Environmental Health Studies Can Inform Uranium Mine Remediation on the Navajo Nation

Navajo Nation Human Research Review Board Biennial Conference

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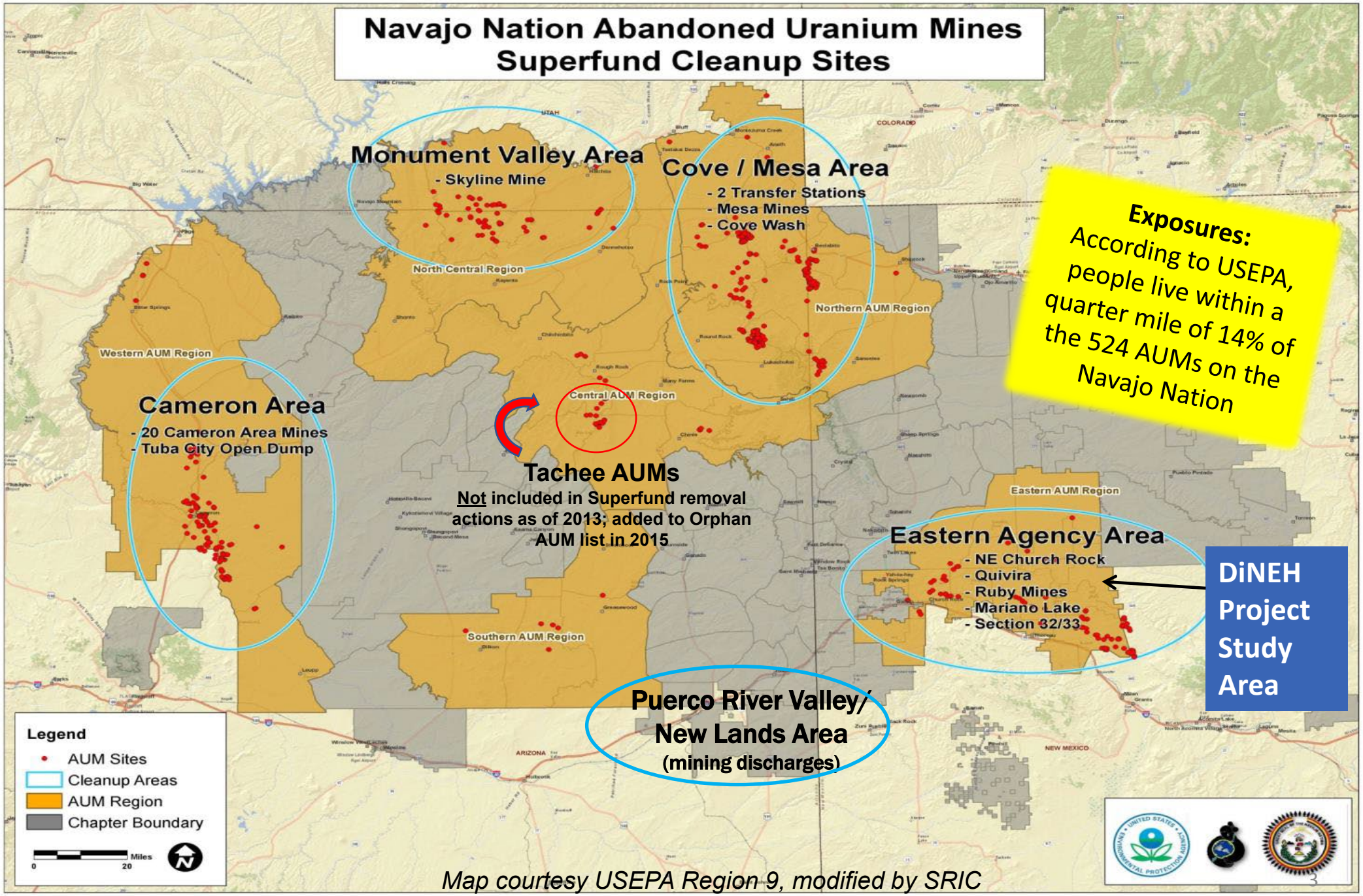
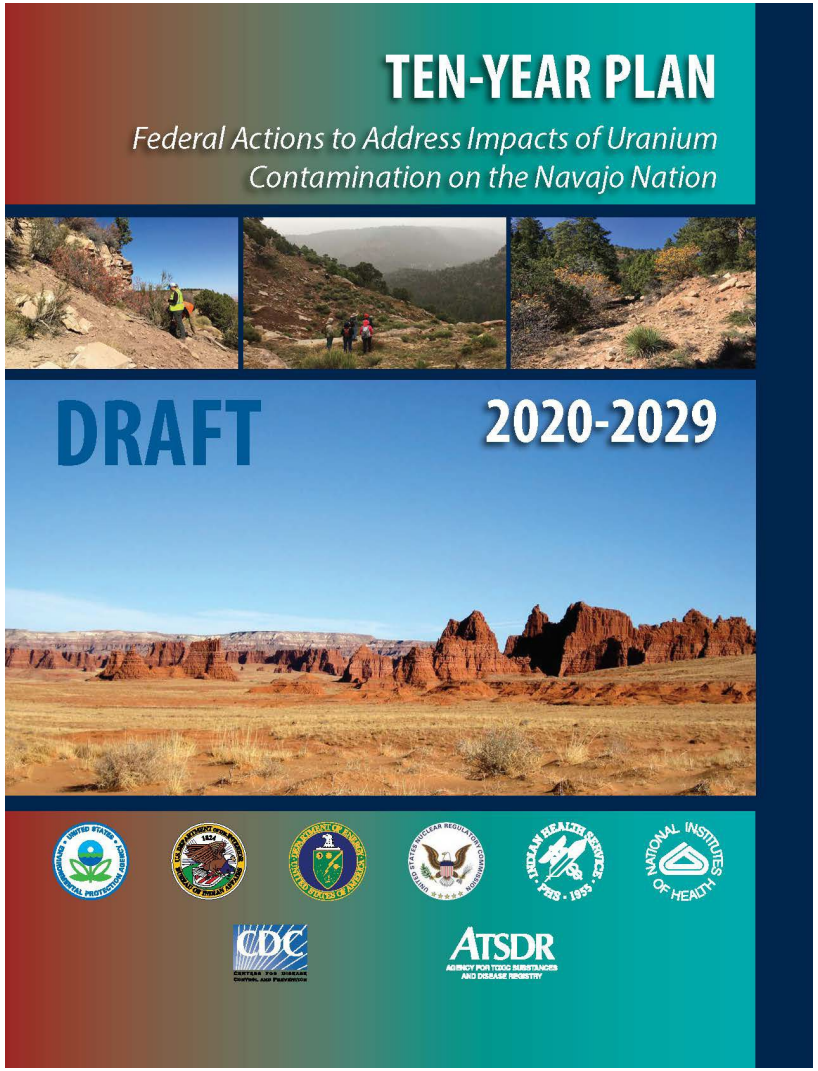
Acknowledgement Statement: *The University of New Mexico sits on the traditional homelands of the Pueblo of Sandia. The original peoples of New Mexico have deep connections to the land and have made significant contributions to the broader community statewide. We honor the land itself and those who remain stewards of this land and acknowledge our committed relationship to Indigenous peoples.*

