Health Consultation

Follow-up Exposure Investigation
Retinol Binding Protein Analysis

SIMPSONVILLE/FOUNTAIN INN
(a/k/a FOUNTAIN INN SUBDIVISION)

SIMPSONVILLE, GREENVILLE COUNTY, SOUTH CAROLINA

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333

HEALTH CONSULTATION

EXPOSURE INVESTIGATION REPORT – III

FOUNTAIN INN/SIMPSONVILLE AREA
(a/k/a FOUNTAIN INN SUBDIVISION)

SIMPSONVILLE, GREENVILLE COUNTY, SOUTH CAROLINA

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Background

The Agency for Toxic Substances and Disease Registry (ATSDR) and the South Carolina Department of Health and Environmental Control (SCDHEC) have completed two Exposure Investigations (EI) in Simpsonville/Fountain Inn, South Carolina. In these investigations, we conducted environmental and biological testing in homes where the residents formerly utilized uranium contaminated wells for potable use. The wells were contaminated with naturally-occurring uranium. As part of these investigations, we collected urine samples from residents in April 2001 and again in October 2001. Most of the participants reported that they were not drinking well water during this time interval. The findings, conclusions, and recommendations from these EIs were presented in two previously released reports [1, 2].

The urine samples were analyzed for uranium at the laboratory of the National Center for Environmental Health. Between the first and second EI, the urine uranium concentrations decreased in most, but not all of the participants. In a few of the participants, the urine uranium concentrations increased several-fold between the first and second EI. Increases in urine uranium concentrations of this scale suggest that these individuals may have had ongoing exposure to uranium.

Purpose of the Third Exposure Investigation

In response to these findings, ATSDR and SCDHEC conducted this EI which had two components:

(1) We repeated urine uranium assays in all members of one family. In this family, 4 of 5 family members had a 2 to 8 fold increase in their urine uranium level between the first and second EI. We collected detailed information from each family member on possible sources of exposure to uranium, use of food supplements and drugs, and a medical history. Two food supplements were collected for uranium analysis from one member of this family.

The purpose of this testing is to determine if the urine uranium levels in the members of this family are still increasing, and if so, what are the possible sources/explanation.

(2) Concurrent with the second EI, SCDHEC had collected urine samples from the residents in this area and tested the samples for retinol binding protein (RBP), a biomarker of damage to the proximal tubule of the kidney. Exposure to uranium can affect the proximal tubule of the kidney. Therefore, measurement of RBP in urine is an early marker of damage to the kidney. Three of 79 people tested in the second EI had an elevated urine concentration of RBP.

In this EI, ATSDR repeated the urine uranium assays for these 3 individuals. Concurrently, SCDHEC repeated RBP levels in the 3 individuals who had previously elevated RBP levels. Only the urine uranium results will be presented in this document.

Site Description

Simpsonville, South Carolina is located about 12 miles southeast of Greenville, South Carolina. Simpsonville occupies 14,301 square kilometers of land, and its population in 1999 was 11,708. The population of Simpsonville is growing, and in the past few years, there has been an increase in new home construction. The town of Fountain Inn is located about 20 miles southeast of Greenville and about 6 miles from Simpsonville. Residents used private wells for their drinking water source because municipal water was not available to many of the area homes.

Recently, after the results of the first EI were released, the Greenville Water District extended public water lines to many of the affected neighborhoods. This installation provided residents with a safe and dependable source of potable water. At the time of the third EI, the public water lines were operating. In May 2002, when the third EI was conducted, some of the homes had been connected to the public water lines for approximately 2 months.

Target Population

The target population for this EI was the 8 eligible residents who participated in the first and second EIs. The first part of the EI focused on a household where the residents experienced large increases in their urine uranium concentrations between the first and second EI. In this household, four of the five family members experienced a several-fold increase (2- to 8-fold) in their urine uranium concentrations, and urine uranium concentrations in five family members exceeded 0.5 μg/g creatinine. (The NCEH reported that the 90[th] percentile for urine uranium levels in the general population was 0.024 μg/g). All family members had urine uranium levels reassayed in this EI.

The second part of the EI focused on 3 individuals with elevated urine RBP levels. All three individuals had their urine uranium levels reassayed in this EI.

Staff from the SCDHEC notified the residents of the third EI and set up an appointment to collect urine samples. Staff from the SCDHEC sent a urine specimen cup to each participant. Participants were instructed to collect a first-morning void urine sample on the day of the appointment and to store it in a refrigerator until it was collected. Each participant was required to complete a written informed consent/assent form. ATSDR and SCDHEC staff also collected medical and exposure history information to help interpret the test results.

