Springerlink Header: Metals and Health (A Barchowsky, Section Editor)

Health Effects and Environmental Justice Concerns of Exposure to Uranium in Drinking Water

Laura Corlin, Tommy Rock, Jamie Cordova, Mark Woodin, John L. Durant, David M. Gute, Jani Ingram, and Doug Brugge

Laura Corlin*, MS, *Tufts University School of Engineering, Department of Civil and Environmental Engineering, 200 College Ave, Medford, MA, (303) 522-6539, laura.corlin@tufts.edu*
Tommy Rock, MS, *Northern Arizona University School of Earth Sciences and Environmental Sustainability, 525 S Beaver St, Flagstaff, AZ, (928) 278-0156, tr73@nau.edu*
Jamie Cordova, BA, *Tufts University School of Arts and Sciences, 200 College Ave, Medford MA United States, (603) 686-6858, jamie.cordova@tufts.edu*
Mark Woodin, ScD, *Tufts University School of Engineering, Department of Civil and Environmental Engineering, 200 College Ave, Medford, MA, and Tufts University School of Medicine, Department of Public Health and Community Medicine, 136 Harrison Ave, Boston, MA, (617) 627-3640, mark.woodin@tufts.edu*
John L. Durant, PhD, *Tufts University School of Engineering, Department of Civil and Environmental Engineering, 200 College Ave, Medford, MA, (617) 627-5489, john.durant@tufts.edu*
David M. Gute, PhD, MPH, *Tufts University School of Engineering, Department of Civil and Environmental Engineering, 200 College Ave, Medford, MA, (617) 627-3452, david.gute@tufts.edu*
Jani Ingram, PhD, *Northern Arizona University Department of Chemistry and Biochemistry, 700 South Osborne Dr., Flagstaff, AZ, (928) 523-7877, jani.ingram@nau.edu*
Doug Brugge, PhD, *Tufts University School of Medicine, Department of Public Health and Community Medicine, 136 Harrison Ave, Boston, MA, Tufts University School of Engineering, Department of Civil and Environmental Engineering, 200 College Ave, Medford, MA, and Tisch College of Civic Life, Medford, MA (617) 636-0326, doug.brugge@gmail.com*

***Corresponding author**

Keywords: uranium, drinking water, health effects, environmental justice, Navajo, arsenic

Abstract

We discuss the recent epidemiologic literature regarding health effects of uranium exposure in drinking water focusing on the chemical characteristics of uranium. While there is strong toxicologic evidence for renal and reproductive effects as well as DNA damage, the epidemiologic evidence for these effects in people exposed to uranium in drinking water is limited. Further, epidemiologic evidence is lacking for cardiovascular and oncogenic effects.

One challenge in characterizing health effects of uranium in drinking water is the paucity of long-term cohort studies with individual level exposure assessment. Nevertheless, there are environmental justice concerns due to the substantial exposures for certain populations. For example, we present original data suggesting that individuals living in the Navajo Nation are exposed to high levels of uranium in unregulated well water used for drinking. In 10 out of 185 samples (5.4%), concentrations of uranium exceeded standards under the Safe Drinking Water Act. Therefore, efforts to mitigate exposure to toxic elements in drinking water are warranted and should be prioritized.

Introduction

Recent water crises in places like Flint, Michigan [1,2] have brought renewed attention to the potential for exposure to toxic elements in drinking water around the United States, though water quality issues have been pervasive in some communities for decades. Uranium is a toxic element that is commonly found in drinking water; the average American ingests approximately 0.9–1.5 μg of uranium per day through drinking water. In some parts of the US and particularly in places that rely on contaminated groundwater, uranium concentrations can substantially exceed this level [3,4]. The renal health effects associated with elevated exposure to uranium in drinking water are not fully established and the maximum contaminant level suggested by the World Health Organization guidelines has changed several times since 1971 when the international community first suggested monitoring uranium concentrations in drinking water [5].

While the original guidelines for uranium exposure were based on literature regarding its radiological characteristics, guidelines in the past 18 years have also considered the chemical characteristics of uranium. The literature suggests possible subclinical renal effects in exposed populations but clinically-relevant health effects may be limited even at relatively high concentrations (>100 μg/L) [6–8]; thus, the guidelines for uranium concentration in drinking water were *increased* in 2011 from 2 μg/L to 30 μg/L [5]. The newest guideline is still designated as provisional and it is possible that it is not sufficiently protective given the health concerns suggested by the relatively strong toxicology and more limited epidemiology evidence [9]. The current US Environmental Protection Agency (EPA) maximum contaminant level for uranium is also set at 30 μg/L under the Safe Drinking Water Act [10].