Cover photo of Quivira Churchrock I Mine waste dump and homes in Red Water Pond Road Community, Coyote Canyon Chapter



Map courtesy USEPA Region 9, modified by SRIC

Navajo Uranium Legacy: By the Numbers

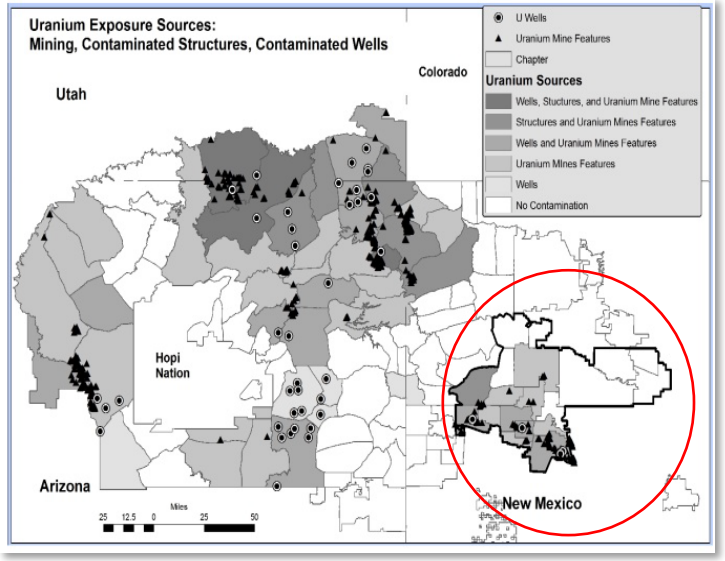


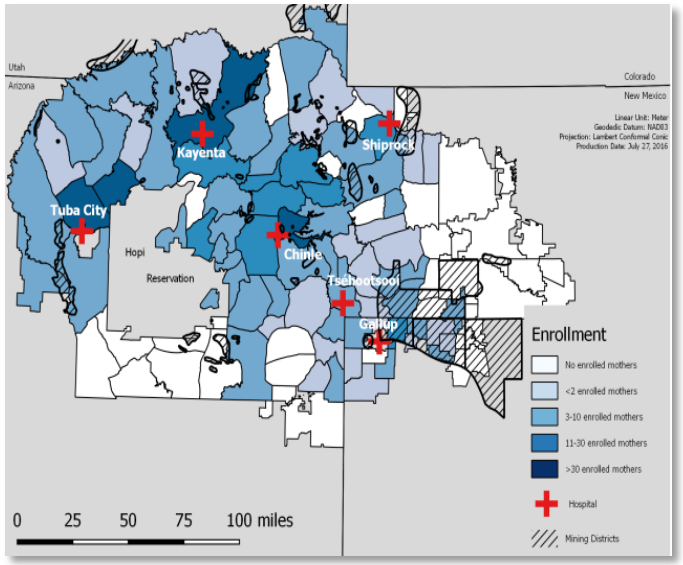
Cover of USEPA Ten-Year Plan, Jan. 2021

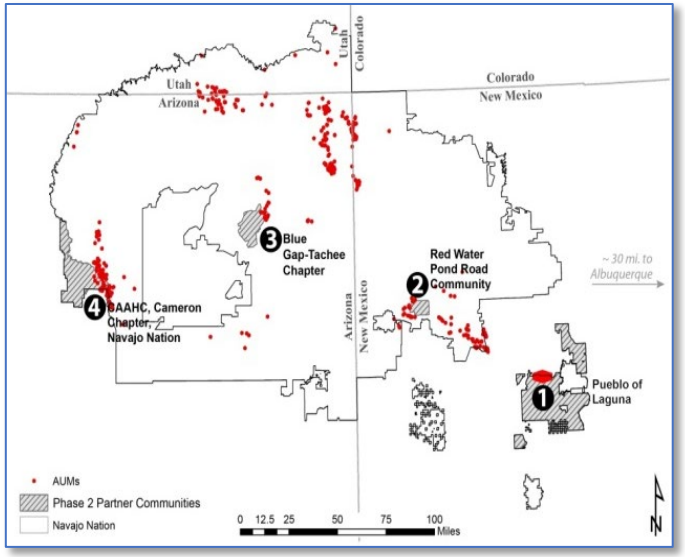
524	Abandoned uranium mines (AUMs), plus >1,100 mine "features"
0	***Fully remediated AUMs***
4	Interim AUM remedial actions to contain wastes
96	AUM site radiation screening reports
130	Site assessments (RSEs) expected to be completed by end of 2022
10-15	EE/CAs* expected to be completed by end of 2022
$1.7 billion	Money USEPA says it has available for remediating **~40% AUMs** through Tronox bankruptcy, settlements with mining companies, federal contributions
3	Congressional hearings: 1979, 1993, 2007
3	Federal response plans: 2008, 2014, 2021
57	Navajo Chapters w/ 1-3 uranium exposure sources (AUMs, water sources, contaminated structures)

