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RENAL EFFECTS OF EXPOSURE TO NATURAL AND DEPLETED URANIUM: A REVIEW OF THE EPIDEMIOLOGIC AND EXPERIMENTAL DATA

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Elevated levels of naturally occurring uranium in groundwater have been found in small geographic areas throughout the world. Relevant research was reviewed pertaining to natural and depleted uranium (DU) exposure and nephrotoxicity, including epidemiologic community-based and occupational studies, studies of Gulf War veterans exposed to DU, and experimental studies in animals. Occupational cohort studies do not provide evidence of an increased risk of kidney-related mortality among uranium-exposed workers. However, occupational and community-based studies of populations chronically exposed to elevated drinking-water concentrations of uranium provide some evidence of adverse renal effects, as assessed by biomarkers of proximal tubule damage such as urinary levels of glucose, calcium, and various low-molecular-weight proteins. Indications of proximal tubule effects, as evidenced by increased urinary β_2 -microglobulin and retinol binding protein levels, were also seen in the most recent follow-up surveillance study of Gulf War veterans exposed to DU. The reported β_2 -microglobulin levels in these studies were generally considered to be within normal limits, but the long-term implications of the observed variation in these levels are not established. The kidney was observed to be a target of uranium toxicity following oral and implantation exposure routes in several animal species. The interpretation and importance of the observed changes in biomarkers of proximal tubule function are important questions that indicate the need for additional clinical, epidemiological, and experimental research.

Natural uranium (U) refers to uranium compounds with a naturally occurring composition of radioisotopes uranium-234, uranium-235, and uranium-238. Uranium is found in all soils and rock, with higher concentrations found in phosphate rock, lignite, and monazite sands (ATSDR, 1999). Uranium enrichment processes increase the concentration of U-235 from <1% to 2–4%. Depleted uranium (DU) refers to the less radioactive form of uranium remaining after enrichment. Depleted uranium is approximately 60% less radioactive than naturally occurring U because of decreased levels of U-235 (Bleise et al., 2003), and U has been

used by the U.S. Department of Defense (DoD) and Armed Forces for various weapons systems since the late 1970s (Arfsten et al., 2001; Abu-Qare and Abou-Donia, 2002).

Elevated concentrations of U greater than 20 $\mu\text{g/L}$ were detected in various Western groundwater systems and scattered pockets in the groundwaters of North Carolina, Maine, Connecticut, and other Eastern states (Orloff et al., 2004; U.S. EPA, 1985, 2000). Areas of high U concentrations in water are also found in many other countries globally, including Canada, Finland, the United Kingdom, and India (WHO, 2001). According

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to biomonitoring data collected by the Centers for Disease Control (CDC, 2005) as part of the Third National Report on Human Exposure to Environmental Chemicals, the geometric mean concentration of U in urine for the U.S. population (ages 6 yr and older) for survey years 2001–2002 was 0.009 $\mu\text{g/L}$ (95th percentile: 0.046 $\mu\text{g/L}$).

Craft et al. (2004) summarized data pertaining to a broad range of adverse health effects due to natural U and DU, including neurotoxicity, nephrotoxicity, reproductive effects, cancer, and effects on other systems. Renal effects were the focus of a recent case study of a family in western Connecticut describing the potential for nephrotoxicity from exposure to well water containing elevated levels of naturally occurring U, and the sensitivity of young children resulting from their increased exposure potential and their state of development (Magdo et al., 2007). In this review, research pertaining to U exposure and nephrotoxicity, focusing on the available epidemiologic data including (1) community-based and occupational studies of biomarkers of kidney damage, (2) occupational studies of kidney-related mortality, and (3) studies of soldiers exposed to DU, is presented. The animal nephrotoxicity and mechanism of action data have been reviewed previously (ATSDR, 1999); a summary of this and recent literature is also included later in this article.

STUDIES IN HUMANS

Measures of Renal Function

Kidney disease varies in severity from kidney failure requiring transplantation or dialysis to a subclinical, asymptomatic phase where some level of kidney damage may occur without detectable decreases in renal function. In clinical studies, such as prognostic studies of patients with diabetes or other conditions with a high risk of chronic kidney disease and its related complications, renal function has often been monitored by blood and 24-h urine samples allowing for the measurement of blood urea nitrogen (BUN) levels, total protein in the urine, and calculation of glomerular filtration

rate (GFR). In community-based studies, less burdensome data collection techniques are usually required, resulting in the collection of a single urine sample at a study visit (a spot urine sample) or an overnight urine sample (i.e., first morning void). Another difference between clinical and community-based studies is that in the latter, it is more important that the methodology is able to accurately assess variability in the earliest phases of disease, when kidney function is still relatively high (Levey et al., 2009).

In addition to general measures of kidney function, other types of measures address specific types of damage that may occur. Larger molecules, such as albumin, are filtered by the glomeruli and reabsorbed by the proximal tubule through receptor mediated endocytosis (Birn and Christensen, 2006). Most of the albumin reabsorbed by the proximal tubule cells (approximately 95%) is returned to the plasma. The remaining amount is degraded in cell lysosomes and excreted in the urine (Comper et al., 2006). Glomerular and tubular injury may result in increased levels of urinary albumin. Tests of general glomerular function include creatinine clearance or GFR, as well as determination of urinary protein and urinary albumin concentrations, with the latter two measures reflecting the integrity of the glomerulus (i.e., the leakage of molecules through the filter). Damage to the proximal tubule decreases small-molecule reabsorption and results in increased urinary levels of glucose, calcium, and phosphate, and of low-molecular-weight proteins such as β_2 -microglobulin, protein human complex forming (HC) [or α -microglobulin], kappa chains, and retinol binding protein (Eneigh & Kinter, 2005; Seldén et al., 2009). β_2 -Microglobulin is an endogenous low-molecular-mass protein (12 kD) that forms part of the class I major histocompatibility complex and is located on the surface of nucleated cells. During cell turnover β_2 -microglobulin is released into the extracellular fluid and normally filtered by the glomerulus and reabsorbed in the proximal tubule (Bagshaw et al., 2007; Tolkoff-Rubin et al., 1988). Retinol binding protein (21 kD) is

primarily expressed in the liver and also reabsorbed by the proximal tubule (Bagshaw et al., 2007). Enzyme activity levels have also been used as markers of tissue damage at specific sites, with alkaline phosphatase (AP), *N*-acetyl- β -D-glucosaminidase (NAG), and γ -glutamyl transferase (GGT) reflecting proximal tubular tissue damage and other enzymes, such as lactate dehydrogenase (LDH), more indicative of damage to the distal tubule (Zalups et al., 1988; Emeigh 2005; Zamora et al., 2009; Seldén et al., 2009).

Community-Based Studies

Several studies of populations chronically exposed to elevated drinking-water concentrations of U were conducted (Kurttio et al., 2002; Kurttio et al., 2006; Mao et al., 1995; Seldén et al., 2009; Zamora et al., 1998; Zamora et al., 2009). Three studies in Canada (in Saskatchewan, Quebec, and Nova Scotia), two in Finland, and one in Sweden evaluated renal function in communities with high concentrations of U in the drinking water supply (Table 1). Mean or median U concentrations in the drinking water of the exposed communities were approximately 7 $\mu\text{g/L}$ in Sweden, 15–20 $\mu\text{g/L}$ in Saskatchewan, 28 $\mu\text{g/L}$ in Finland, 39 $\mu\text{g/L}$ in Quebec (based on the maximum level measured over a 15-yr period), and more than 100 $\mu\text{g/L}$ in Nova Scotia (Figure 1); corresponding values in the comparison nonexposed communities were <1 $\mu\text{g/L}$. Uranium concentrations in urine also varied considerably among these studies, with a median of 0.03 $\mu\text{g/L}$ in Sweden, 0.078 $\mu\text{g/L}$ in Finland, and 0.14 $\mu\text{g/L}$ in Quebec.

The first of these studies, in Saskatchewan, measured urinary albumin in a first morning urine sample from 60 adults in 2 communities with elevated levels of U in drinking water (means of 14.7 and 19.6 $\mu\text{g/L}$) and 40 controls from a comparison (control) community (mean drinking water U concentration of 0.71 $\mu\text{g/L}$) (Mao et al., 1995). Cumulative intake was calculated as the product of concentration of U in water, average number of cups consumed per day, and years at current residence; the mean

or range of this measure was not given. A correlation was seen between cumulative intake and urinary albumin, which was of marginal statistical significance when adjusting for age and diabetes history (Table 1).