The 8 participants ranged in age from 6 to 50 years old. At the time of this EI, the participants had not been drinking the well water for 14 to16 months. One participant was still using bottled water or water provided by the Greenville Water District. The remaining participants were drinking municipal water for approximately 2 months. However, one participant reported that he did occasionally drink his well water or use it for other potable purposes.

Biological and Environmental Sampling

Biological Sampling and Analysis

On May 15, 2002, representatives of ATSDR and SCDHEC visited each home to collect urine samples from the participants in this EI. The urine collection cup was swirled to thoroughly mix the sample and suspend any sediment. A 4.5 milliliter aliquot of the urine was then transferred to a labeled specimen tube using a disposable pipette. During this operation, disposable latex gloves were worn. The urine specimens were stored on ice packs until they were hand-delivered to the National Center for Environmental Health Laboratory at the Centers for Disease Control and Prevention in Atlanta, Georgia for analysis.

The samples were analyzed for uranium 238 using a magnetic-sector inductively coupled argon plasma mass spectroscopy (ICP-MS). In naturally-occurring uranium deposits, uranium 238 accounts for 99.27 percent of the total mass of uranium; therefore, it is not necessary to measure the other minor uranium isotopes. To test for urinary dilution, the urine samples were also analyzed for creatinine using an enzymatic assay.

Environmental Sampling and Analyses

One participant provided two health food supplements, calcium and vitamin E, for uranium analysis. After collection, ATSDR staff hand delivered the specimens to the Georgia Institute of Technology, Environmental Resources Center in Atlanta, Georgia for analyses. The samples were analyzed for uranium isotopes using alpha spectroscopy.

Appropriate chain-of-custody procedures were followed during sample collection and handling.

Results

Biological Sampling

The concentrations of uranium in urine samples from the 8 participants ranged from 0.015 microgram per liter (μg/L) to 0.415 μg/L. The average uranium concentration was 0.102 μg/L, and the median concentration was 0.054 μg/L.

The concentration of creatinine in the urine samples was also measured. Creatinine is a metabolic product of skeletal muscle, and it is excreted by the kidneys at a constant rate regardless of the rate that urine is produced. Therefore, the urinary creatinine concentration is a measure of how concentrated or dilute the urine is.

In the following discussion, urine uranium concentrations are reported as micrograms of uranium per gram of creatinine (μg/g). The use of these units helps to reduce the variability in urine uranium concentrations due to urinary dilution. When normalized to creatinine concentration, the urine uranium concentrations in the participants of this EI ranged from 0.011 to 0.743 µg/g. The average urine uranium concentration in the 8 participants was 0.119 µg/g.

By comparison, in the first and second EI, the average urine uranium concentrations in the same 8 participants were 0.333 and 1.041 µg/g respectively. The median urine uranium concentrations for the same 8 participants in the first, second and third EIs are as follows: 0.166, 0.50, and 0.032 µg/g (Figure 1).

If the creatinine concentration is outside the normal range of 0.5 g/L to 3.0 g/L, the urine sample may be too dilute or concentrated to be reliable. None of the creatinine concentrations were outside the normal range in this EI, therefore, the uranium concentrations in this EI are reliable.

From the second to the third EI, the urine uranium concentration decreased in 7 of 8 (88 %) of the participants and increased in one participant (12 %). Most of the decreases in urine uranium concentrations were large (differences ranging from 2 to 224-fold). All 7 urine uranium concentrations decreased to less than 0.06 µg/g. The maximum decrease was observed in a teenager whose urine uranium decreased 224-fold from the second to the third EI.

In the household where the residents experienced large increases in their urine uranium concentrations from the first to the second EI, all family members had a decrease in their urine uranium concentrations. This household had been connected to public water system for two months at the time of this third EI and all but one family member was using the public water system for potable purposes. This one family member consumed bottled water from a health food store.

Only one participant's urine uranium concentration increased (by 3-fold) between the second and third EI. Between the first and the second EI, this participant's urine uranium level decreased by 1.5 fold. This participant reported no recent consumption of well water and had stopped consuming well water for approximately 16 months. No other sources of uranium exposure were identified.

Based on data from the Nutrition Examination Survey conducted in 1999, the Centers for Disease Control and Prevention reported that urine concentrations of uranium in the general population were as follows [3]:

	Percentile			
	25th	50th	75th	90th
U concentration (µg/g creatinine)	<LOD	0.005	0.011	0.024

LOD = Limit of Detection (0.004 µg/g creatinine)

In this EI, the concentration of uranium in urine samples from 5 of the 8 participants (63 %) exceeded the 90th percentile of the general population. Therefore, even though the urine uranium concentrations decreased in most of the participants, the concentrations remained significantly elevated. As discussed below, the elevated urine uranium concentrations could be the result of previous chronic exposure to uranium which accumulated in the body and is now being slowly excreted.