*EE/CA = Engineering Evaluation/Cost Analysis

Community questions about exposures have driven UNM environmental health research







DiNEH Project, 2002-2012

- Does U in drinking water increase risk of kidney disease?
- Do multi-pathway exposures to metals in mine wastes increase risks of chronic disease?
- *Community-based trainings to develop study design, implementation methods, consents*

Navajo Birth Cohort Study, 2010-present

- Do exposures to U mine waste affect child health, development?
- Do exposures to metals in mine wastes increase chronic disease?
- *Extensive trainings to develop EH capacity among community members hired by UNM, SRIC and NNDOH*

METALS SRP, 2014-present

- Do mixed-metal U mine wastes contribute to air, water and farmland contamination?
- Do exposures to U wastes result in immunologic, cardiovascular, pulmonary effects?
- Status of remediation?
- *Community defines research*

UNM Population-based EH studies to ascertain exposures and health outcomes

Study	Design	Population	Target Health Outcomes
DiNEH Project, Navajo Uranium Assessment Kidney Health	Cross-sectional; iterative, multi-pathway analysis	Phase I – 1,304 participants in 20 chapters of ENA; Phase II – 267 participants in blood and urine collections	▪ Chronic kidney disease ▪ Cardiovascular disease ▪ Autoimmunity
Navajo Birth Cohort Study	Longitudinal cohort	More than 1,800 mothers, fathers, babies in 3 phases across Navajo Nation	▪ Child development ▪ Metals and pre-term births ▪ Upper airway effects
Thinking Zinc	Clinical trial	52 volunteers from Churchrock and Blue Gap-Tachee communities	▪ Zn supplementation to repair metals-induced damage to DNA repair mechanisms
METALS Superfund Research Center	Laboratory animals	Community members exposed to dust from AUMs	▪ Cardiopulmonary effects of exposure to metals-laden “nanoparticles”





Common methods to ascertain exposures, health outcomes

Method	DiNEH Project	NBCS-ECHO+	Thinking Zinc	UNM METALS
Surveys administered Navajo-speaking researchers	●	●	●	
Geospatial analyses (locations of homes, AUMs)	●	●	●	●
Water quality in public water systems, unregulated wells	●	●		●
Home assessments, including radiation surveys, indoor radon, indoor dusts		●		
Assessments of biomarkers of effects	●		●	
Biomonitoring (detection of metals in human tissues, including urine, blood, hair, toenails)	●	●	●	
Child developmental assessments		●		
Laboratory animal studies of environmental exposures to mine dust				●
Administration of zinc supplements to repair damage from metals exposures			●	

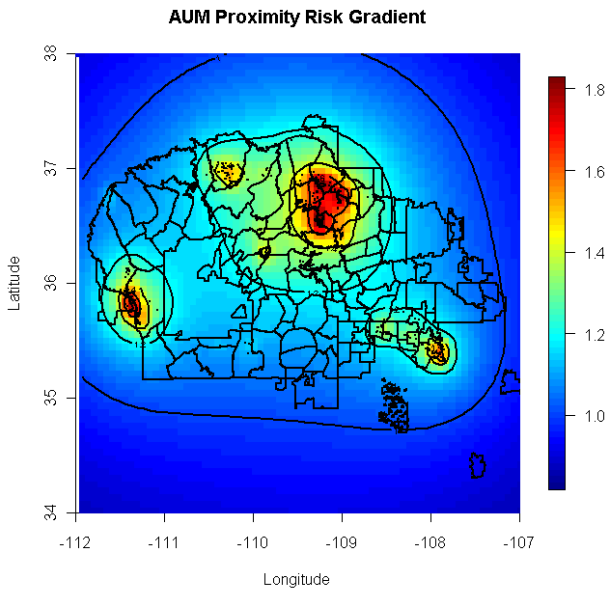
Summary of *Significant* Exposure Variables and Key Findings across UNM Environmental Health Studies (see complete chart at end)

AID = autoimmune disease; CKD = chronic kidney disease; CVD = cardiovascular disease

