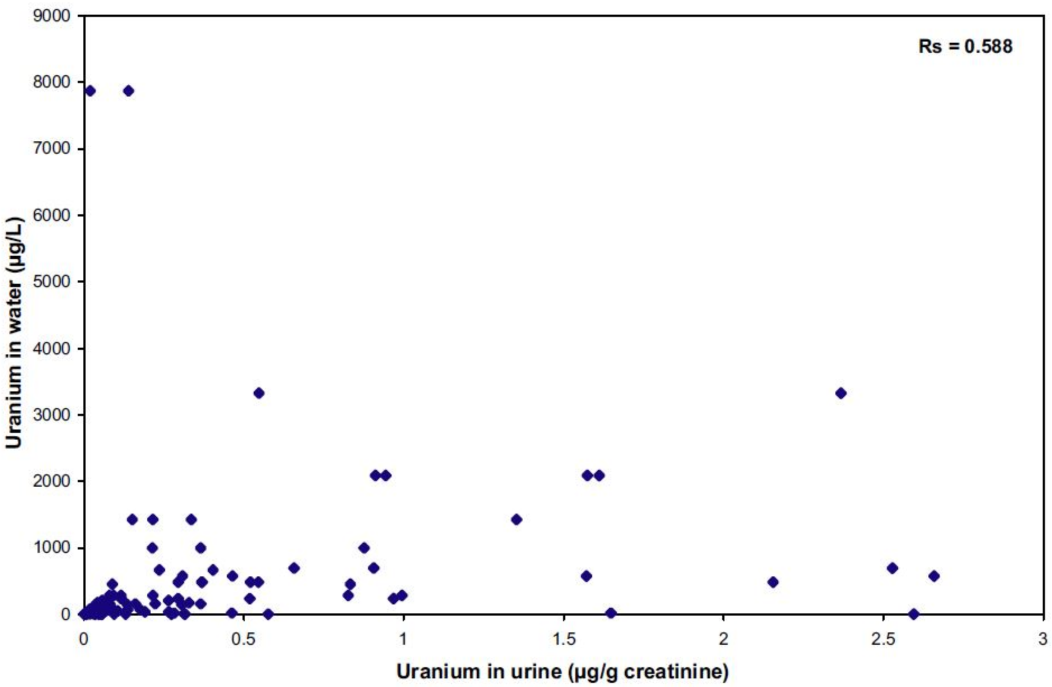

Fig. 2. Uranium concentrations in well water (µg/L) vs uranium concentrations in urine (µg/g creatinine) in sampling round 1. R_s = Spearman's rank correlation coefficient.

Results

Table 2
Summary statistics for urine uranium concentrations ($n = 79$) in two sampling rounds

	Range (μg/L)[a]	Mean (μg/L)[a]	Median (μg/L)[a]	Range (μg/g)[b]	Mean (μg/g)[b]	Median (μg/g)[b]
Round 1	ND–9.550	0.508	0.162	ND–2.659	0.481	0.215
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ND, not detected.

[a] Micrograms uranium/liter urine.

[b] Micrograms uranium/gram creatinine.

Results

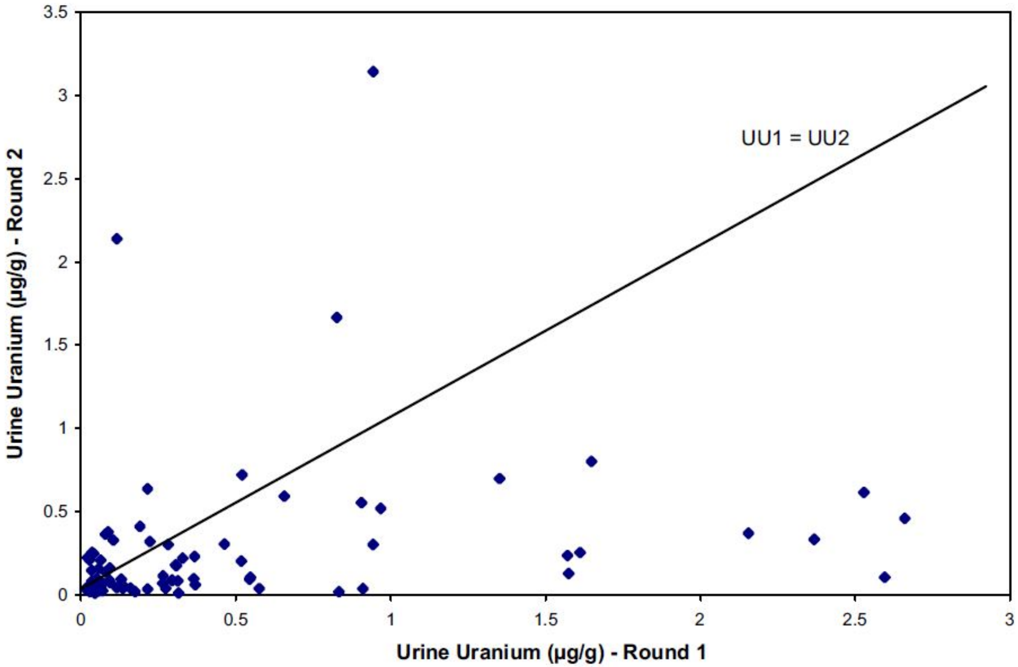


Fig. 3. Uranium concentrations in urine (µg/g creatinine) in sampling round 1 vs those in sampling round 2. The reference line (UU1 = UU2) represents where the values would have plotted if there had been no change in urine uranium concentrations between sampling rounds 1 and 2.