Environmental Sampling

No other potential sources of uranium exposure were identified from an exposure history, other than dietary supplements from one participant.

Two dietary supplements, calcium and vitamin E, were provided by one participant. Low concentrations of uranium were detected in both dietary supplements. The ratio of the concentrations of uranium isotopes in the supplements were within the range of the ratios found in naturally-occurring uranium. Therefore, the uranium in these supplements appears to be derived from naturally-occurring uranium.

The uranium content of the calcium supplement was 60 parts per billion (ppb) or ng/g. The uranium content of the vitamin E supplement was 40 ppb.

Discussion

Only a small fraction of uranium that is ingested is absorbed through the gastrointestinal tract into the body. For uranium in food or drinking water, it has been estimated that 0.3 to 6 percent of the ingested uranium is absorbed [4]. Once absorbed into the systemic circulation, the uranium deposits primarily in the bones, with lesser amounts depositing in the kidney, liver, and other soft tissues.

The elimination of uranium from the body is complex and involves multiple compartments and transfer rates [5]. In an experimental study, uranium was intravenously injected into human subjects [4]. About two-thirds of the injected uranium dose was excreted over the first 24 hours, and about 75 percent was excreted within 5 days. Of the remainder, most was slowly excreted over a period of several months, but a small portion was retained and excreted over a period of years.

In the three EIs, the urine samples were collected at time periods of 2-4 months, 8-10 months, and 14-16 months after most of the participants reported that they had stopped drinking the water. Therefore, in the absence of ongoing exposure to uranium, the urine uranium detected in the EI participants is likely due to uranium that is being slowly released from bone and other tissue storage sites in the body. The uranium concentrations in the urine should gradually decrease as the body storage sites become depleted and reach a new, lower steady-state equilibrium.

In this investigation, urine uranium levels fell an average of 98 % for the 3 participants who had urine uranium concentrations greater than 1.0 μg/g in the second EI (7 month interval). All 3 individuals belong to the same household.

In the household where the participants experienced large increases in their urine uranium concentrations in the second EI, all household members had a significant decrease in urine uranium concentrations in this EI. Three of the household members had a decrease in urine uranium to a concentration that was below the 90th percentile of the general population (0.024 μg/g). A detailed exposure history did not identify other uranium sources that could account for the increase in urine uranium concentrations in the second EI. This household had been connected to the public water system 2 months prior to conducting this EI.

Among the EI participants with initial urine uranium concentrations below 1.0 µg/L in the second EI, the decreases in urine uranium concentrations were somewhat smaller, and in one individual, the concentration increased. In people with low urine uranium concentrations, background exposure to uranium in the diet could cause fluctuations in daily urine uranium concentrations. In a normal population with no unusual exposure to uranium, creatinine normalized concentrations of uranium in spot urine samples were reported to vary as much as 2-fold diurnally[6]. In people with high body burdens of uranium, diurnal variability in urine uranium concentrations is much less [7]. This lower diurnal variability could be due to the relatively small contribution of dietary uranium to a high body burden.

An increase in urine uranium concentrations was observed in one individual, an *increase* of 3-fold between the second and third EI to a concentration of 0.743 μg/g. This increase suggests recent exposure to a source of uranium or release from body stores of uranium. Osteoporosis and other conditions that cause bone loss could release uranium stored in the skeleton into the circulation. This individual did not have a medical history of bone loss or other conditions that could account for this increase in urine uranium. A detailed exposure history did not identify other uranium sources. In fact, this participant was using municipal water 2 months before the collection of this urine specimen and had stopped drinking well water for 16 months.

The health impact, if any, of the observed body burdens of uranium is not known. Studies of workers with occupational exposure to uranium have not demonstrated convincing epidemiological evidence of serious renal disease or other health effects [8]. However, these studies had limited statistical power to detect an increased rate of disease, if it had been present.

The Nuclear Regulatory Commission has recommended that corrective actions be taken when urine uranium concentrations in uranium mill workers exceed 15 µg/L [9]. None of the participants' urine uranium concentrations exceeded this concentration. However, the participants' urine uranium concentrations were probably higher in the past, while they were drinking the water. Furthermore, standards for occupational exposures are derived for healthy adult workers and may not be protective of more sensitive members of the general population. In particular, people with pre-existing renal disease, or people taking potentially nephrotoxic medications (such as aminoglycoside antibiotics), may be more susceptible to the nephrotoxic effects of uranium.