Subsequent studies used a more extensive array of urinary and serological measures to assess kidney function. The studies from Canada were conducted in Nova Scotia (Zamora et al., 1998) and in a Quebec First Nations community (Zamora et al., 2009), with 30 and 54 exposed participants, respectively (Table 1). The study in Nova Scotia calculated a daily U intake based on the product of concentration of U in water or food and the amount consumed (based on 3-d food and water samples) and ranged from 3 to 570 $\mu\text{g/d}$ in the exposed community and from <1 to 20 $\mu\text{g/d}$ in the control community. Urinary U and glucose, protein, and creatinine concentrations were measured in a 24-h urine sample, and β_2 -microglobulin levels were measured in an overnight urine sample. Daily U intake correlated significantly with markers of proximal tubule injury: urinary glucose ($r_s = 0.40$; $p = 0.001$), AP ($r_s = 0.28$; $p = 0.05$), and β_2 -microglobulin ($r_s = 0.39$; $p = 0.01$). Weaker or no correlations were seen with urinary NAG activity ($r_s = 0.15$; 0.29), protein ($r_s = 0.17$; 0.23), creatinine ($r_s = 0.11$; 0.45), and LDH activity ($r_s = 0.02$; 0.89) levels, and a negative correlation coefficient was seen with GGT activity ($r_s = -0.22$; 0.12).

In Quebec, the study protocol was similar to that of the Nova Scotia study. Exposure was measured or calculated as the maximum water U concentration in prior 15 yr, cumulative intake in prior 15 yr (median 87 mg), cumulative intake in past 2.8 yr (median 22 mg), and U concentration in urine (median 0.14 $\mu\text{g/L}$) (Zamora et al., 2009). Adjusting exposure and renal biomarker measures for fluid intake, U concentration in urine was significantly correlated with GGT activity ($r_s = 0.37$) and β_2 -microglobulin ($r_s = 0.49$). Weaker correlations were seen with albumin ($r_s = 0.23$), glucose ($r_s = 0.14$), AP activity ($r_s = 0.15$), and NAG activity ($r_s = 0.15$).

TABLE 1. Community-Based Studies of Markers of Renal Function in Relation to Uranium in Drinking Water

Reference(s)	Study location and participants	Exposure measure(s)	Primary positive results
Canada Mao et al., 1995	Saskatchewan, Canada ($n = 40$ from one control community, $n = 60$ from two exposed communities). Mean age not reported, range 18 to 84 yr.	Cumulative intake ^a (range not given)	Cumulative intake correlated with urine albumin (per mmol creatinine levels, Beta = 0.13, $p = .03$; per mg/L, Beta = 2.19, $p = .07$), adjusting for age and diabetes history.
Zamora et al., 1998	Nova Scotia, Canada ($n = 30$ from a high exposure community (water uranium concentrations > 100 µg/L), $n = 20$ from a low exposure community (water uranium concentrations of < 1 µg). Mean age 37, range 13 to 87 yr.	Uranium concentration in drinking water and daily intake ^b	Daily uranium intake correlated with markers of proximal tubule injury: urinary glucose ($r_s = 0.40$, $p = .001$), alkaline phosphatase ($r_s = 0.28$, $p = .05$), and β_2 -microglobulin ($r_s = 0.39$, $p = .01$).
Zamora et al., 2009	Quebec First Nations Community (Kitigan Zibi), Canada ($n = 54$). Mean age 38, range 12 to 73 yr.	Maximum water uranium concentration in past 15 yr; cumulative intake in past 15 yr; cumulative intake in past 2.8 yr; urinary uranium	In analyses adjusting exposure and renal biomarker measures for fluid intake, urinary uranium correlated with gamma glutamyl transferase ($r_s = 0.37$, $p = .0064$) and β_2 -microglobulin ($r_s = 0.49$, $p = .0047$).
Europe Kurttio et al., 2002	Southern Finland ($n = 325$ from areas with high water uranium levels). Mean age 52, range 15 to 82 yr.	Uranium concentration in drinking water, daily intake, ^c cumulative intake, ^d and urinary uranium	All uranium measures correlated with fractional excretion of calcium and increased systolic and diastolic blood pressure; urinary uranium measures also correlated with fractional excretion of phosphate and glucose.
Kurttio et al., 2006	Southern Finland ($n = 193$, subset of Kurttio et al. 2002). Mean age 56, range 18 to 81 yr.	Uranium concentration in drinking water, daily intake, ^c cumulative intake ^d	Glucose excretion associated with cumulative intake measure ($p = .02$); urinary uranium associated with increased systolic ($p = .01$) and diastolic blood pressure ($p = .07$).
Seldén et al., 2009	Arjäng, Sweden ($n = 301$ exposed, $n = 153$ controls). Mean age 51 (exposed) and 55 (controls), range 18 to 74 yr.	Uranium concentration in drinking water, cumulative intake, ^d urinary uranium	Significant correlation between urinary uranium concentrations and β_2 -microglobulin, protein HC, and kappa chains; in males, cumulative intake was associated with protein HC.

Note. See Figure 1 for more detailed description of water uranium concentrations in exposed communities.

^aThe product of concentration of uranium in the water, average number of cups consumed per day, and years at current residence.

^bThe product of concentration of uranium in the water or food and the amount consumed (based on 3-d food and water samples).

^cThe product of concentration of uranium in the water and volume used per day.

^dThe product of concentration of uranium in the water, volume used, and duration of water consumption.

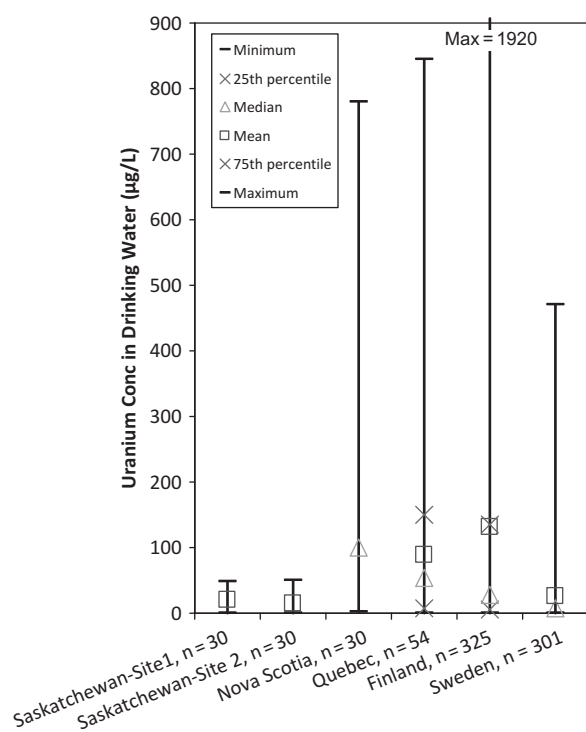


FIGURE 1. Uranium concentrations in drinking ($\mu\text{g/L}$) water in community studies. Saskatchewan sites 1 and 2, Mao et al. (1985), detection limit = $0.1 \mu\text{g/L}$; Nova Scotia, Zamora et al. (1998), detection limit = $0.0006 \mu\text{g/L}$; Quebec, Zamora et al. (2009), detection limit = $0.0006 \mu\text{g/L}$ (concentration values based on table of unadjusted data in Zamora et al., 2009); Finland, Kurttio et al. (2002, 2006), detection limit = $0.0004 \mu\text{g/L}$; Sweden, Seldén et al. (2009), detection limit = $0.2 \mu\text{g/L}$. Control community drinking water uranium concentrations were $<1 \mu\text{g/L}$.

Kurttio et al. (2002) conducted a study in 1999 of 325 individuals from areas in Finland with high uranium levels in the drinking water (Table 1). These individuals had used well water for at least 1 yr, and completed a questionnaire that included information on residential history and water consumption, allowing for calculation of measures of daily and cumulative U intake from water. A drinking-water sample (for measurement of U levels), overnight urine sample (for measurement of urinary U, glucose, creatinine, calcium, phosphate, and albumin), spot urine (for β_2 -microglobulin measurement), and a nonfasting blood sample were collected. Daily intake ranged from <1 to $4128 \mu\text{g/d}$ (median $39 \mu\text{g/d}$), cumulative intake ranged from <1 to $33,100 \text{ mg}$ (median 129 mg), and U concentration in

urine ranged from <1 to $5.65 \mu\text{g/L}$ (median $0.078 \mu\text{g/L}$). Urinary U concentrations were correlated with fractional excretion of calcium (beta per 1 unit $\mu\text{g}/\text{mmol}$ creatinine increase in urinary uranium = 1.5 , 95% CI 0.6 – 2.3) and phosphate (beta = 13 , 95% CI 1.4 – 25), and more weakly with glucose (beta = 0.7 , 95% CI 0.4 – 1.8); associations with systolic and diastolic blood pressure (age, gender, body mass index, and smoking-adjusted beta = 6.8 and 8.5 , respectively) were also seen. Kurttio et al. (2002) did not observe a relationship between U exposure and creatinine clearance, urinary albumin, or β_2 -microglobulin. The high proportion (65%) of β_2 -microglobulin values below the detection limit in the samples was a limitation of this analysis. In a subsequent study, Kurttio et al. (2006) recontacted the cohort in 2003; 222 (68%) lived in the same house as in 1999 and agreed to participate; 193 of these provided water, an overnight urine, and a blood sample for the follow-up study. β_2 -Microglobulin was not measured in this study. Median daily intake of U from drinking water was $36 \mu\text{g/L}$, similar to the mean of $39 \mu\text{g/L}$ in the baseline study reported by Kurttio et al. (2002). In the follow-up study, associations were only seen between urinary U concentrations and systolic and diastolic blood pressure, and between the cumulative intake measure and urinary glucose.