Given the uncertainty regarding the guidelines for uranium in drinking water, we will first review the recent epidemiologic literature on the health effects of uranium exposure in drinking water focusing on the chemical characteristics of uranium. We will then discuss these findings within the context of an environmental justice framework focusing on the disproportionate burden faced by certain vulnerable populations. We will highlight a case study with original data quantifying the levels of exposure to uranium and arsenic in drinking water among individuals living in the Navajo Nation. We will conclude with recommendations regarding future research and public health actions.

Sources of uranium exposure

Uranium is a heavy metal. In its natural state, it is a mixture of three radioactive isotopes (^{238}U, ^{235}U, and ^{234}U). By mass, ^{238}U is the predominant isotope (99.27%) [11]. Uranium undergoes alpha emission, beta emission, and spontaneous fission. Through the decay process, a series of radioactive progeny are produced to eventually form lead. The rate of decay is slow as the half-life for ^{238}U is approximately 4.5 billion years and the half-lives for ^{235}U and ^{234}U are 700 million years and 250,000 years, respectively [3,12]. While the decay products and radiological characteristics are associated with a variety of health effects [13], the specific activity of uranium itself is generally low [3] and therefore our focus in this report is on the chemical as opposed to the radiological effects of ingested uranium.

Additionally, while uranium can be inhaled in dust particles, we will focus on sources from water, and to a lesser extent from soil and food. On average, Americans ingest 1.8–3.0 μg of uranium per day split evenly between food and water sources [3]. The uranium ingested through food is predominately due to uranium adsorbed onto vegetable roots through contact with contaminated soils [3,14]. While soils typically contain approximately 3 ppm of uranium, in some areas where uranium ore is present, concentrations can be as much as 1000 times higher [3]. Uranium can be present in drinking water due to weathering of uranium containing deposits [15], mining activities [16], solubilization of uranium by nitrate (especially in aquifers where agriculture is common) [4,17], and accumulation in sediment and scales in water distribution systems [18].

Health Effects

Several previous reviews have cataloged the health effects associated with uranium exposure based on both toxicologic and epidemiologic evidence [13,19–22]. Additionally, the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for uranium was recently updated [3]. Therefore, our goal is not to provide an exhaustive overview of the toxicologic and epidemiologic evidence linking uranium to human health effects. Rather, we will highlight some of the recent epidemiologic research (2011-2016) pertaining to the health effects of drinking water contaminated with excessive levels of uranium. Since most of the recent epidemiologic literature has addressed the potential for renal, cardiovascular, reproductive and developmental, and oncogenic effects, we will focus our discussion on these processes.

Toxicokinetics

The concentration of toxic elements in drinking water is only relevant to human health if the elements are in contact with the skin or if they are absorbed into the body and distributed to target organs. Absorption of ingested uranium is generally fairly low (<5%) [3]. One cross-sectional study found that concentrations of several toxic elements, including uranium, in drinking water were not correlated with biomarkers of these elements in people who ingested the water [23]. Nevertheless, other studies indicate that some uranium is absorbed from drinking water [24,25] and an ecologic study found that people living in areas with higher environmental uranium concentrations had higher urinary uranium concentrations [26]. Once absorbed, uranium deposits predominantly in the bones, kidneys, and liver. The body burden is concentrated in bone as at least 95% of uranium in the kidneys and liver is excreted through urine or feces within several days [3].

Renal

One of the most commonly cited health effects of exposure to uranium is nephrotoxicity. This has been well documented in the toxicology literature [3,19]. Several epidemiologic studies have also shown associations between exposure to uranium in drinking water and renal damage [3,22,27]. One study indicated that urinary uranium concentrations are weakly associated with biomarkers of renal damage [7] while another study found adverse effects on the proximal tubule but not on the glomerulus [6]. Other studies found no significant adverse renal effects as measured by biomarkers of renal function [28] or found that associations were dependent on how urine concentrations were adjusted for creatinine [29]. In a study that found associations between urinary uranium levels and biomarkers of renal function, the clinical implications were unclear as there were no associations of uranium exposure and clinical renal disease [8]. Furthermore, a review suggested that the nephrotoxicity may be due primarily to high-level acute exposure rather than to low-level chronic exposure [30].

Cardiovascular

The ATSDR profile for uranium states that cardiovascular effects are "unlikely" [3]. Studies have found no association between urinary uranium concentration with cardiovascular disease [31] and limited evidence for an association with heart rate variability [32]. Nevertheless, one study suggested a correlation between uranium concentration in drinking water and blood pressure. This was only observed among people with high urinary uranium levels (>1 µg/L) and the trends were more evident for diastolic blood pressure than for systolic blood pressure [28]. The potential link to cardiovascular impacts was also supported in a cohort where individuals with occupational exposure to uranium were at increased risk of dying from diseases of the circulatory system [33]. Additionally, a survey from the Diné Network for Environmental Health project reported that playing or working near uranium contaminated sites or in uranium mines is associated with hypertension [34].