Discussion

Elimination of uranium is complex

Concentrations in urine expected to gradually decrease

Those with lower initial concentrations had less significant decrease between samples

Discussion

Limitations

No other known sources of uranium exposure in study population

Polling question #1

After prolonged exposure to uranium in drinking water ends, urine uranium concentrations are expected to:

A. Increase linearly
B. Decrease linearly
C. Increase in logarithmic fashion
D. Decrease in logarithmic fashion

Journal Article #2

Kidney Toxicity of Ingested Uranium From Drinking Water

Päivi Kurttio, PhD, Aimo Harmoinen, PhD, Heikki Saha, MD, PhD, Laina Salonen, PhLic, Zeev Karpas, PhD, Hannu Komulainen, PhD, and Anssi Auvinen, MD, PhD

2006. Am J Kidney Disease. 47:972-82

Polling question #2

Prolonged exposure to uranium in drinking water has been shown to cause overt renal dysfunction in humans:

A. True
B. False

Background

High natural uranium concentrations in water

Prior animal studies

Prior human studies

Prior study from same cohort

Research Question

Does long-term exposure to uranium in drinking water cause nephrotoxicity?

Type of Study/Methods

Observational/Cohort

Subset of subjects from previous study

N=193

Inclusion/exclusion criteria

Demographics

Sample Collection

Markers of Cytotoxicity/Kidney Damage

Measured Parameters	Abbreviation
Indicators of cytotoxicity and tissue damage	
Urinary *N*-acetyl-γ-D-glucosaminidase	NAG
Urinary lactate dehydrogenase	LDH
Urinary alkaline phosphatase	ALP
Urinary γ-glutamyltransferase	GGT
Indicators of effects on renal proximal tubules	
Urinary α glutathione-*S*-transferase	GST
Urinary calcium	Uri-Ca
Serum calcium	S-Ca
Urinary phosphate	Uri-Pi
Serum phosphate	S-Pi
Urinary glucose	Uri-Gluc
Serum glucose	S-Gluc
Indicators of glomerular function	
Serum cystatin C	S-CysC
Urinary creatinine	Uri-Crea
Serum creatinine	S-Crea

Potential Confounders

Table 3. Potential Confounders (z_i) Included in Linear Regression Models in Addition to Sex and (Linear) Age, and Number of Possible Outliers Excluded From Analysis

Outcome	z_i	No. of Outliers Excluded
NAG	Smoking	1
LDH	Body mass index, smoking, analgesics	
ALP	Body mass index, smoking, analgesics	
GGT	Analgesics	
GST	Smoking	2
Calcium fractional excretion	Analgesics	
Phosphate fractional excretion	Age^2, body mass index	
Glucose excretion	—	1
Serum CysC	Age^2	1
Creatinine clearance	Analgesics	
Diastolic blood pressure	Age^2, body mass index	
Systolic blood pressure	—	

NOTE. Uranium exposure variable was log-transformed (Ln[value + 1]). Body mass index in kilograms per square meter. Smoking indicates current smoking status (non, exsmoker, current smoker), analgesics indicate regular use of analgesics (no, yes), and age^2 indictates age * age.