Another relatively large study included 301 participants from western Sweden living in areas with elevated levels of uranium in the drinking water obtained from wells and 151 controls from a nearby city using a city water supply (Seldén et al., 2009) (Table 1). Questionnaire data pertaining to drinking water consumption, smoking history, and other potential exposures were collected, and an overnight urine sample was collected from all participants; the members of the exposed groups and 15 randomly selected members of the control group also provided a water sample. Levels of cadmium (Cd), lead (Pb) and mercury (Hg) in the water samples were low (means $\leq 0.50 \mu\text{g/L}$) and similar in both areas. The median U levels in the water were 6.7 and $<0.20 \mu\text{g/L}$ in

the exposed and control samples, respectively, and the median U concentrations in urine were 0.03 and 0.0047 $\mu\text{g/L}$ in exposed and controls, respectively. In the regression analyses adjusting for age, gender, and smoking and excluding 23 participants with diabetes, levels of low-molecular-weight proteins (β_2 -microglobulin, kappa chains, and protein HC) were increased in relation to a 3-level variable for U concentrations in urine (<0.003 , 0.003 – 0.0149 and ≥ 0.015 nmol/mmol creatinine). For β_2 -microglobulin, the geometric mean was approximately 50% higher (i.e., ratio of geometric mean in the higher compared with lowest group = 1.48, 95% CI 1.03–2.13), and for kappa chains and protein HC, the elevations were 30% (ratio 1.32, 95% CI 1.04–1.68) and 20% (ratio 1.21, 95% CI 1.01–1.44), respectively. An association was also seen between protein HC and cumulative intake in males (ratio 1.40, 95% CI 1.08–1.81 in the middle category and 1.45, 95% CI 1.00–2.08) in the highest category of exposure). This pattern was not seen in females.

Occupational Exposure Studies

An occupational exposure study evaluating renal function in workers in a Colorado U mill also provides evidence of an association between natural U exposure and increased levels of urinary and serum β_2 -microglobulin (Thun et al., 1985). In one area of this mill, the yellowcake drying and packaging area, exposure to air concentrations of U dust exceeded occupational standards for several years. Mean U concentrations in workers monitored were 65.2, 18.9, 20.5, and 19.1 $\mu\text{g/L}$ urine in 1975, 1976, 1977, and 1978, respectively; these levels fell to means of 9.1 and 6.2 $\mu\text{g/L}$ urine in 1980 and 1981 after the opening of a new mill in 1979. Workers who had worked at least 1 yr in the yellowcake area ($n = 30$) and workers in the crushing area ($n = 12$) were identified, and 39 of these 42 workers participated in the study. The exposure in the crushing area was to a less soluble form of U. A comparison group, matched by race, gender, and age (within 2 yr), was

drawn from workers in a cement production plant in the area; 43 of the identified matches were recruited to the study but 7 of these were subsequently excluded because they had previously worked at the U mill. The final sample included 36 controls and 33 matched pairs. Cadmium levels were similar in the two groups, but blood Pb levels were higher among the controls (mean 0.45 and 0.78 $\mu\text{mol/L}$ in exposed and controls, respectively). Renal function was evaluated through collection of an 8-h urine sample over the course of a workday, and midshift blood samples. Specific measures included serum creatinine and creatinine clearance as markers of glomerular functions and urinary β_2 -microglobulin levels as markers of proximal tubular function. The ratio of the β_2 -microglobulin clearance to creatinine clearance, denoted the fractional excretion, was calculated to represent the tubular component of β_2 -microglobulin excretion. Urinary excretion of β_2 -microglobulin was significantly increased in the workers compared with controls: where in the exposed group, mean (\pm standard deviation, SD) β_2 -microglobulin concentration was 0.06 (± 0.38) mg/g creatinine, compared with 0.036 (± 0.031) in controls. Similar patterns were seen with measures expressed as micrograms per liter, micrograms per hour, and clearance (ml/min) (Table 2). Among the workers at the U plant, relative clearance of β_2 -microglobulin was markedly correlated with duration of employment in the yellowcake area. In contrast, the tendency shown in the markers of glomerular function such as creatinine clearance was toward improved function in the exposed workers (Table 2).

Several cohort studies of workers at uranium processing facilities have examined mortality risk. Most of the detailed analyses focus on malignant diseases, but some data on mortality due to chronic nephritis (International Classification of Diseases, 9th revision, ICD-9, code 582) or other forms of renal disease are available (Table 3). The standardized mortality ratio of chronic nephritis among 8 cohort studies ranged from 0.67 to 1.88, each with relatively wide confidence intervals, and was approximately evenly distributed

TABLE 2. Renal Function Measures in Uranium Mill Workers and a Comparison Group of Workers From a Cement Plant (Thun et al., 1985)

Variable	Uranium mill, exposed (n = 39)			Cement workers (n = 36)			(p value)
	Mean	SD	Range	Mean	SD	Range	
β_2 -Microglobulin ^a							
Serum ($\mu\text{g}/\text{ml}$)	2.05	0.46	1.28–3.40	1.83	0.26	1.36–2.40	(.01)
Urine ($\mu\text{g}/\text{L}$)	54.9	38.7	4.0–140.0	37.6	39.2	1.0–170.0	(.06)
Urine ($\mu\text{g}/\text{h}$)	4.40	2.99	0.36–13.63	2.50	2.05	0.18–10.01	(.002)
Urine (mg/g creatinine)	0.060	0.38	0.004–0.189	0.036	0.031	0.002–0.164	(.004)
Clearance (ml/min)	0.038	0.27	0.002–0.116	0.023	0.019	0.002–0.087	(.01)
Creatinine ^b							
Serum (mg/100 cm ³)	1.15	0.15	0.92–1.74	1.22	0.11	0.91–1.40	(.02)
Urine (mg/100 cm ³)	102.9	62.6	23.1–285.2	114.6	63.5	11.4–259.6	(.42)
Clearance (ml/min) ^c	95.6	20.6	48.8–172.2	88.4	13.0	39.1–116.6	(.08)
Relative clearance ^d	3.95	2.64	0.23–11.19	2.62	2.17	0.18–10.71	(.02)

^a1 μg β_2 -microglobulin = 1 μmol \times 11,600.

^b1 mg creatinine = 1 mmol \times 113.12.

^cCreatinine standardized to a body surface area of 1.73 m².

^d β_2 -Microglobulin clearance \times 10⁴/creatinine clearance.

between estimates greater than 1 (Boice et al., 2008; Dupree-Ellis et al., 2000; Pinkerton et al., 2004), around 1 (Frome et al., 1990; McGeoghegan & Binks, 2000a), and less than 1 (Loomis & Wolf, 1996; McGeoghegan & Binks, 2000b; Polednak & Frome, 1981). The highest relative risk (standardized mortality ratio [SMR] = 1.88, based on 6 observed cases) was seen in the study by Dupres-Ellis et al. (2000), but the authors noted that the work environment of 4 of these cases was likely to have included high exposure to silica dust, which has also been linked to chronic kidney disease. None of these studies demonstrated an elevated risk for the broader category of genitourinary disease, and two studies observed a statistically significant decreased mortality risk (McGeoghegan & Binks, 2006; Loomis & Wolf, 1996).