Exposure variables	Studies	Selected results
Promixity to AUM sites	Hund et al, 2015; Harmon et al, 2017; Erdei et al, 2019; Erdei et al, 2023	▪ CKD: Doubling risk in active mining era, 1950-1986 (10% of participants were U workers) ▪ CVD: 62%-81% increase in the risk of hypertension during legacy period (after 1986); ▪ CVD: Increased inflammatory potential measured by endothelial transcriptional responses ▪ AID: Proximity predicted autoantibody responses for women (p=0.01), all participants (p=0.0065); AuAbs markers associated with U in drinking water *below* MCL ▪ AID: Twofold increase in ANA positivity; proximity associated with clinically defined ANA response (OR*=3.07, p=0.025)
Environmental metals from biomonitoring	Erdei et al, 2022 (NBCS, N=52); Dashner-Titus et al, 2022 (Thinking Zinc N=52); Hoover et al, 2020 (NBCS, N=783); Harmon et al, 2018 (N=252)	▪ CVD: 92% of babies with detectable urine U at birth born to mothers who had urine-U levels greater than national norms; As exposure increased oxidative stress, a contributor to CVD ▪ 4-fold increase in U levels among Thinking Zinc participants ▪ AID: 7 cytokines indicative of immune dysfunction were higher than U.S. U levels (OR = 2.21 (1.08–4.52)) ▪ Pregnant Navajo women have higher U exposures than all U.S. women
Metals in drinking water	Erdei et al, 2019 (N=239); Harmon et al, 2018 (N=252); Erdei et al, 2023 (N=239) Hoover et al, 2017	▪ CVD: Consumption of U correlated with increased C-reactive protein ▪ AID: Elevated autoantibody biomarkers associated with U at levels <MCL of 30 ug/L ▪ AID: As (OR=1.79; p=0.012) and Ra (OR=1.04, p=0.001) associated with anti-dsDNA serum response for ANA positivity ▪ AID: Hg consumption associated with increased ANA response (OR=2.34; p=0.008); Ni consumption predicts increased serum anti-U1-RNP ▪ CVD: As (15.1%), U (12.5%) most frequently measured metals exceeding their drinking water standards in nearly 500 unregulated water sources on the Navajo Nation, including ~100 in Eastern Agency
Age	Erdei et al, 2023 Erdei et al, 2019	▪ Associated with increased serum ANA response (OR*=1.07, p=0.018) ▪ Associated with increased antibodies to denatured DNA