Reproductive and developmental

Toxicologic research has shown developmental impacts, and especially birth defects, associated with uranium at the typically high levels of exposure used in such studies [3]. One toxicology study, however, found that uranium in drinking water had estrogenic effects in mice with uranium concentrations at or below the EPA and WHO drinking water standard [35]. Nevertheless, there is a paucity of epidemiologic literature examining reproductive effects of uranium in drinking water. The epidemiology studies that have investigated reproductive outcomes have primarily considered inhaled uranium and radiological impacts of uranium. These have found congenital anomalies and sex ratio effects [3,36,37]. The Navajo Birth Cohort Study is currently underway and this study was designed to investigate the relationship between environmental uranium exposure, including uranium in drinking water, with birth outcomes [38].

Genetic damage

The toxicologic literature has shown that uranium may cause DNA strand breaks via its chemical rather than radiological properties [39,40]. Additionally, ecologic studies suggest that people living near or working in uranium mines, as well as field animals living near abandoned uranium mines, show chromosomal damage; however, there is little evidence as to whether these effects might occur from drinking water contaminated with uranium [41,42].

Cancer

Though uranium exposure has been associated with certain types of cancer, such as bone cancer and leukemia, uranium is not classified as carcinogenic by either the International Agency for Research on Cancer or by the National Toxicology Program [43]. While most of the literature on these relationships indicates the associations are likely due to the radioactivity of uranium rather than the chemical properties of ingested uranium [3], recent ecologic studies suggest that uranium in drinking water may be related to the incidence of leukemia, kidney cancer, lung cancer in women, and colorectal cancer [44,45]. Nevertheless, research on the links between environmental uranium exposure and cancer is generally inconclusive as most studies use ecologic exposure assessment, many have inconsistent case definitions, and many do not adequately account for long latency periods [3,13]. Long-term cohort studies could more effectively assess the impact of uranium exposure in drinking water on various types of cancers.

Research challenges

Epidemiologic studies of the health effects of chronic low-dose exposure to uranium in drinking water have lagged behind the toxicologic evidence though there is some emerging epidemiologic evidence for renal effects. Larger, long-term, cohort studies using individual level exposure data would be most useful if further research were pursued. The exposure assessment should ideally consider cumulative exposure. Additionally, these studies should also account for the various exposure pathways for uranium. Furthermore, research should continue to try to distinguish the chemical and radiological health effects of environmental exposure.

Understanding the health effects of uranium is further complicated by the fact that uranium typically also co-occurs with other toxic elements, such as uranium decay products (radium, thorium, and radon), arsenic, and tungsten [26]. A recent study that attempted to characterize the chemical mixtures in well water found that 84% of sampled wells had at least two contaminants present in concentrations exceeding 10% of the maximum contaminant level set under the Safe Drinking Water Act. Of the 25 most common chemical mixtures found in groundwater, arsenic (a known carcinogen) was present in all but two mixtures and uranium was present in all but four [46,47]. Despite how common these chemical mixtures are in well water, and the evidence that these elements can be absorbed by individuals [26], relatively little research has investigated the health effects of mixtures of contaminants in drinking water. Without research into the health effects of mixtures, regulations will only focus on individual contaminants. This regulatory approach focused on individual contaminants may not be sufficiently protective of human health if there are important interactions between contaminants.

<u>Environmental Justice</u>

Beyond the challenges in characterizing health effects of uranium in drinking water, disparities exist in terms of exposure [46,48]. Sensitive or underserved populations, especially in certain geographic regions, may face a disproportionate burden [9] and these populations may be the least well-positioned to handle additional health risks. Frequently, people are unaware of either the presence of toxic elements in their drinking water or of the potential risks associated with exposure. This has been seen for example in several rural Latin American communities and is further complicated by the lack of appropriate mitigation tools [49]. Better surveillance, more transparency, an increased focus on risk communication [50], and the provision of alternative sources of clean water are needed. For communities that are aware of the potential risks, these strategies are equally useful.