Although exposure to high doses of uranium can damage the kidneys, animal experiments indicate that once the exposure stops, the damage may be reversible [6]. Therefore, early signs of renal toxicity due to uranium exposure may not be detectable months after exposure has stopped. Nevertheless, it would be prudent for the participants in this EI to notify their physicians of their elevated exposures to uranium.

One participant provided 2 dietary supplements for analysis, calcium and vitamin E. This participant's urine uranium concentration was below 1.0 μg/g in the second EI and decreased by 33-fold in this EI. This participants's urine uranium concentration decreased well below the 90th percentile of the general population (0.024 μg/g).

The uranium content of the calcium supplement was 60 ppb. The uranium content of the vitamin E supplement was 40 ppb. The uranium in the dietary supplements could have resulted from uranium from various ingredients like water and other ingredients used in their production. The dose from eating these supplements would depend on the rate of consumption. This participant reported daily intake of these supplements as the following: Calcium - 2 tablets per day (75 mg per tablet) and Vitamin E - 2 tablets per day (100 IU per tablet = 67 mg per tablet).

The uranium ingestion rate for this scenario would be:

Calcium: 60 ng/g (ppb) x 0.15 grams (2 tablets) ÷ (70 kg body weight) = 0.13 ng/kg/day

0.13 ng/kg/day is equivalent to 0.00013 μg/kg/day

This estimated uranium dose is much less that ATSDR's intermediate and Chronic Minimal Risk Level (MRL) for uranium of 2 μg/kg/day. By comparison, daily ingestion of 2 vitamin E supplements would yield an estimated dose of 0.00077 μg/kg/day which is also several orders of magnitude below the MRL.

The amount of natural uranium in these supplements is minuscule. The estimated daily dose of uranium from dietary sources is approximately 1-2 μg/day [10] .Therefore, the estimated dose of uranium from the dietary supplements is well below the normal dietary intake and is of no toxicological consequence. Furthermore, the dose of uranium would make a negligible contribution to the urine uranium concentration detected in the person consuming these supplements.

Because the contents of dietary supplements are not regulated by the Food and Drug Administration (FDA), the amount of natural uranium in any given supplement may vary by manufacturer and by bottle. Therefore, it is not possible to estimate the content of uranium in another bottle of the same supplement produced by the same manufacturer.

Kidney Biomonitoring Testing

Exposure to uranium can damage the proximal tubule of the kidney. Damage to this portion of the tubule impairs the ability of the nephron to reabsorb low molecular weight proteins from the urine. Therefore, the appearance of elevated concentrations of low molecular weight protein in the urine, such as retinol binding protein (RBP), is an early marker of damage to the kidney.

In conjunction with this urine uranium testing, SCDHEC conducted a separate test, in which urine samples were analyzed for RBP in three individuals with previously elevated RBP levels. The results of this investigation will be reported by SCDHEC in a separate document.

Reporting Results

ATSDR/SCDHEC provided the participants with their individual test results and an explanation of their significance. ATSDR and SCDHEC also provided toll-free telephone numbers so the participants and their health care providers could contact ATSDR and SCDHEC to further discuss their test results.

Conclusions

(1) Urine uranium concentrations dramatically decreased (by 95 %) in the 4 members of the family that had previously shown urine uranium increases.

(2) Urine uranium concentrations decreased in 7 of 8 (88%) of the EI participants. All seven urine uranium concentrations decreased to less than 0.06 μg/g.

(3) Urine uranium concentrations among 5 of the 8 participants (63 %) exceeded the 90th percentile (0.024 μg/g) for urine uranium levels in the general population.

(4) The urine uranium concentration increased in one participant. A detailed exposure history or a medical history did not identify any contributors to this increase.

Recommendations

(1) Residents with uranium-contaminated wells should continue to use alternate sources of water for potable use. If public water is available or an appropriate water treatment system is installed for potable use, then these are also acceptable.

(2) Individuals with health concerns over exposure to uranium should consult with their

personal physician. ATSDR and SCDHEC physicians are available to discuss individual test results with health care providers.

Public Health Action Plan

(1) SCDHEC will submit a proposal to obtain funding from ATSDR to conduct a community Health Investigation. This study will assess the health impact of exposure to uranium from drinking water on the residents of Simpsonville/Fountain Inn.