Results

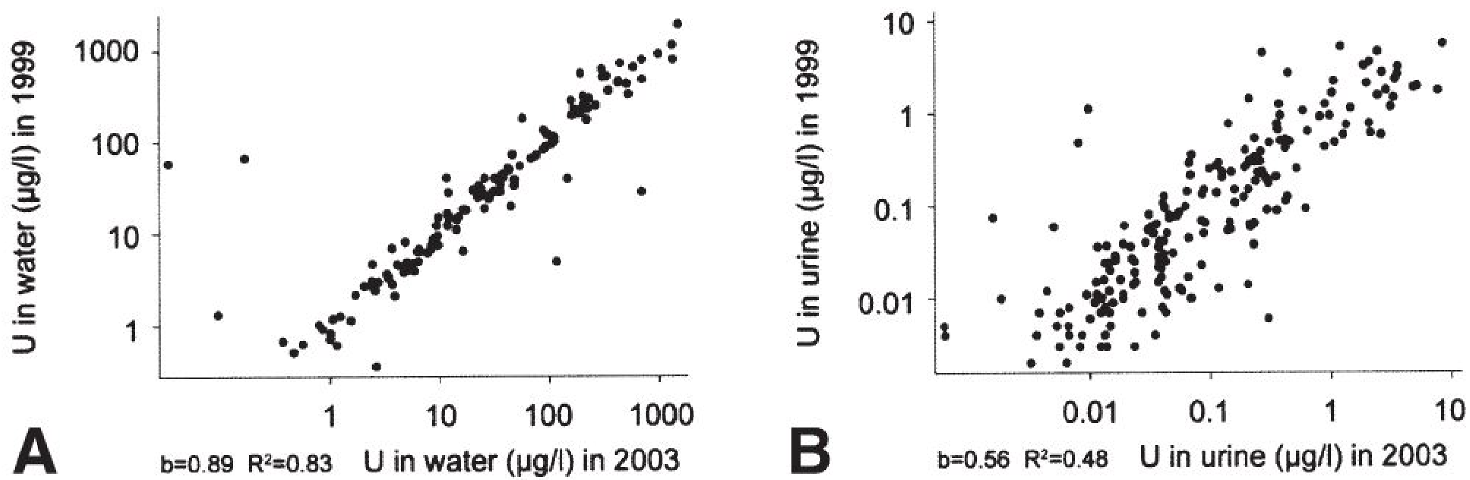
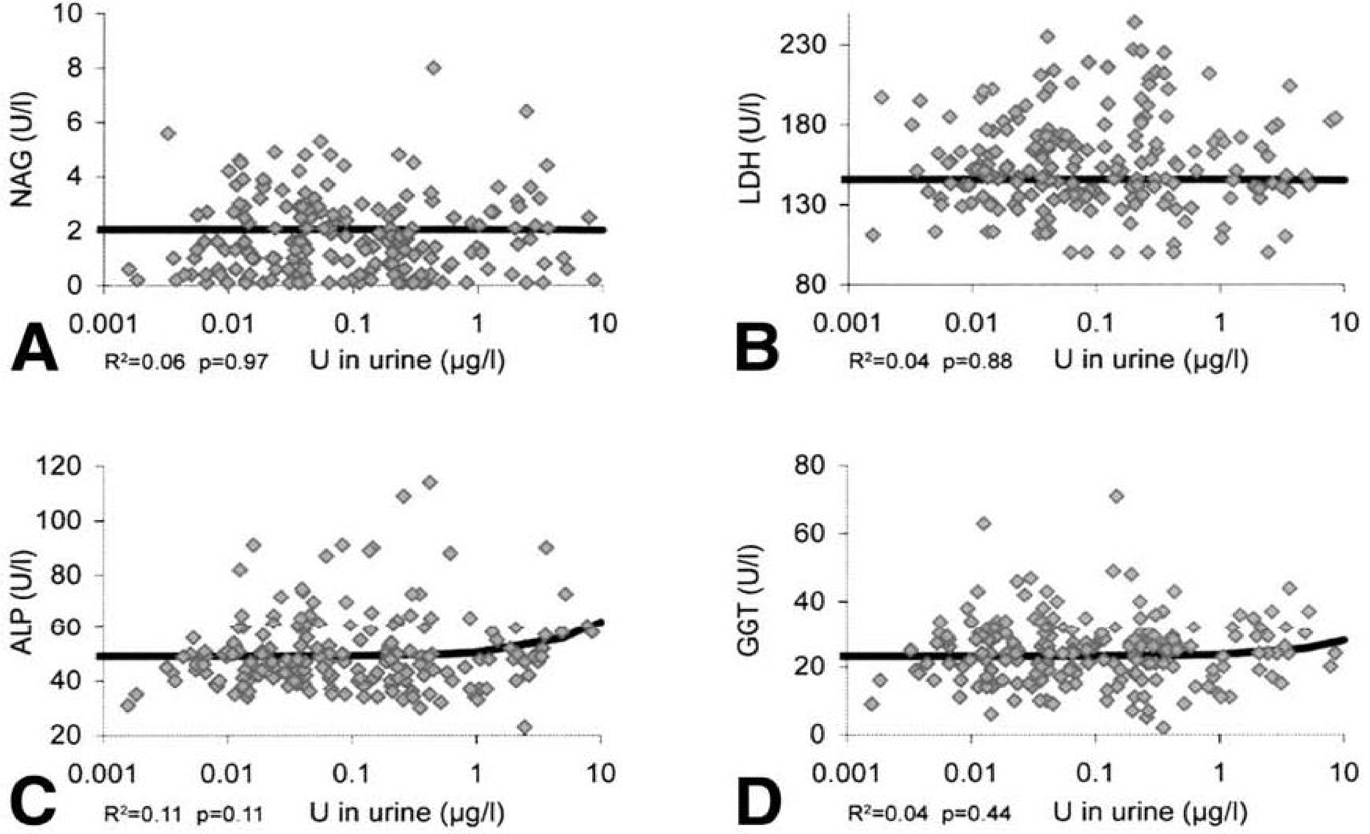