Case Study: Uranium Contamination on the Navajo Nation

The Navajo people are an example of a population that is quite knowledgeable about the potential for exposure to toxic elements in their drinking water as uranium and arsenic are naturally occurring in the region where the Navajo Nation is located. From the 1940s through the 1980s, extensive uranium mining occurred there and the predominant purchaser of uranium was the US government [51,52]. While the Navajo people were initially optimistic about the employment opportunities, the lack of communication about potential health hazards (especially from radon in the mines) and poor and under-regulated working conditions resulted in well documented harm to the miners and concerns about possible effects in nearby communities [52,53]. For the past three decades, the Navajo Nation has been trying to get the US government to take responsibility for their role and to help with the decontamination efforts [52]. This has been partially successful and in recent years, the US government spent over $100 million on remediation efforts as called for by two Five Year Plans (2008-2013, 2014-2018) developed in collaboration with the Navajo Nation [52,54,55]. Despite progress, there is still extensive contamination near the abandoned uranium mines across the Navajo Nation that threatens groundwater supplies. Access to safe drinking water is further compromised by the fact that nearly one-third of the population is not served by public water systems. Instead, approximately 54,000 people rely on hauled water or water obtained from unregulated wells and springs [55]. There is thus public concern that the well water is contaminated with toxic elements.

To describe the distribution of uranium and arsenic contamination in drinking water, we obtained 185 water samples between 2013 and 2015 from 144 wells identified by community members across the Navajo Nation. Uranium sampling and analysis protocols have been described elsewhere [56] and the protocols were the same for arsenic. Water samples were filtered (0.45 µm pore size), preserved with three drops of nitric acid at the time of sampling, and stored in a freezer. Concentrations of both uranium and arsenic were measured using an inductively coupled plasma mass spectrometer (detection limit for both elements was 1 µg/L). There were 40 wells with repeated uranium samples (correlation coefficient = 0.94) and 38 wells with repeated arsenic samples (correlation coefficient = 0.61 or = 0.98 with one outlier excluded). Samples in 2015 (n = 6 wells) were taken to confirm elevated concentrations. Well depth was known for 25% of all samples. Geographic coordinates were obtained for all wells and 30-day average and cumulative precipitation data were obtained from the National Oceanic and Atmospheric Administration [57].

The distribution of uranium and arsenic concentrations are described in Table 1. Nearly 26% of wells had concentrations exceeding the US EPA standards, including 5% of samples that exceeded the 30 µg/L uranium standard, 22% of samples that exceeded the 10 µg/L arsenic standard, and 4% of samples that exceeded both standards. These proportions are generally consistent with a previous water quality monitoring campaign on the Navajo Nation [58]. Additionally, the locations where wells exceeded the US EPA guidelines corresponded to locations where arsenic and uranium contamination might be expected based on geomorphological characteristics (Figure 1).

Table 1. Uranium and arsenic concentrations measured in well-water samples.

	Uranium (µg/L) (number of samples = 185)	Arsenic (µg/L) (number of samples = 181)
Minimum	<1.0	<1.0
Median	2.3	2.7
Maximum	170	120
Mean	9.9	8.4
Standard Deviation	23	16

To see if there were external factors that affected the toxic element concentrations, we considered precipitation, season, and well depth. In models of log-transformed concentrations accounting for repeated sampling of certain wells, neither season nor average precipitation were significant predictors of either uranium or arsenic concentrations ($p > 0.05$ for all tests). Increasing well depth was correlated with lower concentrations of uranium; however, well depth was not known for the wells with uranium or arsenic concentrations exceeding the US EPA standards and well depth might not have a consistent relationship with concentrations in different geographic areas. As with other studies [59], (natural log) arsenic and uranium concentrations were found to be highly correlated ($r = 0.387$, $p < 0.001$; Figure 1).

Based on our water quality monitoring campaign, we found that arsenic contamination, and to a lesser extent uranium contamination, are widespread in currently unregulated wells used for drinking water. While it is unclear without more detailed exposure assessment whether the levels of contamination we observed are associated directly with meaningful biological levels of these toxic elements [23], health effects, especially related to arsenic exposure, are possible at these concentrations. Additionally, the high concentration of both uranium and arsenic within drinking water might pose greater health risks due to potential joint effects of these exposures. Reports that minority, low-income, and rural populations are likely to have higher exposures to these toxic elements [60] suggests the need for more extensive monitoring of water quality in currently unregulated wells, especially in locations where contamination is likely and where populations are most likely to face other environmental hazards.

Finally, while the Navajo people tend to be concerned about the potential for uranium contamination of groundwater, it may be at least as important to consider the potential for arsenic exposure in groundwater since the percent of wells that exceeded the standard was much higher and since the health effects of arsenic, including carcinogenicity and cardiovascular impacts, are more well-established at concentrations near the current standard [47,61–64]. It is possible that uranium, arsenic, and other toxic elements interact within the groundwater. With future research, which should be performed either after or concomitantly with clean-up and exposure mitigation actions, it may become evident that the current levels of uranium contamination are too high. Additionally, there are other reasons to support clean-up efforts of the abandoned uranium mines as the radiological characteristics make exposure to uranium and its decay products potentially dangerous.