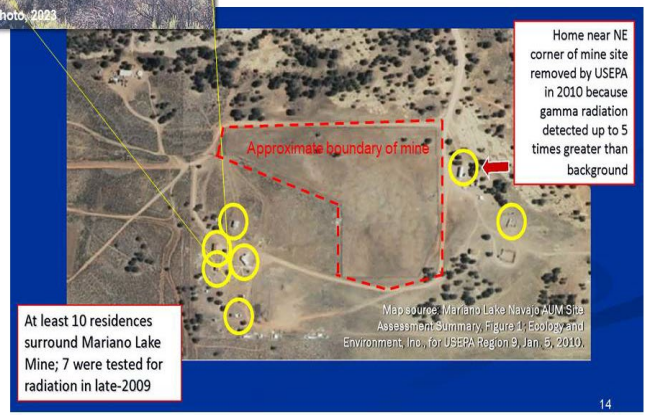
This is what "proximity" looks like

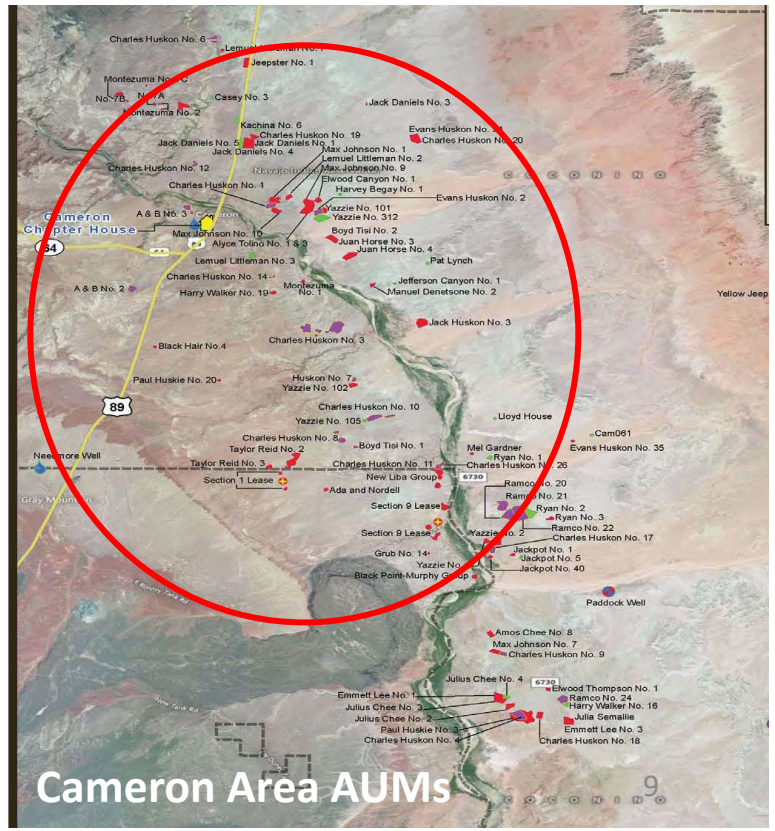
Claim 28 Mine in Blue Gap-Tachee



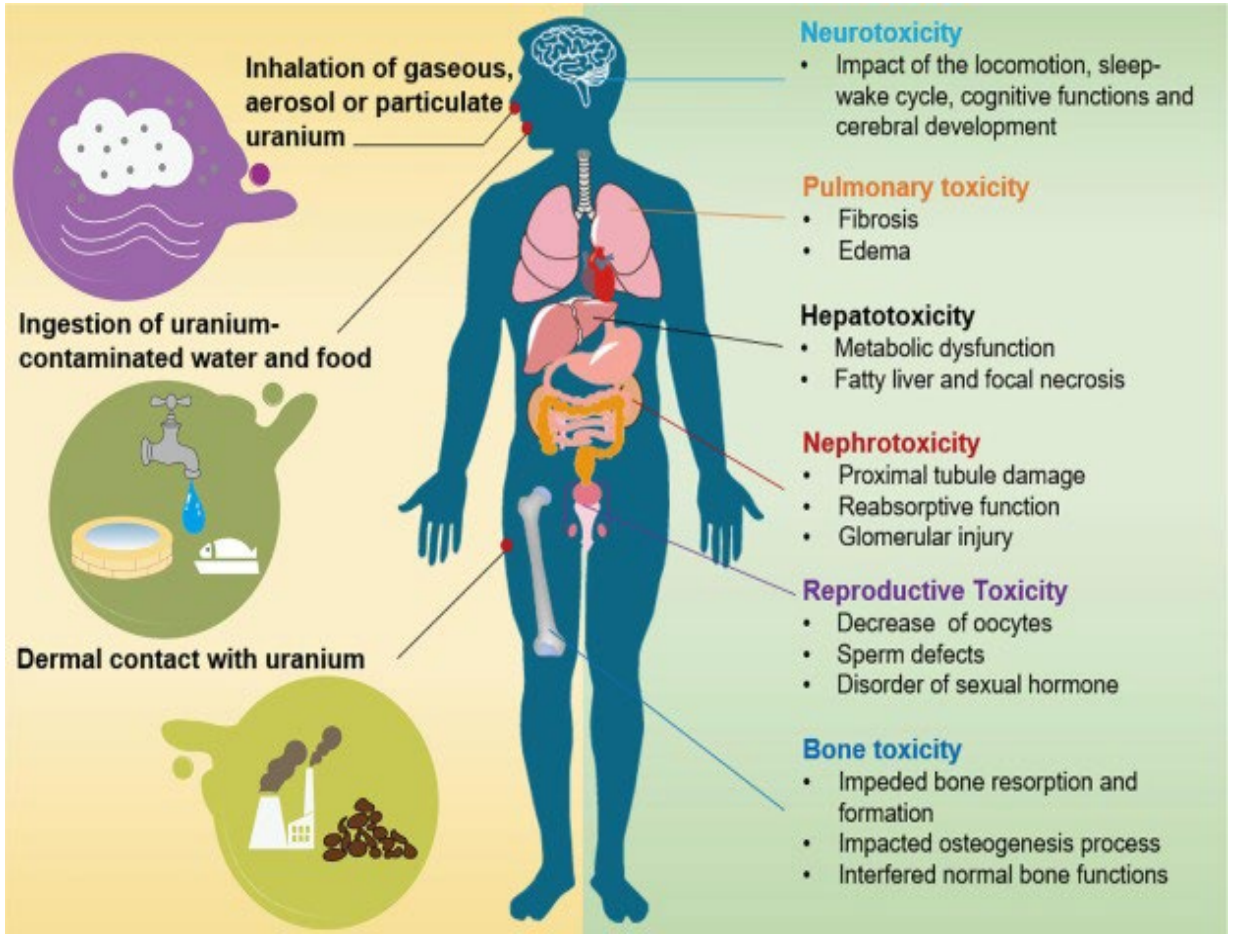
Example: Mariano Lake Mine

- Operated by Gulf Mineral Resources 1977-1982; closed 1986; Chevron current responsible party
- Interim actions: buildings removed, site graded and fenced; one home abandoned
- 10 to 15 residences surround the mine site





Uranium exposure and nephrotoxicity – damage to the kidney, our current focus of study



From Ma et al., Environment International, 2020

- Prior "evidence" from dozens of epidemiological and animal studies on the possible role of uranium in causing kidney disease
- **DiNEH Project:** Urine analyses of biomarkers to characterize kidney injury associated with uranium exposure
- Identify multiple kidney sites of injury with kidney biomarkers panel
- Exploring impact of U exposure on cardiovascular health occurring together with kidney disease
- Implications for understanding the burden of kidney disease on the health of individuals and families and for measuring the success of mine remediation