Clinical Studies in Gulf War Veterans

Depleted uranium applications include armor plating for military vehicles, munitions used to penetrate armored targets, helicopter blade rotor tips, and aircraft landing gear. Approximately 10 and 300 tons of DU were expended by the U.S. Armed Forces during the Kosovo air campaign and the Persian Gulf War, respectively (Arfsten et al., 2001). Depleted uranium dusts and vapors, which may be inhaled or ingested, are generated

during structure impact and perforation by DU munitions (Arfsten et al., 2001; Parkhurst & Guilmette, 2009). Several clinical studies evaluated the effects of exposure to DU in Gulf War veterans who had been mistakenly fired upon by U.S. forces in incidents that took place in February 1991. Exposure occurred via inhalation and ingestion of DU dust in the immediate aftermath of an incident, and through embedded metal fragments in some individuals who were hit by a high-density, penetrating device. In total, 74 soldiers who had been in or on an Army vehicle during one of these incidents have been followed through the Baltimore Veterans Affairs Depleted Uranium Follow-up program, initiated in 1993. This program has followed the majority of the approximately 90 soldiers involved in these incidents who survived and for whom contact information was available. After the initial study visit in 1994, biennial exams were conducted in 1997, 1999, 2001, and 2003 (reviewed in Squibb and McDiarmid, 2006), 2005, and 2007 (McDiarmid et al., 2007, 2009). The clinical and laboratory evaluations included 24-h urinary uranium concentration, with serum and urinary renal function measures. Examination of the 24-h urinary U concentration data over the 14-yr follow-up period revealed continued elevation of U, with levels ranging from 0.003

TABLE 3. Studies of Noncancer Renal Disease Mortality Risk in Uranium Mill Workers

Reference(s) ^a	Sample size (n), inclusion criteria, follow-up, ICD revision ^b	All genitourinary disease			Chronic nephritis		
		Obs	Exp	SMR (CI)	Obs	Exp	SMR (95% CI)
Oak Ridge facilities							
Checkoway et al., 1988; Loomis and Wolf, 1996	n = 8116, Tennessee Eastman Corporation, Y-12 plant, Oak Ridge, TN. Worked ≥30 d between 1947 and 1974, began work after 1947. Follow-up through 1990. ICD-8.	15	NR	0.59 (0.33, 0.97)	5	NR	0.83 (0.27, 1.95)
Frome et al., 1990	n = 28,008 white males, Tennessee Eastman Corporation, several plants, Oak Ridge, TN. World War II workers. Worked ≥30 d before 1948 and did not work after January 1, 1948. Follow-up 1950 through 1979. ICD-8.	148	145.3	1.02 (NR)	52	52.65	0.99 (NR)
Polednak and Frome, 1981	n = 18,869 white males, Tennessee Eastman Corporation, Y-12 plant, Oak Ridge, TN. World War II workers. Worked ≥2 d between 1943 and 1947 and did not work after January 1, 1948. Follow-up through 1974. ICD-8.	63	99.04	0.64 (NR)	30	39.14	0.77 (NR)
Other U.S. facilities							
Boice et al., 2008	n = 718, Grants, NM uranium mill workers without mining experience and with likely exposure to uranium. Worked ≥6 mo between 1955 and 2004; 28% worked ≥5 yr. Follow-up through 2005. ICD-9.			NR	3	2.3	1.30 (0.27, 3.79)
Pinkerton et al., 2004; Waxweiler et al., 1983	n = 1484, white males, 7 mills, Colorado Plateau. Worked ≥1 year in mill, never worked in uranium mine, worked ≥1 d after 1940. 43% worked <3 yr. Follow-up through 1998. Total person-years = 49,925. ICD-9.	13	13.03	1.00 (0.53, 1.71)	8	5.91	1.35 (0.58, 2.67)
Dupree-Ellis et al., 2000	n = 2514, white males, Mallinckrodt Chemical Works, St. Louis, MO. Employed between 1942 and 1966. Average work duration 5.2 yr. Follow-up through 1993. ICD-8.	14	NR	0.95 (0.53, 1.54)	6	NR	1.88 (0.75, 3.81)
Ritz et al., 2000	n = 2218, males, Rocketdyne/Atomics International. Worked 1950–1993, monitored for radiation. Follow-up through 1994. Total person-years = 56,610. ICD-8.	5	6.44	0.78 (0.25, 1.81)	NR		
United Kingdom facilities							
McGeoghegan and Binks, 2000b	n = 19,454 (n = 13,950 radiation workers and n = 5489 nonradiation workers), Springfields, Lancashire, United Kingdom. Ever employed before 1996, follow-up through 1995. ICD-8.			Total: 42 67.32 0.62 (NR) ^c Rad: 28 48.94 0.57 (NR) ^c Non-rad: 14 18.38 0.76 (NR)			Total: 15 22.50 0.67 (NR) Rad: 10 16.48 0.61 (NR) Non-rad: 5 6.02 0.83 (NR) (disease category = chronic renal failure)
McGeoghegan and Binks, 2000a	n = 12,544 (n = 3244 radiation workers and n = 9296 nonradiation workers), Capenhurst, Cheshire, United Kingdom. Ever employed before 1996, follow-up through 1995. ICD-8.			Total: 45 52.14 0.86 (NR) Rad: 7 7.13 0.98 (NR) Non-rad: 38 45.01 0.84 (NR)			Total: 19 17.17 1.1 (NR) Rad: 4 2.20 1.8 (NR) Non-rad: 15 14.97 1.0 (NR) (disease category = chronic renal failure)

Note. Abbreviations: Obs = observed; Exp = expected; CI = confidence interval; ICD = International Classification of Disease; NR = not reported; Rad = radiation workers; Non-rad = nonradiation workers.

^aWhen more than one study is available for a cohort, the earlier references are noted but the results from the latest follow-up are provided in the table.

^bIn the studies using ICD-8, all genitourinary disease is based on codes 580–629 and chronic nephritis is based on code 582. In Pinkerton et al. (2004), all genitourinary disease is based on codes 580–629 and chronic nephritis is based on code 582–583 and 585–587. In Boice et al. (2008), the chronic nephritis category is based on code 580–589. McGeoghegan and Binks (2000a, 2000b) do not specify the codes used in their tables of results; all genitourinary disease and the chronic nephritis correspond, respectively, to their categories of genitourinary disease and chronic renal failure.

^cSignificant at $p < .01$.

to 44.1 $\mu\text{g/g}$ creatinine (Squibb & McDiarmid, 2006). Levels above 0.1 $\mu\text{g/g}$ creatinine (the cut point used to define a high-exposure group) were found in most of the individuals who had retained DU shrapnel. Some indication of renal damage was seen in the 2001 assessment, with increased levels of urinary retinol binding protein (65.68 and 46.13 $\mu\text{g/g}$ creatinine in the high- and low-exposure groups, respectively) and total protein (78.69 and 54.63 mg/g creatinine in the high- and low-exposure groups, respectively) (Table 4). Serum creatinine was quantitatively decreased, however, in the high-exposure group (mean 0.85 and 0.95 mg/dl in the high- and low-exposure groups, respectively). There was little evidence of renal damage in the 2003 and 2005 assessments. In the latest assessment conducted in 2007, however, a trend of elevated urinary retinol binding protein and increased urinary β_2 -microglobulin levels was seen in the high-exposure compared with the low-exposure group (McDiarmid et al., 2009).

STUDIES IN ANIMALS

Studies in experimental animals involving different routes and durations of exposure support the conclusion that the kidney is likely to be a sensitive target organ for U toxicity. In addition, data from experimental animals suggest that U compounds of relatively higher solubility are associated with greater kidney damage (Craft et al., 2004; Dygert et al., 1949; Hindin et al., 2005; Maynard et al., 1953). In acute oral exposure studies with uranyl acetate (exposure duration ranging from 1–5 d) changes in kidney function, as evidenced by increases in urinary protein, blood creatinine, and BUN, were reported (Domingo et al., 1987; Ozmen & Yurekli, 1998). Renal damage reported in rabbits, rats, and dogs exposed to uranyl nitrate in the diet for 30 d or less included increased plasma protein plus degenerative changes (particularly of the proximal tubular epithelium and glomeruli) and necrosis (Goel et al., 1980; Maynard & Hodge 1949; Ortega et al., 1989).