Recommendations and Conclusions

We provided a brief overview of the current understanding of the health effects of exposure to uranium in drinking water and we considered the environmental justice implications with a case study. While there are areas of uncertainty regarding health effects of exposure to uranium in drinking water, several actions can be taken. From a research perspective, there could be an effort to develop the research to a state where there is a well justified minimal risk level for chronic exposure (>365 days) to ingested uranium. In our opinion, questions remain about the proper level. We would support efforts to be protective of the most sensitive populations, especially since there is some toxicologic and epidemiologic evidence suggesting that there could be health effects below the current standard [19,35]. To do this and to more appropriately assess the health risks, future work should focus on improving exposure assessment. Individual-level exposure assessment accounting for changes in water source over time is necessary. Future studies would be most useful if they were large, long-term cohort studies focused on environmentally-relevant concentrations and cumulative exposure given the nature of chronic, low-level exposures present in drinking water. Such studies can be used to better protect public health by informing WHO guidelines and US EPA standards.

Nevertheless, future research should not delay or divert resources from clean-up action or from investments in improving the water infrastructure. As Ken Rothman said:

> A cynic might note that research is a form of public health policy action that is politically advantageous, in that it forestalls other actions that might be more direct and costly, and it offers the promise of a technical solution (S9) [65].

While Rothman was referring to cluster investigations, the point is also relevant here. The Navajo people and others in their position deserve access to safe drinking water. If a study is likely to be inconclusive because of methodological limitations or if the study would divert resources from improving water infrastructure, cleaning up abandoned uranium mines, or finding water treatment solutions that could improve the health and well-being of the local community, the study should not be performed. If an environmental health study is deemed worthwhile, it should be conducted as part of a larger effort to improve access to safe water and should directly benefit the affected community.

Of likely greater importance than future research, there are several practical steps that can be taken to mitigate the environmental justice concerns. First, exposure should be characterized in high-risk communities and water quality should be actively monitored in wells used for drinking. Second, community members in affected regions should be notified of these levels and of the potential for toxicity. Third, it may be useful to investigate the effectiveness of small-scale and household treatment systems as these systems have been shown to potentially reduce exposure to toxic elements [66–70]. Development of small-scale treatment systems that can remove multiple elements that co-occur in drinking water should be considered. Implementing mitigation strategies should be a high priority, even given the current uncertainties regarding health effects associated with uranium in drinking water.

Acknowledgment

Funding was provided by NSF 0966093, USGS (2015AZ544B), NCI Partnership for Native American Cancer Prevention (U54CA143925), and Tufts Institute of the Environment.

Compliance with Ethics Guidelines

Conflict of Interest

L. Corlin, T. Rock, J. Cordova, M. Woodin, J.L. Durant, D.M. Gute, and J. Ingram declare that they have no conflict of interest. D. Brugge reports paid travel expenses to South Africa from International Physicians for the Prevention of Nuclear War to present talks on uranium health effects.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

•Of importance

1. Hanna-Attisha M, LaChance J, Sadler RC, Champney Schnepp A. Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response. Am. J. Public Health. 2015;106:283–90.

2. Bellinger DC. Lead Contamination in Flint — An Abject Failure to Protect Public Health. N. Engl. J. Med. 2016;374:1101–3.

3. • Agency for Toxic Substances and Disease Registry. Toxicological Profile: Uranium [Internet]. 2013. Report No.: 7440-61–1. Available from: http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=440&tid=77

A more extensive review of the health effects and characteristics of uranium is presented in the newly revised ATSDR Toxicological Profile.

4. Nolan J, Weber KA. Natural Uranium Contamination in Major U.S. Aquifers Linked to Nitrate. Environ. Sci. Technol. Lett. 2015;2:215–20.

5. Ansoborlo E, Lebaron-Jacobs L, Prat O. Uranium in drinking-water: A unique case of guideline value increases and discrepancies between chemical and radiochemical guidelines. Environ. Int. 2015;77:1–4.

6. Zamora ML, Tracy BL, Zielinski JM, Meyerhof DP, Moss MA. Chronic Ingestion of Uranium in Drinking Water: A Study of Kidney Bioeffects in Humans. Toxicol. Sci. 1998;43:68–77.

7. Seldén AI, Lundholm C, Edlund B, Högdahl C, Ek B-M, Bergström BE, et al. Nephrotoxicity of uranium in drinking water from private drilled wells. Environ. Res. 2009;109:486–94.

8. Okaneku J, Vearrier D, Mckeever R, Lasala G, Greenberg MI. Urine uranium concentrations and renal function in residents of the United States—2001 to 2010. Clin. Toxicol. 2015;53:931–4.