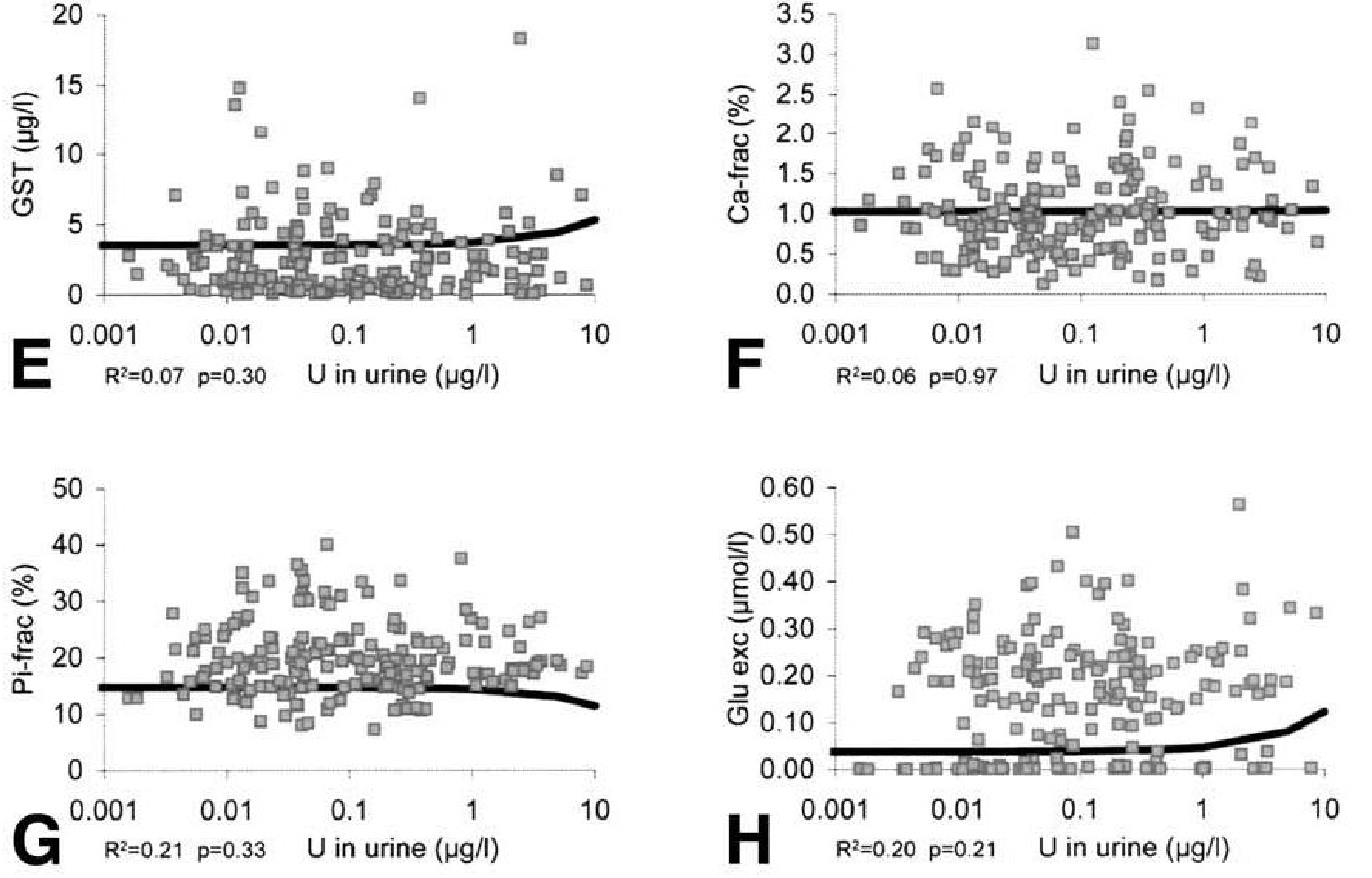
Fig 3. Comparison between uranium (U) (A) in drinking water and (B) in urine in the previous sampling in 1999 (y-axis) and current sampling in 2003 (x-axis). Abbreviations: b, coefficient; R^2, regression coefficient.

Results

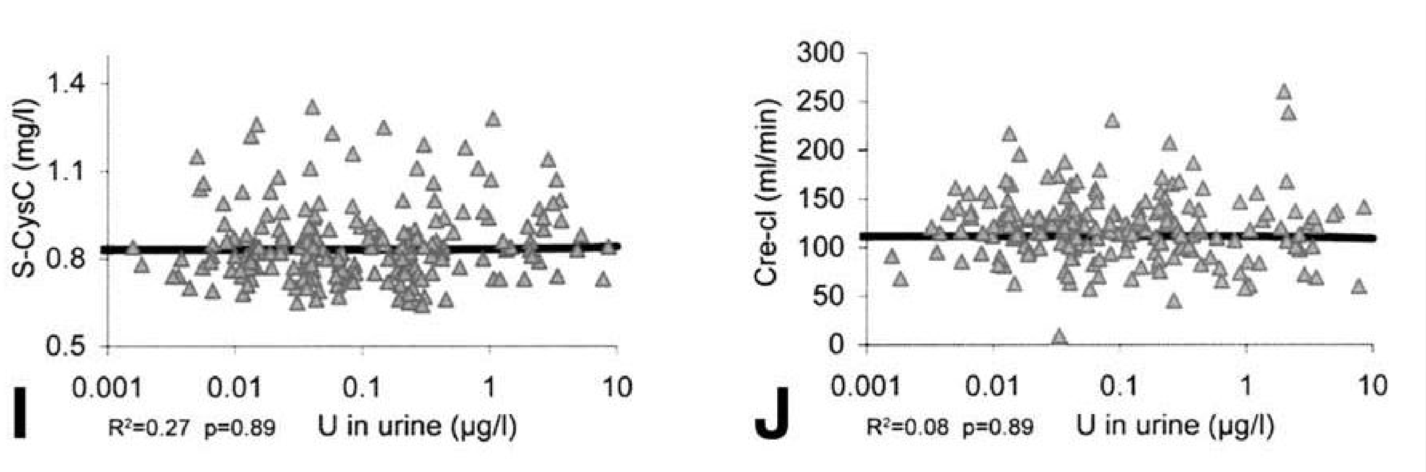


NAG (U/l)
A
R²=0.06 p=0.97
U in urine (µg/l)
LDH (U/l)
B
R²=0.04 p=0.88
U in urine (µg/l)
ALP (U/l)
C
R²=0.11 p=0.11
U in urine (µg/l)
GGT (U/l)
D
R²=0.04 p=0.44
U in urine (µg/l)