The only investigation of chronic oral toxicity of U compounds is the series of experiments performed by Maynard and colleagues in support of the Manhattan Project (Maynard et al., 1953; Maynard & Hodge, 1949). Rats and dogs were exposed to uranyl fluoride, uranyl tetrachloride, uranyl nitrate hexahydrate, uranium dioxide, and uranium tetrafluoride in the diet (or in dogs by capsule if the diet became unpalatable) for 1 yr (dogs) or 2 yr (rats). Exposure protocols are described in Table 5. With the exception of exposure of rats to uranium dioxide, all uranium compounds produced some degree of renal toxicity, which was strongly influenced by compound solubility. For example, administration of 0.5% uranyl nitrate hexahydrate in the diet of rats (approximately 200 mg/kg-d U) produced degeneration of kidney tubules, necrosis, and regeneration. Serial sacrifices revealed that the tubular changes observed after 6 wk of exposure showed no appreciable progression even after 2 yr of exposure (Maynard et al., 1953). More recent subchronic (91-d) drinking-water studies of uranyl nitrate in the rat and rabbit (Gilman et al., 1998a, 1998b, 1998c; McDonald-Taylor et al., 1992, 1997) provide an examination of uranium compound toxicity at lower doses (0.06 to 54 mg/kg-d). See Table 5 for a more detailed summary of renal histopathologic changes reported by these investigators. McDonald-Taylor et al. (1992, 1997) reported histopathologic changes in kidney proximal tubules of rabbits at 1.7 mg/kg-d U, the lowest dose tested. Gilman et al. (1998b, 1998c) similarly reported histopathologic changes of the kidney at the lowest doses tested in rabbits and rats (0.05 and 0.06 mg/kg-d U, respectively). The incidences of renal histopathologic changes (including changes of the renal tubules, glomeruli, and interstitium) reported by Gilman et al. (1998b, 1998c), particular in the rat, were elevated at all dose levels; however, these changes showed a poor dose-response relationship and little if any rise in severity with increasing dose, despite a 600-fold range between the low and high doses used in this study and documentation of a rise in kidney uranium residues with

TABLE 4. Renal Function Measures in Biennial Evaluations of Gulf War Veterans Exposed to Depleted Uranium in 1991

	Year of evaluation				
	1999	2001	2003	2005	
				Current exposure	Cumulative exposure
<i>n</i> low exposure, <i>n</i> high exposure ^a	37, 13	26, 13	19, 13	24, 10	24, 10
<i>p</i> Value and direction of difference ^b					
Renal function measures—urinary					
Creatinine	0.07 H < L	0.29	0.31	0.24	0.08 H < L
Calcium		0.35	0.79	0.59	0.56
Phosphate (PO ₄)		0.40	0.44	0.29	0.27
β ₂ -Microglobulin	0.27	0.78	0.53	0.22	0.83
Intestinal alkaline phosphatase			0.85	0.67	0.52
N-Acetyl β-glucosaminidase			0.38	0.96	0.90
Total protein	0.89	0.01 H > L	0.21	0.50	0.25
Microalbumin			0.85	0.40	0.32
Retinol binding protein	0.15 H > L	0.06 H > L	0.54	0.25	0.56
Renal function measures—serum					
Creatinine	0.14 H < L				0.56
Calcium		0.67	0.85	0.24	0.56
Phosphate (PO ₄)		0.63	0.03 H > L	0.70	0.64
Uric acid	0.12 H < L	0.45	0.32	0.10 H < L	0.03 H < L

Note. Sources: McDiarmid et al. (2001), McDiarmid et al. (2004), McDiarmid et al. (2006), McDiarmid et al. (2007), and McDiarmid et al. (2009) for the 1999, 2001, 2003, 2005, and 2007 evaluations, respectively.

^aLow (L) exposure defined as <0.10 μg uranium/g creatinine and high (H) defined as ≥0.10 μg uranium/g creatinine; *n* for specific assays may vary by 1–2 participants because of sample processing errors.

^bDirection of difference given for tests in which the *p* value was ≤.20.

TABLE 5. Summary of Subchronic and Chronic Oral Toxicity Studies of Uranium in Experimental Animals

Reference	Uranium compound	Species, sex, group size	Exposure conditions	Response and LOAEL
Subchronic studies McDonald-Taylor et al., 1992, 1997	Uranyl nitrate hexahydrate	Rabbit, New Zealand, M (3/group)	0, 24, 600 mg/L in drinking water (0, 1.7, 42 mg/kg-d U); 91 d. Followed by recovery periods of 0, 45, or 91 d	Kidney histopathology, including increases in glomerular basement membrane thickness and changes in proximal tubule cells seen in lowest dose group.
Gilman et al., 1998c	Uranyl nitrate hexahydrate	Rat, Sprague-Dawley, M & F (15/sex/group)	0, 0.96, 4.8, 24, 120, 600 mg/L in drinking water (M: 0, 0.06, 0.31, 1.52, 7.54, 36.7 mg/kg-d U; F: 0, 0.09, 0.42, 2.01, 9.98, 53.6 mg/kg-d U); 91 d	Histopathologic lesions of the kidney seen in lowest dose group; changes included dilation of tubules, apical displacement, and vesiculation of tubular nuclei and cytoplasmic vacuolation and degranulation in males and capsular sclerosis and reticulin sclerosis of tubular basement membranes and interstitial scarring in females.
Gilman et al., 1998b	Uranyl nitrate hexahydrate	Rabbit, New Zealand, M and F (10/sex/group)	M: 0, 0.96, 4.8, 24, 120, 600 mg/L in drinking water (0, 0.05, 0.20, 0.88, 4.82, 28.7 mg/kg-d U) F: 0, 4.8, 24, 600 mg/L in drinking water (0, 0.49, 1.32, 43.0 mg/kg-d U); 91 d	Histopathologic lesions of the kidney (male) seen in lowest dose group. Lesions included cytoplasmic vacuolation, anisokaryosis, and nuclear vesiculation.
Gilman et al., 1998a	Uranyl nitrate hexahydrate	Rabbit, SPF, M (5-8/group)	0, 24, 600 mg/L in drinking water (0, 1.4, 41.0 mg/kg-d U); 91 d followed by recovery periods of 0, 8, 14, 45, or 91 d	Histopathologic lesions of the kidney seen in 600 mg/L group, no attenuation of effect seen with any recovery period. Observed lesions included cytoplasmic vacuolation, anisokaryosis, nuclear hyperchromicity and vesiculation, tubular dilation, and reticulin sclerosis of the renal interstitial tissue.
Ortega et al., 1989	Uranyl acetate dihydrate	Rat, Sprague-Dawley, M (8/group)	0, 2, 4, 8, or 16 mg uranyl acetate dihydrate/kg-d (0, 1.1, 2.2, 3.4, 4.5, 9.0 mg/kg-d U); 28 d	Increase in total plasma protein seen in lowest dose group; urinary biochemical endpoints were not significantly altered by uranium treatment at any dose.

(Continued)

TABLE 5. (Continued)

Reference	Uranium compound	Species, sex, group size	Exposure conditions	Response and LOAEL
Ciúéguen et al., 2007	Uranyl nitrate	Rat, Sprague-Dawley, M (3/group)	0, 40 mg/L in drinking water (0, 3, 3 mg/kg-d U); 9 mo	Following single exposure to acetaminophen, increased renal proximal tubular cell necrosis, increased gene expression of xenobiotic metabolizing enzymes in kidney relative to animals not exposed to uranium.
Chronic studies Maynard et al., 1953	Uranyl fluoride	Rat, Wistar, M and F (15–25/group)	0, 0.01, 0.05, 0.1, 0.15, 0.25, 0.5% in diet; up to 24 mo	Minimal renal changes in 0.15% diet group (~85 mg/kg-d U); marked tubular atrophy with later regeneration seen in 0.5% diet group (~280 mg/kg-d U)
	Uranyl nitrate hexahydrate		0, 0.01, 0.05, 0.1, 0.5, 1, 2% in diet; up to 24 mo	Slight traces of renal injury seen in 0.5% diet group (~200 mg/kg-d U); renal abnormalities (tubular atrophy, and increase in stroma and a narrowing of the cortex in 2% diet group (~700 mg/kg-d U)
	Uranium dioxide Uranium tetrafluoride		0, 0.5, 2, 20% in diet; up to 24 mo 0, 0.5, 2, 20% in diet; up to 24 mo	No effects seen at any dose Mild renal tubular degeneration seen in 20% diet group (~9200 mg/kg-d U)

dose. McDonald-Taylor et al. (1992, 1997) and Gilman et al. (1998a, 1998b, 1998c) reported a significant increase in ultrastructural and histopathological alterations associated with tubular cell necrosis (Greaves, 2007; Walling, 1991) in U-exposed animals. These effects included thickening of the glomerular basement membrane. Neither McDonald-Taylor et al. (1992) nor Gilman et al. (1998a) found evidence of reversibility of kidney histopathologic changes after 91-d recovery periods.

The available subchronic and chronic oral toxicity studies on U compounds included limited evaluation of biomarkers of kidney function. Gilman et al. (1998a, 1998b, 1998c) examined urinary parameters in the rabbit, but not rat. In the first rabbit study Gilman et al. (1998b) measured various urinary parameters including levels of urea nitrogen, glucose, creatinine, total protein, and albumin as well as activities of LDH activity and NAG. Gilman et al. (1998a, 1998b, 1998c) found no marked effects after exposure to 29 mg U/kg-d for 91 d, but reported urinary parameter effects with the most persistent being increased glucose excretion in a second study in male rabbits exposed to 41 mg U/kg-d for 91 d (Gilman et al., 1998a). A dye clearance test used to assess renal function showed reduced rate of phenolsulfonphthalein excretion in male rabbits exposed to ≥ 120 mg/L uranyl nitrate (5 mg U/kg-d) but not in females (Gilman et al., 1998b). Rabbits exposed to lower levels of U in drinking water showed no marked changes in urinary parameters (Gilman et al., 1998a, 1998b).