9. • Frisbie SH, Mitchell EJ, Sarkar B. World Health Organization increases its drinking-water guideline for uranium. Environ. Sci. Process. Impacts. 2013;15:1817–23.

This article discusses the decision to change the WHO guideline for uranium contamination in drinking water.

10. Environmental Protection Agency. Radionuclides Rule [Internet]. 2015 [cited 2016 May 9]. Available from: https://www.epa.gov/dwreginfo/radionuclides-rule

11. Ferrante M, OliveriConti G, RasicMilutinovic Z. Health Effects of Metals and Related Substances in Drinking Water. Jovanovic D, editor. 2014.

12. Aieta EM, Singley JE, Trussell AR, Thorbjarnarson KW, McGuire MJ. Radionuclides in Drinking Water: An Overview. J. Am. Water Works Assoc. 1987;79:144–52.

13. Canu IG, Laurent O, Pires N, Laurier D, Dublineau I. Health Effects of Naturally Radioactive Water Ingestion: The Need for Enhanced Studies. Environ. Health Perspect. 2011;119:1676–80.

14. Tracy BL, Prantl FA, Quinn JM. Transfer of 226Ra, 210Pb and Uranium from Soil to Garden Pro... : Health Physics. Health Phys. [Internet]. 1983 [cited 2016 May 13];44. Available from: http://journals.lww.com/health-physics/Fulltext/1983/05000/Transfer_of_226Ra,_210Pb_and_Uranium_from_Soil_to.1.aspx

15. Banning A, Rüde TR. Apatite weathering as a geological driver of high uranium concentrations in groundwater. Appl. Geochem. 2015;59:139–46.

16. Ruedig E, Johnson TE. An evaluation of health risk to the public as a consequence of in situ uranium mining in Wyoming, USA. J. Environ. Radioact. 2015;150:170–8.

17. Wigginton NS. Fertilizing water contamination. Science. 2015;349:1297–8.

18. Lytle DA, Sorg T, Wang L, Chen A. The accumulation of radioactive contaminants in drinking water distribution systems. Water Res. 2014;50:396–407.

19. Brugge D, Buchner V. Health effects of uranium: new research findings. Rev. Environ. Health. 2011;26:231–49.

20. Hindin R, Brugge D, Panikkar B. Teratogenicity of depleted uranium aerosols: A review from an epidemiological perspective. Environ. Health. 2005;4:17.

21. Brugge D, deLemos JL, Oldmixon B. Exposure Pathways and Health Effects Associated with Chemical and Radiological Toxicity of Natural Uranium: A Review. Rev. Environ. Health. 2011;20:177–194.

22. Kurttio P, Auvinen A, Salonen L, Saha H, Pekkanen J, Mäkeläinen I, et al. Renal effects of uranium in drinking water. Environ. Health Perspect. 2002;110:337–42.

23. Yard E, Bayleyegn T, Abebe A, Mekonnen A, Murphy M, Caldwell KL, et al. Metals Exposures of Residents Living Near the Akaki River in Addis Ababa, Ethiopia: A Cross-Sectional Study. J. Environ. Public Health. 2015;2015:1–8.

24. Limson Zamora M, Zielinski JM, Meyerhof DP, Tracy BL. Gastrointestinal absorption of uranium in humans. Health Phys. 2002;83:35–45.

25. Harduin JC, Royer P, Piechowski J. Uptake and Urinary Excretion of Uranium after Oral Administration in Man. Radiat. Prot. Dosimetry. 1994;53:245–8.

26. Pang Y, Peng RD, Jones MR, Francesconi KA, Goessler W, Howard BV, et al. Metal mixtures in urban and rural populations in the US: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study. Environ. Res. 2016;147:356–64.

27. Mao Y, Desmeules M, Schaubel D, Bérubé D, Dyck R, Brûlé D, et al. Inorganic components of drinking water and microalbuminuria. Environ. Res. 1995;71:135–40.

28. Kurttio P, Harmoinen A, Saha H, Salonen L, Karpas Z, Komulainen H, et al. Kidney Toxicity of Ingested Uranium From Drinking Water. Am. J. Kidney Dis. 2006;47:972–82.

29. Shelley R, Kim N-S, Parsons PJ, Lee B-K, Agnew J, Jaar BG, et al. Uranium associations with kidney outcomes vary by urine concentration adjustment method. J. Expo. Sci. Environ. Epidemiol. 2014;24:58–64.

30. Vicente-Vicente L, Quiros Y, Pérez-Barriocanal F, López-Novoa JM, López-Hernández FJ, Morales AI. Nephrotoxicity of Uranium: Pathophysiological, Diagnostic and Therapeutic Perspectives. Toxicol. Sci. 2010;118:324–47.