Results


20
15
10
5
0
GST (µg/l)
0.001
0.01
0.1
1
10
E
R²=0.07 p=0.30
U in urine (µg/l)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Ca-frac (%)
0.001
0.01
0.1
1
10
F
R²=0.06 p=0.97
U in urine (µg/l)
50
40
30
20
10
0
Pi-frac (%)
0.001
0.01
0.1
1
10
G
R²=0.21 p=0.33
U in urine (µg/l)
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Glu exc (µmol/l)
0.001
0.01
0.1
1
10
H
R²=0.20 p=0.21
U in urine (µg/l)

Results



1.4
1.1
0.8
0.5
S-CysC (mg/l)
0.001
0.01
0.1
1
10
I
R²=0.27 p=0.89
U in urine (µg/l)
300
250
200
150
100
50
0
Cre-cl (ml/min)
0.001
0.01
0.1
1
10
J
R²=0.08 p=0.89
U in urine (µg/l)

Results

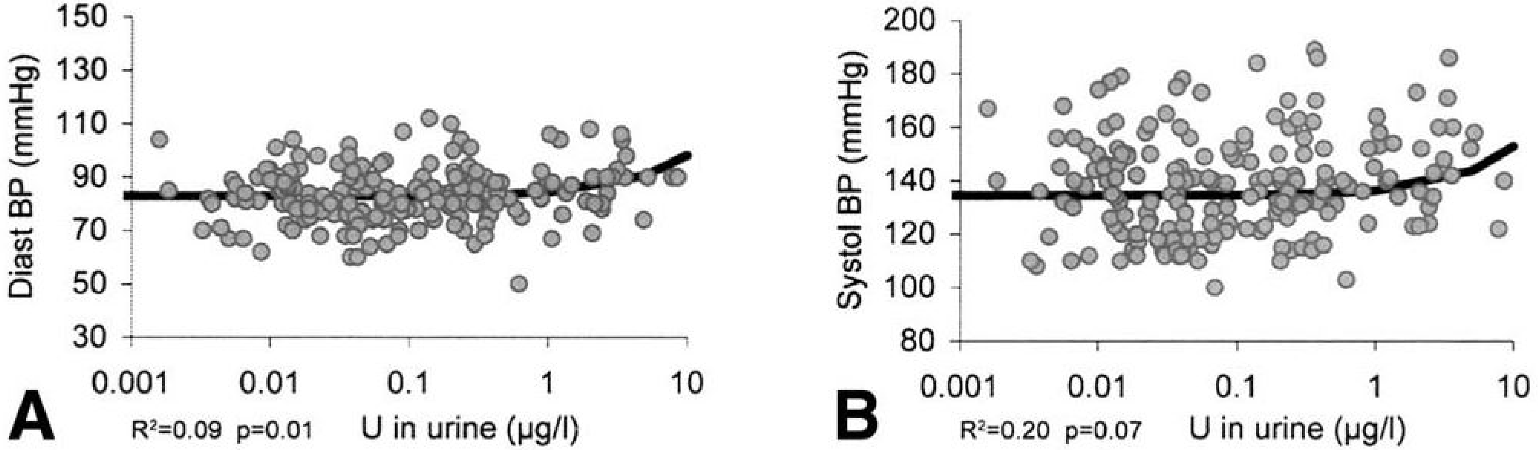


Fig 6. Associations between uranium (U) in urine and (a) diastolic (diast BP) and (b) systolic blood pressure (systol BP). Lines represent results from regressions described in Methods. Adjusted R^2 for models and *P* for exposure are shown.

Discussion

Biomarkers

Blood pressure

Comparisons to prior study

68% of urine samples exceeded the 95^{th} percentile

Discussion

Confounders

Threats to external validity

Comparing this study to other studies

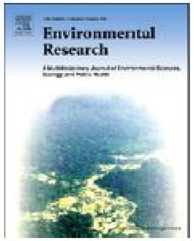
Journal Article #3

Environmental Research 109 (2009) 486–494

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres



Nephrotoxicity of uranium in drinking water from private drilled wells☆

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Research Question

Is there an association between exposure to uranium in drinking water and changes in markers of kidney function?

Type of Study/Methods

Observational/Cohort

Study area selected

Owners of wells in the designated area identified and contacted

Control group

Type of Study/Methods

N=301 in exposure group

N=152 in control group

Inclusion/exclusion criteria

Demographics

Water and Urine Analysis

www.nwbrhc.org

commons.wikimedia.org

Markers of Cytotoxicity/Kidney Damage

Analysis	Method/instrument	Calibrated range
Glucose	Enzymatic/Vitros 250, Johnson & Johnson, Rochester, NY	1.1–36.0 mmol/l
Phosphate	Colorimetric/Vitros 250, Johnson & Johnson, Rochester, NY	1.8–46.0 mmol/l
Calcium	Colorimetric/Vitros 250, Johnson & Johnson, Rochester, NY	0.3–4.4 mmol/l
β_2-Microglobulin	Chemiluminiscent immunometric/ Immulite, Diagnostics Products Co, Los Angeles, CA	4–500 μg/l
NAG	Enzymatic/Hitachi 911, Roche/ Hitachi Systems, Roche Diagnostics Scandinavia, Stockholm, Sweden	0–28 U/l
Kappa chains	Immunoturbidimetric/Hitachi 911, Roche/Hitachi Systems, Roche Diagnostics Scandinavia, Stockholm, Sweden	7–3000 mg/l
Lambda chains	Immunoturbidimetric/Hitachi 911, Roche/Hitachi Systems, Roche Diagnostics Scandinavia, Stockholm, Sweden	7–3000 mg/l
Protein HC	Immunoturbidimetric/Hitachi 911, Roche/Hitachi Systems, Roche Diagnostics Scandinavia, Stockholm, Sweden	2–220 mg/l
Albumin	Immunoturbidimetric/Hitachi 911, Roche/Hitachi Systems, Roche Diagnostics Scandinavia, Stockholm, Sweden	3–8000 mg/l
Creatinine	Enzymatic/Hitachi 911, Roche/ Hitachi Systems, Roche Diagnostics Scandinavia, Stockholm, Sweden	0.03–35 mmol/l