Two animal studies that explored the renal effects of implanted DU particles in rats provide toxicity information relevant to the hazard associated with exposure of soldiers to embedded fragments of DU (Pellmar et al., 1998, 1999; Zhu et al., 2009). Pellmar et al. (1998, 1999) did not observe significant changes in biochemical or histologic markers of renal damage, while Zhu et al. (2009) reported that DU exposure led to increased renal damage as measured by light and electron microscopy including hypertrophy of epithelial

cells, necrosis, fibrosis, increased mitochondria size, glomerulus thickening, and inflammatory-cell infiltration, and biochemical assays as evidenced by increased urinary β_2 -microglobulin, albumin, serum creatinine, and BUN. Although both of these studies used similar methodologies for DU pellet implantation within the gastrocnemius muscle in the lower leg of Sprague-Dawley rats, the actual doses of implanted DU can not be compared based upon data provided. Pellmar et al. (1998, 1999) implanted rats with 0, 4, 10, and 20 U pellets (pellet weights not reported). Zhu et al. (2009) implanted rats with 0, 0.1, 0.2, and 0.3 g of DU fragments. After 6 mo of exposure, the highest renal U concentration reported by Pellmar et al. (1999) was 6920 ± 770 ng/g, while Zhu et al. (2009) reported a renal U concentration of $27,439 \pm 2291$ ng/g in the high-dose group. The differences in U-induced renal toxicity observed in these two studies may have been due to differences in U dose, tissue uptake, or diffusion from the implanted pellets.

STUDIES OF MECHANISMS OF RENAL TOXICITY

The cellular, molecular, and biochemical mechanisms for renal U uptake and toxicity have been previously reviewed (ATSDR, 1999). Recent studies using proximal and distal tubule cell lines (MDCK and LLC-PK₁ cells) suggest that U-induced renal toxicity is dependent on the formation of uranyl phosphate complexes, specifically $\text{UO}_2(\text{PO}_4)^-$ and $\text{UO}_2(\text{HPO}_4)$, and their uptake by the sodium dependent co-transporter NaPi-II and absorptive endocytosis (Muller et al., 2006, 2008). Furthermore, in vitro studies using isolated human and murine kidney cortex tubules suggest that U exposure inhibits cellular ATP content and gluconeogenesis through enzymatic inhibition of LDH, pyruvate carboxylase, glucose 6-phosphatase, and phosphoenolpyruvate carboxykinase. Toxicogenomic and proteomic studies using human renal HEK293 cells also suggest that U exposure altered expression of genes associated with calcium-dependent cell signaling such as IP3 cascade kinases PI4KII

and PIK3R1, the intracellular calcium receptor calmodulin, and calmodulin-dependent proteins and cell trafficking pathways such as the potassium channel ABC subunits ATP6V1A1 and ABCC8 (Prat et al., 2005). Both in vivo and in vitro experiments showed that U exposure depleted cellular antioxidants such as glutathione (GSH) and glutathione reductase activity, increased reactive oxygen species (ROS) production and DNA damage, and promoted apoptosis (Banday et al., 2008; Linares et al., 2006; Thiebault et al., 2007). In vivo toxicogenomic studies reported that chronic exposure to U significantly enhanced expression of genes associated with oxidative stress responses such as superoxide dismutase 1 and ion transporters including NaPi-II and Slc34a1 (Taulan et al., 2004).

DISCUSSION

Some evidence of adverse renal effects, particularly with respect to biomarkers of proximal tubule damage, is seen in community-based studies of populations chronically exposed to elevated drinking water concentrations of U. The biomarker for which effects were most consistently seen was urinary levels of β_2 -microglobulin (Zamora et al., 1998, 2009; Seldén et al., 2009). The study in Finland (Kurttio et al., 2002) did not demonstrate an association of toxicity to U with β_2 -microglobulin levels. Prat et al. (2009) suggested that the calcium-dependent species seen in speciation analyses of the Finnish water samples may result in a low toxicity profile. It should also be noted, however, that 65% of the samples in Kurttio et al. (2002) were below the β_2 -microglobulin limit of detection, and in contrast to the other studies, this measure was based on a spot urine rather than an overnight urine sample. β_2 -Microglobulin was not included in the measurements used in the follow-up study in Finland (Kurttio et al., 2006). Thun et al. (1985) also reported strong associations between U exposure and β_2 -microglobulin measures in urine and serum among workers in a U processing mill. Two of these studies included measures of other

metals (Cd and Pb in Seldén et al. [2009] and Cd and Pb in Thun et al. [1985]), and there was no indication that the associations seen with U were the result of confounding by these other exposures. In addition, in the most recent follow-up surveillance study of Gulf War veterans exposed to DU, some indications of proximal tubule effects, as evidenced by increased urinary β_2 -microglobulin and retinol binding protein levels, were noted (McDiarmid et al., 2009). Thus, although the subsets of renal tests, sensitivity of assays, and type of exposure measure varied across studies, as a group these studies show considerable consistency with respect to an indicator of proximal tubule damage and either measures of intake or U concentrations in urine. Occupational cohort studies do not provide evidence of an increased risk of kidney-related mortality among U-exposed workers. This outcome would be a relatively insensitive endpoint for the detection of renal damage, however, as it relies on cause of death as reported on death certificates. The reliability of this recording for chronic conditions, such as kidney disease, is much lower than for most cancers and acute events such as accidents and myocardial infarction (Harteloh et al., 2010).

Studies in experimental animals confirm that the kidney is a target of U toxicity following oral and implantation exposure. Both routes of exposure are relevant to human exposure situations. The available animal studies, however, provide an incomplete characterization of the dose-response relationship for kidney effects associated with chronic exposure at low environmental exposure levels. With the exception of early (1940s) studies conducted in support of the Manhattan Project (Dygart et al., 1949; Maynard et al., 1953; Maynard and Hodge, 1949), animal studies are generally limited to exposures of 90 d duration. Further, the majority of subchronic oral toxicity studies (Gilman et al., 1998a, 1998b, 1998c; McDonald-Taylor et al., 1992, 1997) of U compounds failed to identify a no-observed-adverse-effect level, and the kidney effects reported by some investigators (Gilman et al., 1998b, 1998c) did not exhibit a dose response. Investigation of clinical

biomarkers of renal toxicity in experimental animal studies is limited. Mechanistic studies suggest that cell toxicity may result from altered function of cell signaling pathways, increased ROS production, and depletion of endogenous cellular antioxidants.

In summary, various lines of evidence suggest that relatively low levels of U exposure may result in detectable changes in markers of renal damage in humans. The epidemiological studies do not provide evidence of clinically diagnosed kidney disease or renal failure within the exposed populations. Given the limited sample sizes and the potential selection of relatively healthy individuals in these types of community-based and occupational studies, the absence of the observation of this type of kidney disease is not surprising. Rather, these studies are better designed to examine associations within what would be considered the normal range of specific biomarkers of renal function. The question of the interpretation and importance of the observed effects of biomarkers of proximal tubule function is an important question that would benefit from additional clinical, epidemiological, and experimental research.