31. Agarwal S, Zaman T, Tuzcu EM, Kapadia SR. Heavy Metals and Cardiovascular Disease: Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2006. Angiology. 2011;62:422–9.

32. Feng W, He X, Chen M, Deng S, Qiu G, Li X, et al. Urinary Metals and Heart Rate Variability: A Cross-Sectional Study of Urban Adults in Wuhan, China. Environ. Health Perspect. 2015;123:217–22.

33. Canu IG, Garsi J-P, Caër-Lorho S, Jacob S, Collomb P, Acker A, et al. Does uranium induce circulatory diseases? First results from a French cohort of uranium workers. Occup. Environ. Med. 2012;69:404–9.

34. Hund L, Bedrick EJ, Miller C, Huerta G, Nez T, Ramone S, et al. A Bayesian framework for estimating disease risk due to exposure to uranium mine and mill waste on the Navajo Nation. J. R. Stat. Soc. Ser. A Stat. Soc. 2015;178:1069–91.

35. Raymond-Whish S, Mayer LP, O'Neal T, Martinez A, Sellers MA, Christian PJ, et al. Drinking Water with Uranium below the U.S. EPA Water Standard Causes Estrogen Receptor–Dependent Responses in Female Mice. Environ. Health Perspect. 2007;115:1711–6.

36. Alaani S, Tafash M, Busby C, Hamdan M, Blaurock-Busch E. Uranium and other contaminants in hair from the parents of children with congenital anomalies in Fallujah, Iraq. Confl. Health. 2011;5:15.

37. Shields LM, Wiese WH, Skipper BJ, Charley B, Benally L. Navajo birth outcomes in the Shiprock uranium mining area. Health Phys. 1992;63:542–51.

38. • Lewis J, Gonzales M, Burnette C, Benally M, Seanez P, Shuey C, et al. Environmental Exposures to Metals in Native Communities and Implications for Child Development: Basis for the Navajo Birth Cohort Study. J. Soc. Work Disabil. Rehabil. 2015;14:245–69.

This study discusses the ongoing Navajo Birth Cohort Study which may indicate whether uranium in drinking water is associated with reproductive or developmental health effects.

39. Wilson J, Young A, Civitello ER, Stearns DM. Analysis of heat-labile sites generated by reactions of depleted uranium and ascorbate in plasmid DNA. J. Biol. Inorg. Chem. JBIC Publ. Soc. Biol. Inorg. Chem. 2014;19:45–57.

40. George SA, Whittaker AM, Stearns DM. Photoactivated uranyl ion produces single strand breaks in plasmid DNA. Chem. Res. Toxicol. 2011;24:1830–2.

41. Lourenço J, Pereira R, Gonçalves F, Mendo S. Metal bioaccumulation, genotoxicity and gene expression in the European wood mouse (Apodemus sylvaticus) inhabiting an abandoned uranium mining area. Sci. Total Environ. 2013;443:673–80.

42. Lourenço J, Pereira R, Pinto F, Caetano T, Silva A, Carvalheiro T, et al. Biomonitoring a human population inhabiting nearby a deactivated uranium mine. Toxicology. 2013;305:89–98.

43. Agency for Toxic Substances and Disease Registry. Public Health Statement for Uranium [Internet]. 2013 [cited 2016 May 11]. Available from: http://www.atsdr.cdc.gov/PHS/PHS.asp?id=438&tid=77

44. Radespiel-Tröger M, Meyer M. Association between drinking water uranium content and cancer risk in Bavaria, Germany. Int. Arch. Occup. Environ. Health. 2012;86:767–76.

45. Wagner SE, Burch JB, Bottai M, Puett R, Porter D, Bolick-Aldrich S, et al. Groundwater uranium and cancer incidence in South Carolina. Cancer Causes Control. 2010;22:41–50.

46. Toccalino PL, Norman JE, Scott JC. Chemical mixtures in untreated water from public-supply wells in the U.S. — Occurrence, composition, and potential toxicity. Sci. Total Environ. 2012;431:262–70.

47. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009;10:453–4.

48. VanDerslice J. Drinking Water Infrastructure and Environmental Disparities: Evidence and Methodological Considerations. Am. J. Public Health. 2011;101:S109–14.

49. Bundschuh J, Litter M, Ciminelli VST, Morgada ME, Cornejo L, Hoyos SG, et al. Emerging mitigation needs and sustainable options for solving the arsenic problems of rural and isolated urban areas in Latin America - a critical analysis. Water Res. 2010;44:5828–45.