Nephron – functional unit of the kidney; each kidney has 1 million nephrons

***Cells of the interstitial compartment. Structural, nutritional, immunologic and functional/ hormonal support.

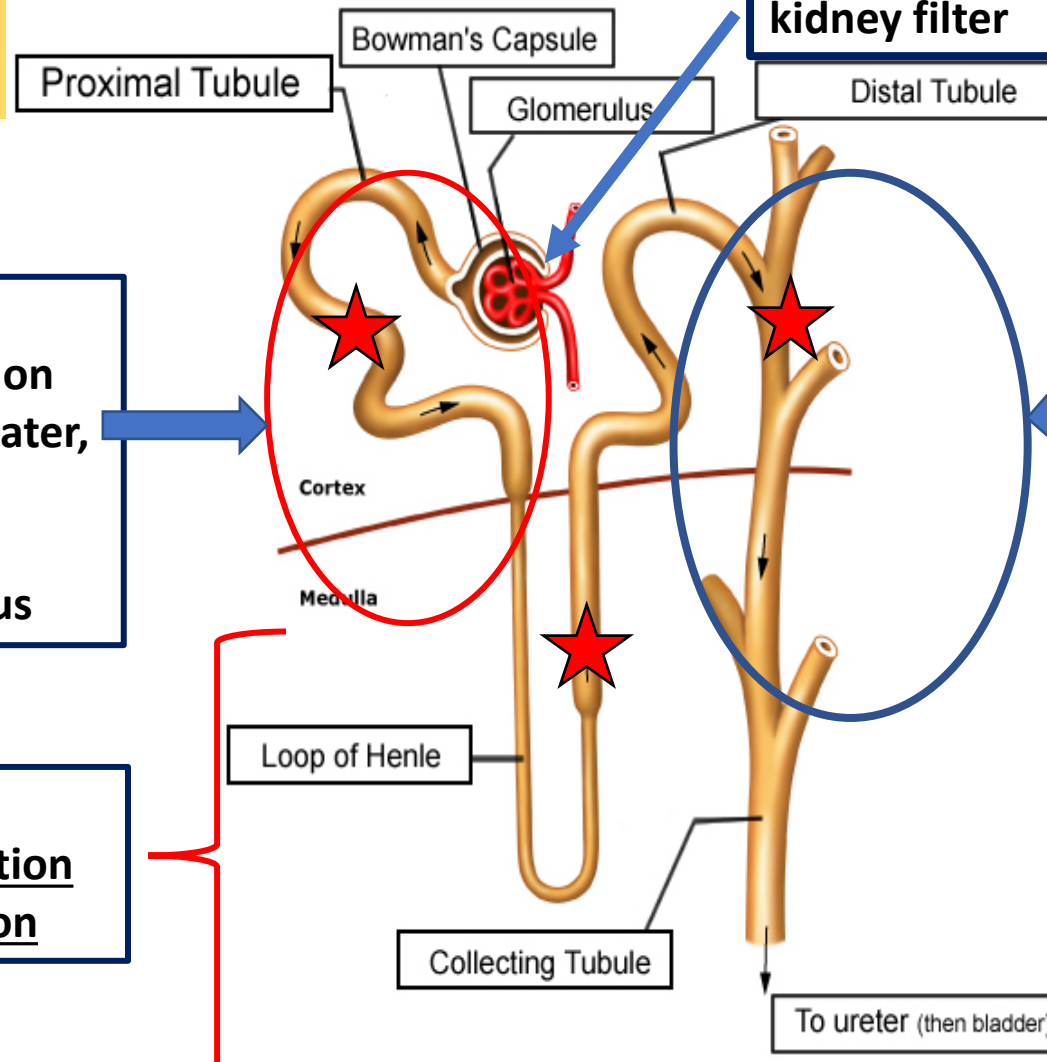
Tubular interstitial structures key

1. Glomerular filtration: The kidney filter

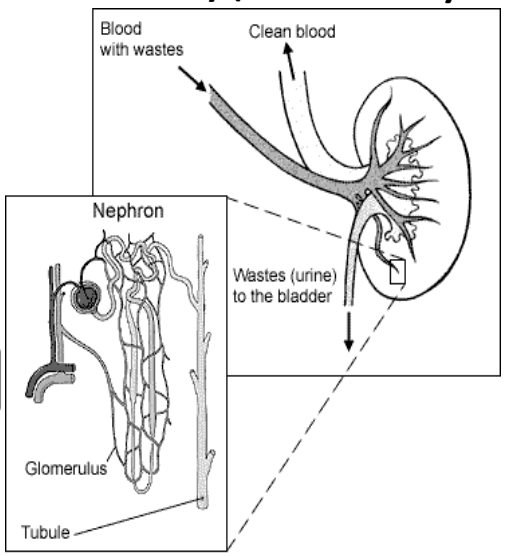
2. Bulk reabsorption of NaCl, water, proteins, glucose, phosphorus

3. Powers concentration and dilution

4. Final regulation of NaCl, potassium, acid- base balance



Kidney (cross-section)

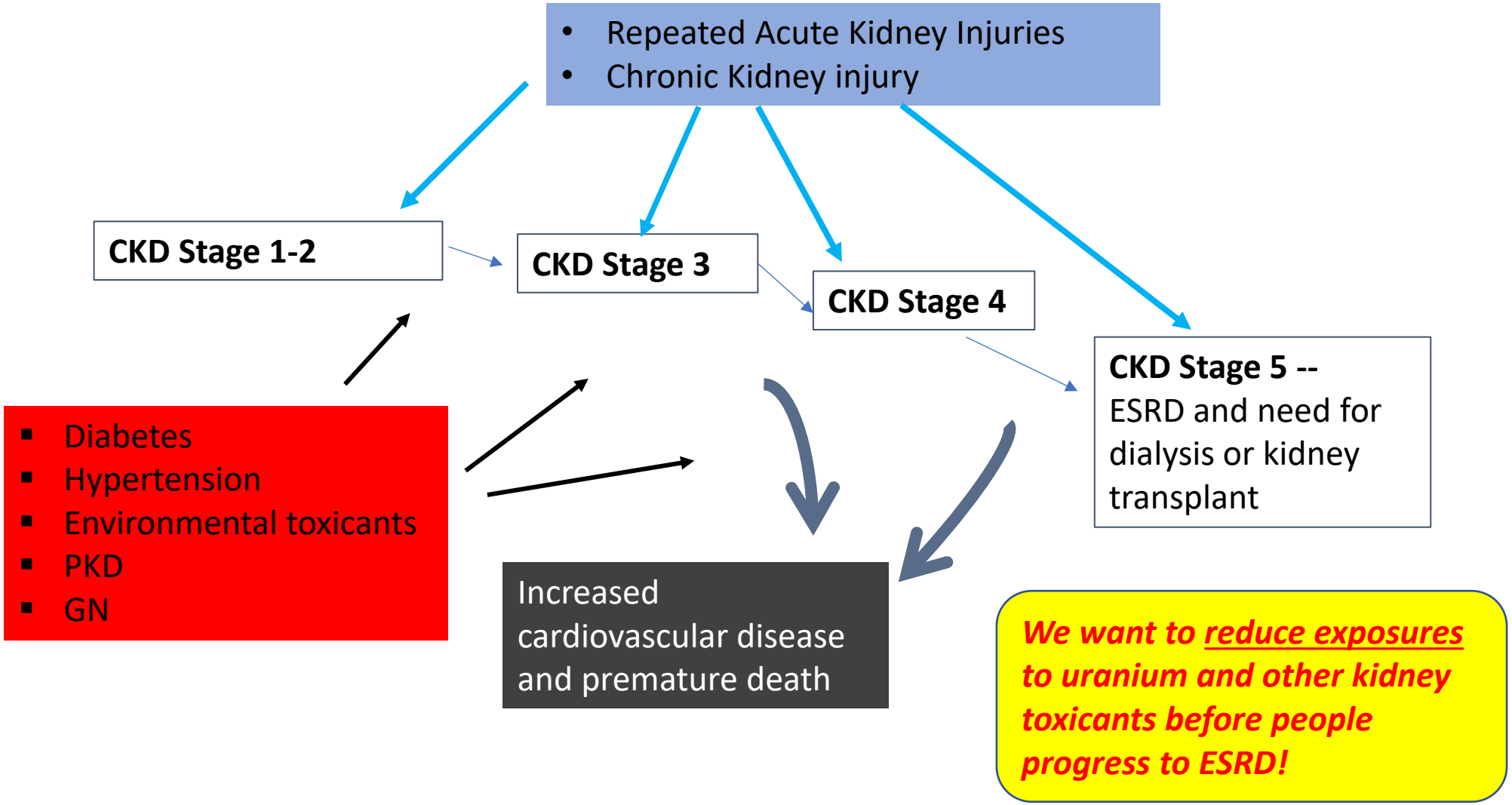


★ **Sites of uranium toxicity; large molecular size of the U ion contributes to cell death, inhibiting proximal and distal tubules' reabsorption of low-molecular weight proteins**