REFERENCES

- Abu-Qare, A. W., and Abou-Donia, M. B. 2002. Depleted uranium—The growing concern. *J. Appl. Toxicol.* 22:149–152.
- Arfsten, D. P., Still, K. R., and Ritchie, G. D. 2001. A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development. *Toxicol. Ind. Health* 17:180–191.
- Agency for Toxic Substances and Disease Registry. 1999. *Toxicological profile for uranium*. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp150.pdf>
- Bagshaw, S. M., Langenberg, C., Haase, M., Wan, L., May, C. N., and Bellomo, R. 2007. Urinary biomarkers in septic acute kidney injury. *Intens. Care Med.* 33:1285–1296.
- Banday, A. A., Priyamvada, S., Farooq, N., Yusufi, A. N., and Khan, F. 2008. Effect of uranyl nitrate on enzymes of carbohydrate metabolism and brush border membrane in different kidney tissues. *Food Chem. Toxicol.* 46:2080–2088.
- Birn, H., and Christensen, E. I. 2006. Renal albumin absorption in physiology and pathology. *Kidney Int.* 69:440–449.
- Bleise, A., Danesi, P. R., and Burkart, W. 2003. Properties, use and health effects of depleted uranium (DU): A general overview. *J. Environ. Radioact.* 64:93–112.
- Boice, J. D., Jr., Cohen, S. S., Mumma, M. T., Chadda, B., and Blot, W. J. 2008. A cohort study of uranium millers and miners of Grants, New Mexico, 1979–2005. *J. Radiol. Prot.* 28:303–325.
- Centers for Disease Control and Prevention. 2005. *Third national report on human exposure to environmental chemicals*. Atlanta, GA: U.S. Centers for Disease Control and Prevention. <http://www.cdc.gov/exposurereport/pdf/thirdreport.pdf>
- Checkoway, H., Pearce, N., Crawford-Brown, D. J., and Cragle, D. L. 1988. Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. *Am. J. Epidemiol.* 127:255–266.
- Comper, W. D., Hilliard, L. M., Nikolic-Paterson, D. J., and Russo, L.M. 2008. Disease-dependent mechanisms of albuminuria. *Am. J. Physiol. Renal Physiol.* 295:F1589–F1600.
- Craft, E., Abu-Qare, A., Flaherty, M., Garofolo, M., Rincavage, H., and Abou-Donia, M. 2004. Depleted and natural uranium: Chemistry and toxicological effects. *J. Toxicol. Environ. Health B* 7:297–317.
- Domingo, J. L., Llobet, J. M., Tomas, J. M., and Corbella, J. 1987. Acute toxicity of uranium in rats and mice. *Bull. Environ. Contam. Toxicol.* 39:168–174.
- Dupree-Ellis, E., Watkins, J., Ingle, J. N., and Phillips, J. 2000. External radiation exposure and mortality in a cohort of uranium processing workers. *Am. J. Epidemiol.* 152:9195.

- Dygert, H. P., LaBelle, C. W., Laskin, S., Pozzani, U. C., Roberts, E., Rothermel, J. J., Rothstein, A., Spiegl, C. J., Sprague, G. F., and Stokinger, H. E. 1949. Toxicity following inhalation. In *Pharmacology and Toxicology of Uranium Compounds*, eds. C. Voegtlin and H. C. Hodge, pp. 423–524. New York: McGraw-Hill.
- Emeigh, S., and Kinter, L. 2005. Assessing renal effects of toxicants in vitro. In *Toxicology of the kidney*, 3rd ed., ed. J. Tarloff and L. Lash, pp 81–147. Washington, D.C.: CRC Press.
- Emeigh Hart, S. 2005. Assessment of renal injury in vivo. *J. Pharmacol. Toxicol. Methods* 52:30–45.
- Frome, E. L., Cragle, D. L., and McLain, R. W. 1990. Poisson regression analysis of the mortality among a cohort of World War II nuclear industry workers. *Radiat. Res.* 123:138–152.
- Gilman, A. P., Moss, M. A., Villeneuve, D. C., Secours, V. E., Yagminas, A. P., Tracy, B. L., Quinn, J. M., Long, G., and Valli, V. E. 1998a. Uranyl nitrate: 91-Day exposure and recovery studies in the male New Zealand white rabbit. *Toxicol. Sci.* 41:138–151.
- Gilman, A. P., Villeneuve, D. C., Secours, V. E., Yagminas, A. P., Tracy, B. L., Quinn, J. M., Valli, V. E., and Moss, M. A. 1998b. Uranyl nitrate: 91-Day toxicity studies in the New Zealand white rabbit. *Toxicol. Sci.* 41:129–137.
- Gilman, A. P., Villeneuve, D. C., Secours, V. E., Yagminas, A. P., Tracy, B. L., Quinn, J. M., Valli, V. E., Willes, R. J., and Moss, M. A. 1998c. Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. *Toxicol. Sci.* 41:117–128.
- Goel, K. A., Garg, V. K., and Garg, V. 1980. Histopathology of kidney of albino rat poisoned with uranyl nitrate. *Bull. Environ. Contam. Toxicol.* 24:9–12.
- Greaves, P. 2007. *Histopathology of preclinical toxicity studies: Interpretation and relevance in drug safety evaluation*, 3rd ed., pp. 570–623. Boston: Academic Press.
- Guéguen, Y., L. Grandcolas, C. Baudelin, S. Grison, E. Tissandié, J. R. Jourdain, F. Paquet, P. Voisin, J. Aigueperse, P. Gourmelon, and M. Souidi. 2007. Effect of acetaminophen administration to rats chronically exposed to depleted uranium. *Toxicology* 229:62–72.
- Harteloh, P., de Bruin, K., and Kardaun, J. 2010. The reliability of cause-of-death coding in the Netherlands. *Eur. J. Epidemiol.* March 23 [Epub ahead of print].
- Hindin, R., Brugge, D., and Panikkar, B. 2005. Teratogenicity of depleted uranium aerosols: A review from an epidemiological perspective. *Environ. Health* 4:17.
- Kurttio, P., Auvinen, A., Salonen, L., Saha, H., Pekkanen, J., Makelainen, I., Vaisanen, S. B., Penttila, I. M., and Komulainen, H. 2002. Renal effects of uranium in drinking water. *Environ. Health Perspect.* 110:337–342. Erratum: *Environ. Health Perspect.* 111:632 (2003).
- Kurttio, P., Harmoinen, A., Saha, H., Salonen, L., Karpas, Z., Komulainen, H., and Auvinen, A. 2006. Kidney toxicity of ingested uranium from drinking water. *Am. J. Kidney Dis.* 47:972–982.
- Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F. 3rd, Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., and Coresh, J. 2009. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* 150:604–612.
- Linares, V., Belles, M., Albina, M. L., Sirvent, J. J., Sanchez, D. J., and Domingo, J. L. 2006. Assessment of the pro-oxidant activity of uranium in kidney and testis of rats. *Toxicol. Lett.* 167:152–161.
- Loomis, D. P., and Wolf, S. H. 1996. Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947–1990. *Am. J. Ind. Med.* 29:131–141.
- Magdo, H. S., Forman, J., Graber, N., Newman, B., Klein, K., Satlin, L., Amler, R. W., Winston, J. A., and Landrigan, P. J. 2007. Grand rounds: Nephrotoxicity in a young child exposed to uranium from contaminated well water. *Environ. Health Perspect.* 115:1237–1241.
- Mao, Y., Desmeules, M., Schaubel, D., Berube, D., Dyck, R., Brule, D., and Thomas, B. 1995. Inorganic components of drinking water and microalbuminuria. *Environ. Res.* 71:135–140.

- Maynard, E. A., and Hodge, H. C. 1949. Study of toxicity of various uranium compounds when fed to experiment animals. In *Pharmacology and toxicology of uranium compounds*, eds. C. Voegtlin and H. C. Hodge, pp. 309–376. New York: McGraw-Hill.
- Maynard, E. A., Downs, W. L., and Hodge, H. C. 1953. Oral toxicity of uranium compounds. In *Pharmacology and toxicology of uranium compounds*, eds. C. Voegtlin and H. C. Hodge, pp. 1221–1369. New York: McGraw-Hill.
- McDiarmid, M. A., Squibb, K., Engelhardt, S., Oliver, M., Gucer, P., Wilson, P. D., Kane, R., Kabat, M., Kaup, B., Anderson, L., Hoover, D., Brown, L. D., Jacobson-Kram, D., and Depleted Uranium Follow-Up Program. 2001. Surveillance of depleted uranium exposed Gulf War veterans: Health effects observed in an enlarged “friendly fire” cohort. *J. Occup. Environ. Med.* 43:991–1000.
- McDiarmid, M. A., Engelhardt, S., Oliver, M., Gucer, P., Wilson, P. D., Kane, R., Kabat, M., Kaup, B., Anderson, L., Hoover, D., Brown, L., Handwerger, B., Albertini, R. J., Jacobson-Kram, D., Thorne, C. D., and Squibb, K. S. 2004. Health effects of depleted uranium on exposed Gulf War veterans: A 10-year follow-up. *J. Toxicol. Environ. Health A* 67:277–296.
- McDiarmid, M. A., Engelhardt, S. M., Oliver, M., Gucer, P., Wilson, P. D., Kane, R., Kabat, M., Kaup, B., Anderson, L., Hoover, D., Brown, L., Albertini, R. J., Gudi, R., Jacobson-Kram, D., Thorne, C. D., and Squibb, K. S. 2006. Biological monitoring and surveillance results of Gulf War I veterans exposed to depleted uranium. *Int. Arch. Occup. Environ. Health* 79:11–21.
- McDiarmid, M. A., Engelhardt, S. M., Oliver, M., Gucer, P., Wilson, P. D., Kane, R., Cernich, A., Kaup, B., Anderson, L., Hoover, D., Brown, L., Albertini, R., Gudi, R., Jacobson-Kram, D., and Squibb, K. S. 2007. Health surveillance of Gulf War I veterans exposed to depleted uranium: updating the cohort. *Health Phys.* 93:60–73.
- McDiarmid, M. A., Engelhardt, S. M., Dorsey, C. D., Oliver, M., Gucer, P., Wilson, P. D., Kane, R., Cernich, A., Kaup, B., Anderson, L., Hoover, D., Brown, L., Albertini, R., Gudi, R., and Squibb, K. S. 2009. Surveillance results of depleted uranium-exposed Gulf War I veterans: Sixteen years of follow-up. *J. Toxicol. Environ. Health A* 72:14–29.
- McDonald-Taylor, C. K., Bhatnagar, M. K., Gilman, A., Yagminas, A., and Singh, A. 1992. Uranyl nitrate-induced glomerular basement membrane alterations in rabbits: A quantitative analysis. *Bull. Environ. Contam. Toxicol.* 48:367–373.
- McDonald-Taylor, C. K., Singh, A., and Gilman, A. 1997. Uranyl nitrate-induced proximal tubule alterations in rabbits: A quantitative analysis. *Toxicol. Pathol.* 25:381–389.
- McGeoghegan, D., and Binks, K. 2000a. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946–95. *J. Radiol. Prot.* 20:381–401.
- McGeoghegan, D., and Binks, K. 2000b. The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946–95. *J. Radiol. Prot.* 20:111–137.
- Muller, D., Houpert, P., Cambar, J., and Henge-Napoli, M. H. 2006. Role of the sodium-dependent phosphate co-transporters and of the phosphate complexes of uranyl in the cytotoxicity of uranium in LLC-PK1 cells. *Toxicol. Appl. Pharmacol.* 214:166–177.
- Muller, D. S., Houpert, P., Cambar, J., and Henge-Napoli, M. H. 2008. Role of the sodium-dependent phosphate cotransporters and absorptive endocytosis in the uptake of low concentrations of uranium and its toxicity at higher concentrations in LLC-PK1 cells. *Toxicol. Sci.* 101:254–262.
- Orloff, K. G., Mistry, K., Charp, P., Metcalf, S., Marino, R., Shelly, T., Melaro, E., Donohoe, A. M., and Jones, R. L. 2004. Human exposure to uranium in groundwater. *Environ. Res.* 94:319–326.