Type of Study/Methods

Three indices of exposure used for analysis:

1) Uranium concentration in water samples
2) Estimated cumulative uranium exposure
3) Uranium concentration in urine samples

Subgroup analysis

Analyses for confounding factors

Results

Water Analysis

Table 3
Levels (µg/l) of uranium and some other nephrotoxic elements in water samples from private drilled wells ($n = 153$[a]) and the municipal waterworks ($n = 14$), Årjäng municipality.

Element	Drilled wells Median (range)	Municipal water Median (range)
Cadmium	<0.20 (<0.20–0.40)	<0.20
Lead	<0.50 (<0.50–61.3)	<0.50
Mercury	<0.20 (<0.20–0.60)	<0.20
Uranium	6.7 (<0.20–470)	<0.20

[a] Three wells missing due to unclear identity.

Results

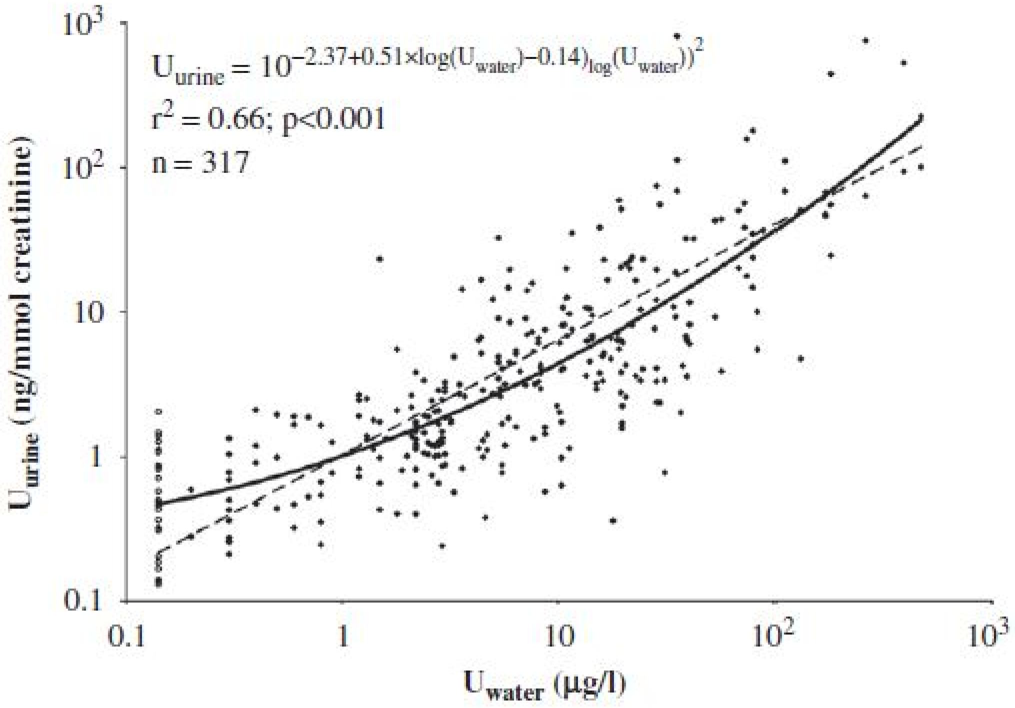

Fig. 3. Associations between uranium levels in urine samples from exposed subjects (◆) and controls (○) and uranium levels in water from drilled wells and municipal water, respectively, Årjäng municipality. Dashed regression line from Kurttio et al. (2002).

Results

Table 7
Results of regression analysis of levels of biochemical analytes (adjusted for creatinine and log transformed) in urine in relation to uranium exposure assessed by either water or urine levels, controlling for age, gender and smoking.

Exposure	*n*	Calcium	β_2-Microglobulin	NAG	Kappa chains	Lambda chains	Protein HC	Albumin
Uranium in water (μg/l)								
Controls (<0.2)	152	1	1	1	1	1	1	1
⩽14.9	200	0.91 (0.77–1.08)	1.37 (0.98–1.90)	0.86 (0.73–1.02)	1.14 (0.92–1.42)	0.93 (0.83–1.04)	1.14 (0.97–1.35)	1.08 (0.75–1.56)
⩾15.0	101	0.82 (0.67–1.01)	1.03 (0.70–1.53)	0.85 (0.70–1.03)	1.11 (0.86–1.44)	1.00 (0.87–1.14)	1.18 (0.97–1.43)	0.99 (0.64–1.54)
Uranium in urine (nmol/mmol creatinine)								
<0.003	140	1	1	1	1	1	1	1
0.003–0.0149	172	1.09 (0.91–1.30)	**1.44** (1.02–2.03)	0.97 (0.82–1.16)	**1.28** (1.02–1.61)	1.09 (0.97–1.23)	**1.24** (1.04–1.47)	1.08 (0.73–1.59)
⩾0.015	141	0.86 (0.72–1.04)	**1.43** (1.00–2.06)	0.98 (0.82–1.18)	**1.32** (1.04–1.68)	1.07 (0.95–1.21)	**1.25** (1.04–1.50)	1.16 (0.78–1.74)

Presented values (significantly different from unity in bold) are values of e^{β} (with 95% confidence intervals in parenthesis), which denotes the estimated ratio of the stratum-specific geometric mean to that of the reference category.