Biomarkers of effect – Recognizing the injury before renal failure develops

Site of Kidney Injury	Kidney Biomarkers
Proximal Tubule	• Deaminase Binding Protein • Alkaline Phosphatase • Beta-**macro**globulin • N-Acetyl-B-D-glucosaminidase (NAG) • N-GAL; KIM-1; MCP-1; RBP
Thick Ascending Limb	• Uromodulin - Tamm Horsfall • Kallikrein /EGF • LDH
Collecting Duct	• Kallikrein

Can We Interrupt the Natural History of Chronic Kidney Disease (CKD) to End-Stage Renal Disease (ESRD)?

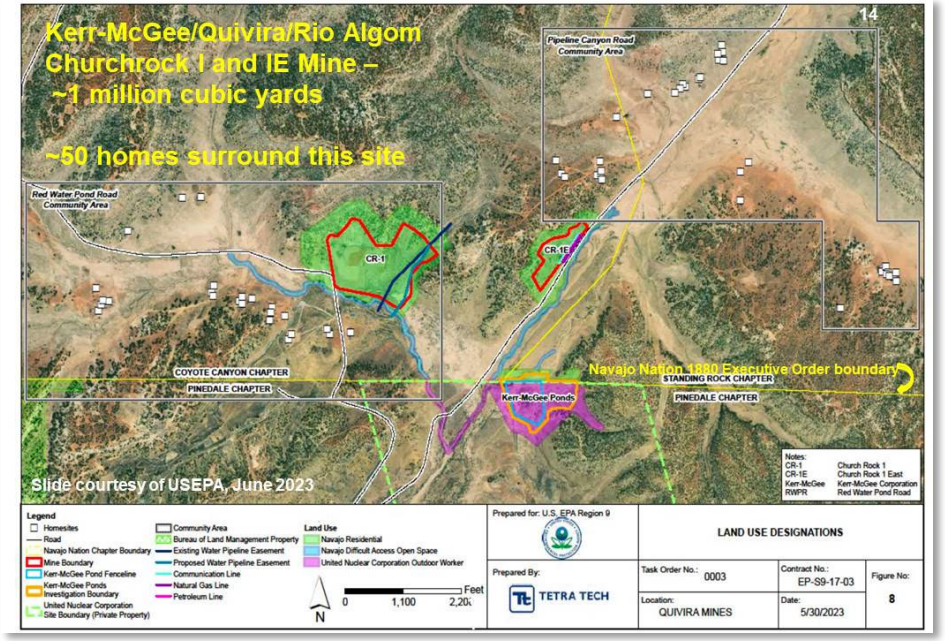


In preparation: "Biomarkers of Chronic Kidney Disease among Navajo Community Members Living in Proximity to Abandoned Uranium Mines and Associated Waste Sites"

- Community concern about uranium exposure focused on high rates of chronic kidney disease and diabetes observed in the Eastern Navajo Agency in early-2000s
- In previous research (Harmon et al., 2018), our team detected oxidative molecular damage that is considered a cardiovascular disease (CVS) risk
  - Linked to consumption of arsenic in drinking water sources
  - Provided evidence of *circulatory and inflammatory* conditions that affected the kidneys
- Diabetes, as measured by hemaglobin A1c, was not a significant predictor of kidney disease among DiNEH participants, suggesting that environmental factors may be at play in development of CKD independent of diabetes-2 status
- For research purposes and to directly address long-standing community concerns, using a wide range of renal biomarkers allows us to see early effects of uranium and metal mixtures on the DiNEH participants' kidneys
- This overall approach is useful to use later as well because it can guide IHS primary care visits and would help to find susceptible community members

Implications for remediation

- Recognize “proximity” as a risk factor — prioritize remediation of AUM waste sites located near where people live
- Consider synergism between kidney disease and cardiovascular disease in the Navajo population – increased risks of both from U exposures!
- Consider cultural practices that tie *Diné* people to their homelands — resist the practice of relocating people unless exposures cannot be mitigated
- Use biomonitoring — assessment of contaminants in bodily fluids — as companion to regulatory risk assessment that depends on environmental data only
- Embrace environmental health findings in remediation decision making
- Consolidate wastes into fewer sites to reduce exposures; e.g., Cameron, Churchrock, Smith Lake, Mariano Lake, Lukachukai Mountains



Conclusions

- DiNEH Project – Largest cross-sectional study of exposure to uranium on the Navajo Nation
- Navajo Birth Cohort Study – Largest cohort study of mothers, fathers and babies
- Thinking Zinc – First-ever community-based clinical trial showing elevated concentrations of metals in blood and urine, exceeding national norms
- Studies developed in partnership with community members, designed to answer community questions about effects of exposures to uranium wastes
- Exposure to mine wastes, contaminants in drinking water, and metals in blood and urine associated with increased risks of chronic, metabolic diseases
- Proximity to uranium wastes consistent significant relationship to disease outcomes