- Ortega, A., Domingo, J. L., Llobet, J. M., Tomas, J. M., and Paternain, J. L. 1989. Evaluation of the oral toxicity of uranium in a 4-week drinking-water study in rats. *Bull. Environ. Contam. Toxicol.* 42:935–941.
- Ozmen, M., and Yurekli, M. 1998. Subacute toxicity of uranyl acetate in Swiss-albino mice. *Environ. Toxicol. Pharmacol.* 6:111–115.
- Parkhurst, M. A., and Guilmette, R. A. 2009. Overview of the Capstone depleted uranium study of aerosols from impact with armored vehicles: Test setup and aerosol generation, characterization, and application in assessing dose and risk. *Health Phys.* 96:207–220.
- Pellmar, T. C., Hogan, J. B., Benson, K. A., and Landauer, M. R. 1998. *Toxicological evaluation of depleted uranium in rats: Six-month evaluation point*. Bethesda, MD: Uniformed Services University of the Health Sciences. ADA410643.
- Pellmar, T. C., Fuciarelli, A. F., Ejniak, J. W., Hamilton, M., Hogan, J., Strocko, S., Emond, C., Mottaz, H. M., and Landauer, M. R. 1999. Distribution of uranium in rats implanted with depleted uranium pellets. *Toxicol. Sci.* 49:29–39.
- Pinkerton, L. E., Bloom, T. F., Hein, M. J., and Ward, E. M. 2004. Mortality among a cohort of uranium mill workers: An update. *Occup. Environ. Med.* 61:57–64.
- Polednak, A. P., and Frome, E. L. 1981. Mortality among men employed between 1943 and 1947 at a uranium-processing plant. *J. Occup. Med.* 23:169–178.
- Prat, O., Berenguer, F., Malard, V., Tavan, E., Sage, N., Steinmetz, G., and Quemeneur, E. 2005. Transcriptomic and proteomic responses of human renal HEK293 cells to uranium toxicity. *Proteomics* 5:297–306.
- Prat, O., Vercouter, T., Ansoborlo, E., Fichet, P., Perret, P., Kurttio, P., and Salonen, L. 2009. Uranium speciation in drinking water from drilled wells in southern Finland and its potential links to health effects. *Environ. Sci. Technol.* 43:3941–3946.
- Renault, S., Faiz, H., Gadet, R., Ferrier, B., Martin, G., Baverel, G., and Conjard-Duplany, A. 2010. Uranyl nitrate inhibits lactate gluconeogenesis in isolated human and mouse renal proximal tubules: A ^{13}C -NMR study. *Toxicol. Appl. Pharmacol.* 242:9–17.
- Ritz, B., Morgenstern, H., Crawford-Brown, D., and Young, B. 2000. The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne/Atomics International. *Environ. Health Perspect.* 108:743–751.
- Seldén, A. I., Lundholm, C., Edlund, B., Hogdahl, C., Ek, B. M., Bergstrom, B. E., and Ohlson, C. G. 2009. Nephrotoxicity of uranium in drinking water from private drilled wells. *Environ. Res.* 109:486–494.
- Squibb, K. S., and McDiarmid, M. A. 2006. Depleted uranium exposure and health effects in Gulf War veterans. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 361:639–648.
- Taulan, M., Paquet, F., Maubert, C., Delissen, O., Demaille, J., and Romey, M. C. 2004. Renal toxicogenomic response to chronic uranyl nitrate insult in mice. *Environ. Health Perspect.* 112:1628–1635.
- Thiebault, C., Carriere, M., Milgram, S., Simon, A., Avoscan, L., and Gouget, B. 2007. Uranium induces apoptosis and is genotoxic to normal rat kidney (NRK-52E) proximal cells. *Toxicol. Sci.* 98:479–487.
- Thun, M. J., Baker, D. B., Steenland, K., Smith, A. B., Halperin, W., and Berl, T. 1985. Renal toxicity in uranium mill workers. *Scand. J. Work Environ. Health* 11:83–90.
- Tolkoff-Rubin, N. E., Rubin, R. H., and Bonventre, J. V. 1988. Noninvasive renal diagnostic studies. *Clin. Lab. Med.* 8:507–526.
- U. S. Environmental Protection Agency. 1985. *Nationwide occurrence of radon and other natural radioactivity in public water supplies*. Montgomery, AL: U. S. Environmental Protection Agency. EPA Number 520585008.
- U. S. Environmental Protection Agency. 2000. *Radionuclides notice of data availability technical support document*. Washington, DC: U. S. Environmental Protection Agency.

- http://www.epa.gov/OGWDW/radionuclides/pdfs/regulation_radionuclides_rulemaking_techsupportdoc.pdf
- Walling, M. A. 1991. Morphologic manifestation of toxic cell injury. In *Handbook of toxicologic pathology*, vol. 2, eds. W. M. Haschek, C. G. Rousseaux, and M. A. Wallig, pp. 39–64. San Diego: Academic Press.
- Waxweiler, R. J., Archer, V. E., and Roscoe, R. J. 1983. Mortality patterns among a retrospective cohort of uranium mill workers. In *Epidemiology applied to health physics, Sixteenth midyear topical meeting of the Health Physics Society*, Albuquerque, NM, pp. 428–435.
- World Health Organization. 2001. *Depleted uranium sources, Exposure and health effects*. Geneva, Switzerland: World Health Organization. http://whqlibdoc.who.int/hq/2001/WHO_SDE_PHE_01.1.pdf
- Zalups, R. K., Gelein, R. M., Morrow, P. E., and Diamond, G. L. 1988. Nephrotoxicity of uranyl fluoride in uninephrectomized and sham-operated rats. *Toxicol. Appl. Pharmacol.* 94:11–22.
- Zamora M. L. L., Zielinski, J. M., Moodie, G. B., Falcomer, R. A. F., Hunt, W. C., and Capello, K. 2009. Uranium in drinking water: Renal effects of long-term ingestion by an Aboriginal community. *Arch. Environ. Occup. Health* 64:228–241.
- Zamora, M. L., Tracy, B. L., Zielinski, J. M., Meyerhof, D. P., and Moss, M. A. 1998. Chronic ingestion of uranium in drinking water: A study of kidney bioeffects in humans. *Toxicol. Sci.* 43:68–77.
- Zhu, G., Xiang, X., Chen, X., Wang, L., Hu, H., and Weng, S. 2009. Renal dysfunction induced by long-term exposure to depleted uranium in rats. *Arch. Toxicol.* 83:37–46.