Results

Urine Analysis

Table 8

Results of regression analysis of levels of biochemical analytes (adjusted for creatinine and log transformed) in urine in relation to uranium in urine from study participants, controlling for age, gender and smoking. Subjects with diabetes ($n = 23$) were excluded.

Uranium in urine (nmol/mmol creatinine)	*n*	Calcium	β_2-Microglobulin	NAG	Kappa chains	Lambda chains	Protein HC	Albumin
<0.003	132	1	1	1	1	1	1	1
0.003–0.0149	161	1.07 (0.89–1.28)	1.38 (0.97–1.97)	0.94 (0.78–1.12)	1.20 (0.95–1.52)	1.06 (0.94–1.20)	1.13 (0.95–1.34)	1.05 (0.70–1.57)
⩾0.015	137	0.86 (0.71–1.03)	**1.48** (1.03–2.13)	0.98 (0.82–1.18)	**1.32** (1.04–1.68)	1.07 (0.94–1.21)	**1.21** (1.01–1.44)	1.17 (0.78–1.78)

Presented values (significantly different from unity in bold) are values of e^{β} (with 95% confidence intervals in parenthesis), which denotes the estimated ratio of the stratum-specific geometric mean to that of the reference category.

Discussion

Positive correlation to urine uranium concentration:

1) B2-microglobulin
2) Kappa chains
3) Protein HC

No clear dose-response, except excluding diabetes

Discussion

Confounders

Threats to external validity

Possibility of Type 1 error(s)

Polling question #2

Prolonged exposure to uranium in drinking water has been shown to cause overt renal dysfunction in humans:

A. True
B. False

Journal Article #4

Available online at www.sciencedirect.com

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Environmental Research 102 (2006) 333–338

Environmental Research

www.elsevier.com/locate/envres

Well water radioactivity and risk of cancers of the urinary organs

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Available online 31 January 2006

Polling question #3

Currently available data in humans shows an association between uranium in drinking water and:

A. Renal cell carcinoma
B. Bladder malignancies
C. Both of the above
D. Neither of the above

Background

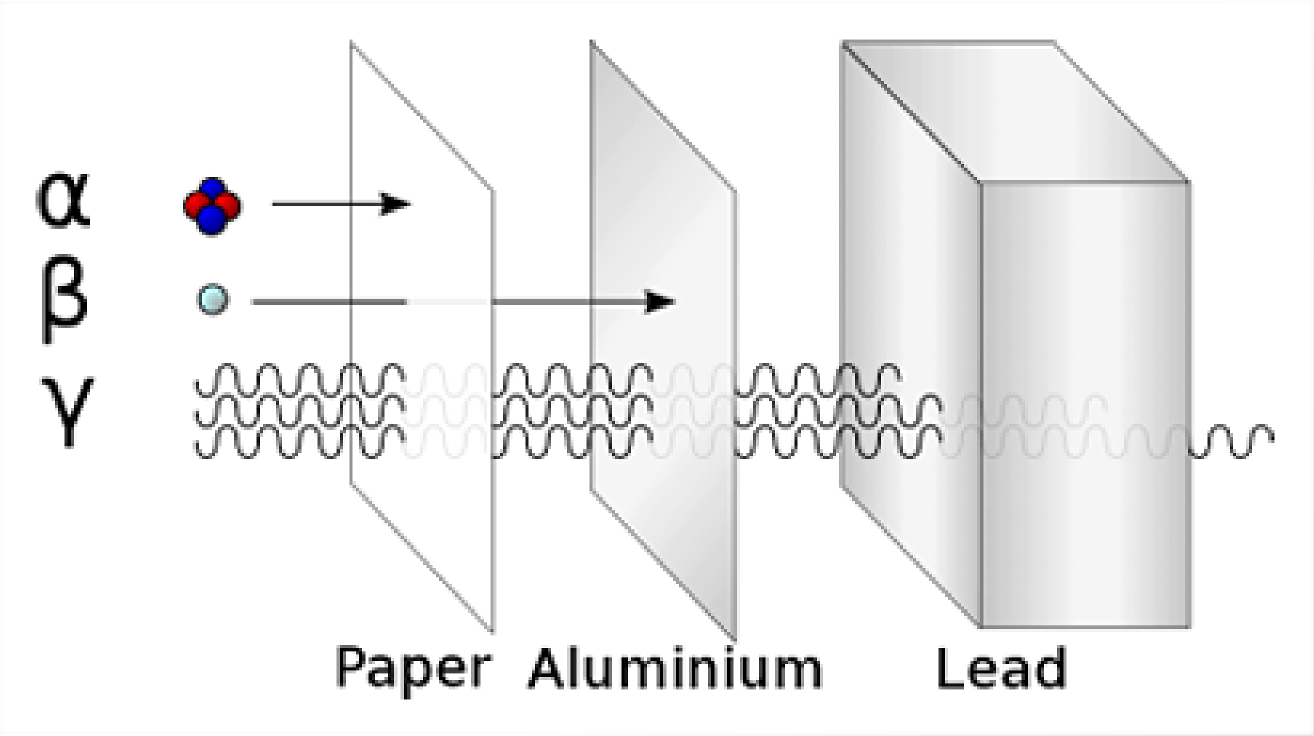
Ionizing radiation is one of the best established human carcinogens