50. deLemos JL, Brugge D, Cajero M, Downs M, Durant JL, George CM, et al. Development of risk maps to minimize uranium exposures in the Navajo Churchrock mining district. Environ. Health. 2009;8:29.

51. Pearson J. Hazard visibility and occupational health problem solving the case of the uranium industry. J. Community Health. 1980;6:136–47.

52. Brugge D, Goble R. The History of Uranium Mining and the Navajo People. Am. J. Public Health. 2002;92:1410–9.

53. National Research Council (US) Committee on Health Risks of Exposure to Radon (BEIR VI). Health Effects of Exposure to Radon: BEIR VI [Internet]. Washington (DC): National Academies Press (US); 1999 [cited 2016 Aug 16]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK233262/

54. USEPA, NNEPA. Federal Actions to Address Impacts of Uranium Contamination in the Navajo Nation [Internet]. 2014. Available from: http://www3.epa.gov/region09/superfund/navajo-nation/pdf/nn-five-year-plan-2014.pdf

55. US EPA. Addressing Uranium Contamination on the Navajo Nation [Internet]. 2016 [cited 2016 May 8]. Available from: https://www3.epa.gov/region9/superfund/navajo-nation/contaminated-water.html

56. Campbell NR. Characterizing 234U/238U activity ratios and inorganic complexation species in water sources on the Navajo Reservation [Internet]. Northern Arizona University; 2012 [cited 2016 May 14]. Available from: http://gradworks.umi.com/15/11/1511247.html

57. National Centers for Environmental Information. Climatological Data Publications [Internet]. [cited 2016 Feb 3]. Available from: http://www.ncdc.noaa.gov/IPS/cd/cd.html?_finish=0.6073968623403997

58. Murphy M, Lewis L, Sabogal R, Carlos Bell. Survey of unregulated drinking water sources on navajo nation. Am. J. Public Health. 2009;Abstract 208881.

59. Pfeiffer M, Batbayar G, Hofmann J, Siegfried K, Karthe D, Hahn-Tomer S. Investigating arsenic (As) occurrence and sources in ground, surface, waste and drinking water in northern Mongolia. Environ. Earth Sci. 2014;73:649–62.

60. • Joca L, Sacks JD, Moore D, Lee JS, Sams II R, Cowden J. Systematic review of differential inorganic arsenic exposure in minority, low-income, and indigenous populations in the United States. Environ. Int. 2016;92–93:707–15.

This review highlights disparities in exposure to toxic elements throughout the U.S.

61. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Arsenic. 2007. Report No.: 7440-38–2.

62. Moon KA, Guallar E, Umans JG, Devereux RB, Best LG, Francesconi KA, et al. Association between exposure to low to moderate arsenic levels and incident cardiovascular disease. A prospective cohort study. Ann. Intern. Med. 2013;159:649–59.

63. García-Esquinas E, Pollán M, Umans JG, Francesconi KA, Goessler W, Guallar E, et al. Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 2013;22:1944–53.

64. James KA, Byers T, Hokanson JE, Meliker JR, Zerbe GO, Marshall JA. Association between lifetime exposure to inorganic arsenic in drinking water and coronary heart disease in Colorado residents. Environ. Health Perspect. 2015;123:128–34.

65. Rothman KJ. A Sobering Start for the Cluster Busters' Conference. Am. J. Epidemiol. 1990;132:6–13.

66. Slotnick MJ, Meliker JR, Nriagu JO. Effects of time and point-of-use devices on arsenic levels in Southeastern Michigan drinking water, USA. Sci. Total Environ. 2006;369:42–50.

67. Litter MI, Alarcón-Herrera MT, Arenas MJ, Armienta MA, Avilés M, Cáceres RE, et al. Small-scale and household methods to remove arsenic from water for drinking purposes in Latin America. Sci. Total Environ. 2012;429:107–22.

68. Walker M, Seiler RL, Meinert M. Effectiveness of household reverse-osmosis systems in a Western U.S. region with high arsenic in groundwater. Sci. Total Environ. 2008;389:245–52.

69. Katsoyiannis IA, Zouboulis AI. Removal of uranium from contaminated drinking water: a mini review of available treatment methods. Desalination Water Treat. 2013;51:2915–25.

70. George CM. Participatory Interventions to Reduce Arsenic in American Indian Communities [Internet]. [cited 2016 Aug 10]. Available from: http://tools.niehs.nih.gov/portfolio/index.cfm/portfolio/grantDetail/grant_number/R01ES025135

Figure 1. Spatial distribution or uranium and arsenic (**panel A**) and correlation between the natural log concentration of uranium and arsenic (**panel B**). *Red lines* in **panel B** indicate the EPA guidelines for each toxic element.