- Metal contaminants in drinking water – As, Ra, Hg, Ni, U – associated with biomarkers of cardiovascular disease, autoimmunity
- Critical findings of these studies can inform federal investigations of abandoned uranium mines and plans for remediation
- Biomonitoring of contaminant levels in people living near mines should supplement regulatory risk assessments
- More complete understanding of the magnitude and effects of exposures on cardiovascular and kidney health best characterized through continuation of long-term cross-sectional and longitudinal studies


Summary of *Significant* Exposure Variables and Key Findings across UNM environmental health studies

Exposure Variable	Population	Cardiovascular Disease-Hypertenson	Autoimmunity	Chronic Kidney Disease	References
Proximity to uranium waste sites	DiNEH Project cohort subset (N=239)		Twofold increase in ANA positivity versus national rate; proximity associated with clinically defined increased ANA response (OR*=3.07, p=0.025)		Erdei et al., 2023
	DiNEH Project cohort subset (N=267)	Increased inflammatory potential (as measured by endothelial transcriptional responses) associated with proximity to AUMs suggests a role for inhalation exposure as a contributor to cardiovascular disease	Age and the extent of exposure to legacy waste from 100 abandoned uranium mine and mill sites were associated with antibodies to denatured DNA		Erdei et al., 2019 Harmon et al., 2017
	DiNEH Project, 2004-2012 (N=1,304)	A 62% to 81% increase in the risk of hypertension was found during the environmental legacy period (after 1986)		A more than doubling of the risk of kidney disease detected for exposures during the active mining era, 1950-1986 (~10% of cohort were U workers)	Hund et al, 2015
Environmental metals exposures from biomonitoring	Thinking Zinc Supplementation Intervention (N=51)	Thinking Zinc participants have elevated levels of uranium approximately 4-fold greater than those detected in the general US population (NHANES). "Episodic" exposures to specific metals differ between Navajo communities.			Dashner-Titus et al., 2022
	Navajo Birth Cohort Study (52 matched serum samples)	92% of babies with detectable urine U at birth were born from mothers who had urine U concentrations greater than national norms during pregnancy	7 cytokines indicative of immune dysfunction were higher than the national U concentrations (OR = 2.21 (1.08–4.52)).		Erdei et al., 2022
	Navajo Birth Cohort Study (327 children)	Prenatal exposures to lead, arsenic, copper, barium, antimony, and molybdenum negatively affected at least one ASQ:I domain scores. Mothers with lower socioeconomic status (e.g., maternal educational attainment, annual income), were at higher risk for metal exposure and having children with lower ASQ scores.			Nozadi et al., 2021
	Navajo Birth Cohort Study (783 pregnant women)	Median and 95th percentile values of maternal NBCS urine concentrations of uranium, manganese, cadmium, and lead exceeded respective percentiles for NHANES (2011-2012) among women ages 14–45. Median NBCS maternal urine U concentrations were 2.67 (enrollment) and 2.8 (delivery) times greater than the NHANES median concentration, indicating that pregnant Navajo women are exposed to metal mixtures and have higher uranium exposure compared with national data for women.			Hoover et al., 2020
	DiNEH Project water monitoring data from 130 sources	Arsenic (15.1%) and uranium (12.5%) were the most frequently measured metals exceeding their drinking water standards in nearly 500 unregulated water sources on the Navajo Nation, including ~100 in Eastern Agency			Hoover et al., 2017

Summary of *Significant* Exposure Variables and Key Findings across UNM environmental health studies (continued)

Exposure Variable	Population	Cardiovascular Disease-Hypertenson	Autoimmunity	Chronic Kidney Disease	References
Environmental arsenic exposure from biomonitoring	Navajo Birth Cohort Study (pregnant women) (N=132)	Associated with increased oxidative stress, a contributor to CVD			Dashner-Titus et al., 2018
	DiNEH Project cohort subset (N=252)	As promotes oxidation of oxLDL, a crucial step in vascular inflammation and chronic vascular disease			Harmon et al., 2018
Nanoparticle (i.e., dust) exposure from abandoned U mine	METALS SRP: Laboratory animal study	Increased neutrophil activity in mice lungs lavaged w/ solution of submicron particles from an AUM site			Zychowski, et al., 2018
Consumption of uranium in drinking water	DiNEH Project cohort subset (N=239)	Correlated with increased C-reactive protein, a CVD marker	Associated with urinary specific autoantibodies at U concentrations <MCL		Harmon et al., 2018; Erdei et al., 2019
Age			Associated with increased serum ANA response (OR*=1.07, p=0.018)		Erdei et al., 2023
Consumption of arsenic and radium in drinking water			Associated with anti-dsDNA serum response for ANA positivity: As (OR=1.79; p=0.012) Ra (OR=1.04, p=0.001)		
Consumption of mercury in drinking water			Associated with increased ANA response (OR=2.34; p=0.008)		
Consumption of nickel in drinking water			Ni consumption significantly predicts increased serum anti-U1-RNP production		

Full references available upon request to Mr. Shuey (sric.chris@gmail.com): Dashner-Titus et al., 2022; Dashner-Titus et al., 2018; Erdei et al., 2023; Erdei et al., 2022; Erdei et al., 2019; Harmon et al., 2018; Harmon et al., 2017; Hoover et al., 2020; Hoover et al., 2017; Hund et al, 2015; Nozadi et al., 2021; Zychowski, et al., 2018.

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Navajo Team Members
Other Native Team Members
Bold indicates Current Team
Non-bold are former team members

The people of the Navajo Nation:
- > 1000 participating Navajo families
- Many supporting chapters
- HEHSC, Tribal and Agency Councils, Executive Branch, NNEPA, GIB
- NAIHS & PL-638 hospital laboratory staff, leadership, and health boards

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NBCS Navajo Birth Cohort Study
Jiná Nizhóní

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UNM HEALTH SCIENCES

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Ahéhee'! Questions?