(2) According to a 1997 survey, more than 750,000 people in South Carolina use a residential well as their primary source of drinking water [11]. The residential well program in South Carolina recommends testing well water if owners experience problems with water discoloration or odor. Therefore, not all wells are uniformly tested for chemical, metal or radionuclide contaminants. ATSDR and SCDHEC will work together to develop guidelines to test for uranium and other radionuclides in well water for at risk areas in the state.

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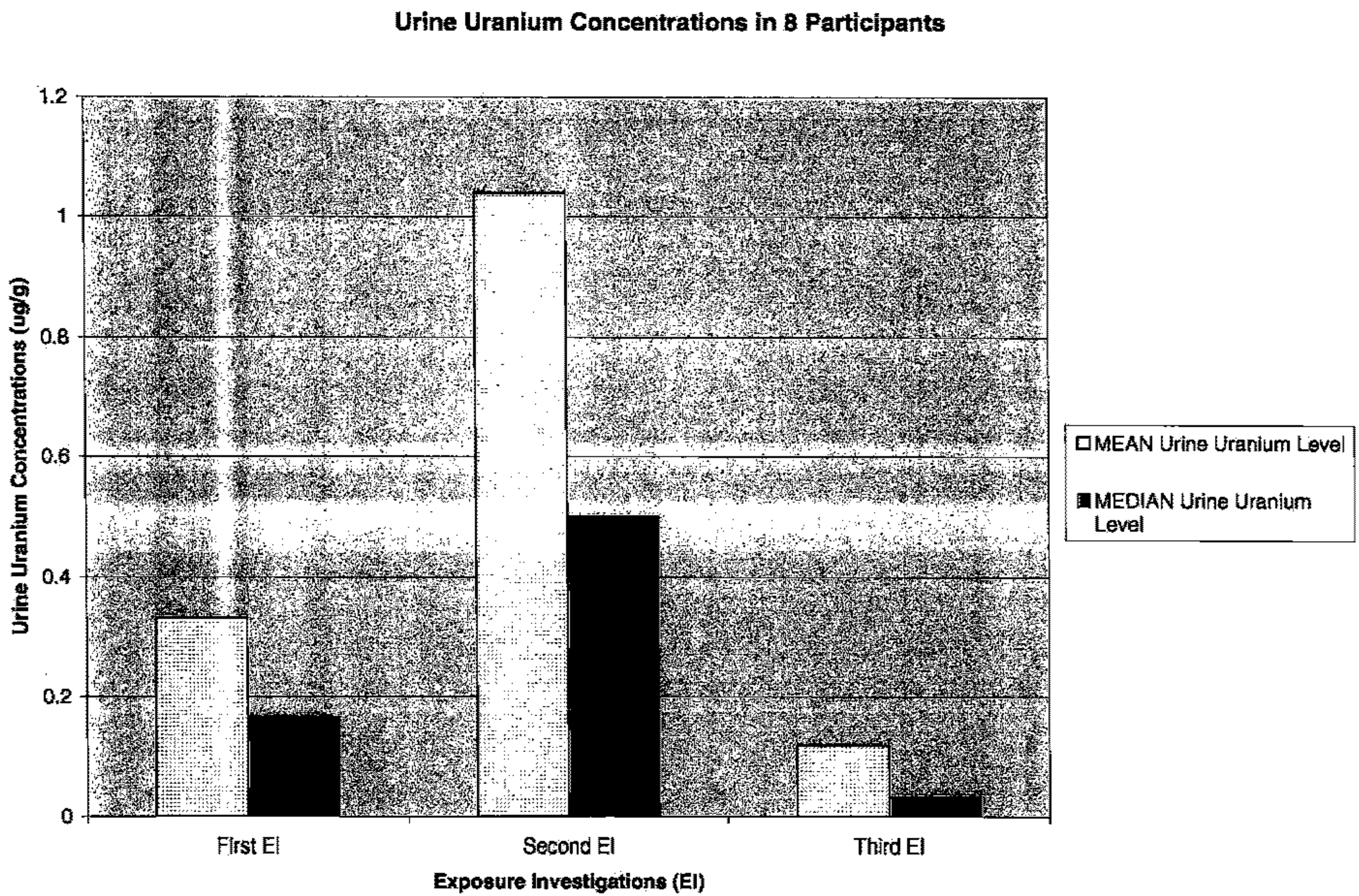
Urine Uranium Concentrations in 8 Participants
Urine Uranium Concentrations (ug/g)
1.2
1
0.8
0.6
0.4
0.2
0
First EI
Second EI
Third EI
Exposure Investigations (EI)
MEAN Urine Uranium Level
MEDIAN Urine Uranium Level