Radionuclide levels in drilled wells are clearly higher than in shallow wells

Important nuclides include radon, uranium, and radium

Background

Types of radiation



www.cooking-hacks.com

Background

Possible effects on the kidney and bladder

Radionuclide absorption and elimination

Prior data

Research Question

Is there an association between exposure to naturally occurring radionuclides in drinking water and risk of bladder or kidney cancers?

Type of Study/Methods

Case-cohort study

274 controls

61 bladder cancer cases

51 kidney cancer cases

Methods: Exposure Assessment

Blind analysis of water samples

Sampling/resampling technique

Calculation of equivalent organ doses and cumulative organ doses

Results

Guidelines for radon levels exceeded in 8% of wells

Radium activity concentration guidelines exceeded in only 2 wells

Uranium concentrations exceeded WHO guidelines in 12% of wells

Results

Table 1
Activity concentrations of radionuclides in drinking waters and radiation doses due to consumption of radionuclides in drinking water by cancer status

Level of		Bladder cancer cases ($n = 61$)	Kidney cancer cases ($n = 51$)	Reference cohort ($n = 274$)
Radon (^{222}Rn) (Bq/L)	Mean	556	438	321
	Median	170	140	130
	25–75th percentile	34–550	49–350	39–340
Radium (^{226}Ra) (Bq/L)	Mean	0.05	0.02	0.03
	Median	0.01	0.01	0.01
	25–75th percentile	0.005–0.02	0.005–0.03	0.005–0.02
Total uranium ($^{234}U + ^{235}U + ^{238}U$) (Bq/L)	Mean	0.28	0.35	0.45
	Median	0.08	0.07	0.06
	25–75th percentile	0.02–0.17	0.02–0.18	0.01–0.23
Effective dose (μSv/year)	Mean	438	327	244
	Median	112	91	93
	25–75th percentile	25–413	39–224	28–239
Equivalent bladder dose (μSv/year)	Mean	19		16
	Median	5		5
	25–75th percentile	2–15		2–14
Equivalent kidney dose (μSv/year)	Mean		175	166
	Median		49	52
	25–75th percentile		23–141	16–154
Duration of well water consumption by the end of the follow-up (years)	Mean	19	19	21
	Median	18	19	20
	25–75th percentile	15–24	12–23	15–25
Cumulative effective dose by the end of the follow-up (mSv)	Mean	7.8	6.4	4.9
	Median	1.9	1.6	1.8
	25–75th percentile	0.5–7.7	0.6–5.2	0.5–5.2

Results

Table 2
Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for bladder and kidney cancers by level of exposure to radionuclides in drinking water

Exposure	*n* (reference cohort)	Bladder cancer			Kidney cancer		
		n (cases)	HR[a]	95% CI	*n* (cases)	HR[b]	95% CI
Radon (Bq/L)							
<130	139	28	1		25	1	
130–399	73	13	0.67	0.31–1.44	14	0.64	0.30–1.38
400–19,000	62	20	1.34	0.66–2.72	12	0.70	0.29–1.67
Radium (Bq/L)							
<0.01	159	37	1		25	1	
0.01–0.02	69	14	1.07	0.54–2.09	13	0.53	0.25–1.16
0.03–1.9	46	10	0.82	0.37–1.83	13	0.70	0.30–1.65
Total uranium (Bq/L)							
<0.06	136	27	1		23	1	
0.06–0.19	62	19	1.56	0.73–3.48	16	1.04	0.49–2.22
0.20–21	76	15	0.90	0.41–1.98	12	0.74	0.33–1.66
Effective dose (μSv/year)							
<100	141	28	1		28	1	
100–299	75	14	0.78	0.35–1.72	12	0.55	0.24–1.26
300–11,246	58	19	1.33	0.62–2.82	11	0.69	0.29–1.65
Equivalent organ dose (μSv/year)							
<5	139/134[c]	31	1		26	1	
5–14	70/70[c]	12	0.72	0.31–1.65	13	0.63	0.27–1.44
15–460	65/70[c]	18	1.02	0.47–2.19	12	0.76	0.32–1.79

[a]Adjusted for age, sex, and smoking.
[b]Adjusted for age, sex, smoking, and body mass index.
[c]Number of reference cohort members in the equivalent bladder/kidney dose group in the analysis of bladder/kidney cancer risk.

Discussion

No statistically significant association found between exposure variables and bladder or kidney cancer risk

Other studies have not shown association between ingested radionuclides and stomach cancer or leukemia

Discussion

Background exposure vs those in this study

Inhaled radon

Confounders

Low statistical power of this study

Polling question #3

Currently available data in humans shows an association between uranium in drinking water and:

A. Renal cell carcinoma
B. Bladder malignancies
C. Both of the above
D. Neither of the above

Testing and patient management

What do I need to do if my patient has been exposed to uranium in drinking water?

What do I tell my patient about their exposure?

Is there a treatment for uranium exposure?

What resources are available for providers and patients?

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Questions?

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