Overview of Community-partnered Research to Assess Health Effects of Environmental Exposures to Uranium in Tribal Communities

New Mexico Public Health Association Annual Meeting
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Chris Shuey, MPH, Community Engagement Core Lead
Jose Cerrato, Ph.D., Mineralogy and Toxicity of Mine Wastes
Eliane El Hayek, Soil and Plant Uptake in Agricultural Areas Near Mines
Esther Erdei, Ph.D., DiNEH Project Methods and Findings
Debra MacKenzie, Ph.D., Navajo Birth Cohort Study-ECHO+
Sarah Henio-Adeky, BA, Navajo Translation of Thinking Zinc Clinical Trial

Funding: NIH/NIEHS P42 ES025589 (UNM METALS)

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Contributors, Funding, Disclosures, Disclaimer, Approvals

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UNM Comprehensive Cancer Center P30 CA118100 UNM

UNM Clinical Translational Science Center UL1TR001449

Navajo Birth Cohort Study-ECHO+ – NIH/OD UG3/UH3D023344; CDC U01TS 000135

DiNEH Project – NIH/ES-014565, ES-012972

METALS Leadership: Johnnye L. Lewis, Ph.D., director; Matthew Campen, Ph.D., and Sarah Blossom, Ph.D., deputy directors

Relationships with commercial interests:

- Grants/Research Support: All funding through federal agencies, including NIH, CDC, EPA
- Speakers Bureau/Honoraria: None
- Consulting Fees: None

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Approvals:

Human research is monitored and approved by UNM Human Research Protections Office (HRPO), the Navajo Nation Human Research Review Board (NNHRRB) and the New Mexico Cancer Care Alliance, as required by federal, state and Tribal law.
The Problem: U Mine Wastes Pervasive on Navajo, Laguna

The Numbers:
- 524 AUMs on Navajo Nation
- >10,400 AUMs in Western U.S.
- Jackpile Mine at Laguna – once largest open-pit U mine in world
- All AUMs fall under federal Superfund law for assessment, remediation

Map from USEPA, modified by SRIC
Community Engagement: Overarching Questions

- How did Native communities impacted by uranium mining help inform 25+ years of UNM’s environmental health research?
- How have impacted Native communities participated in EH research?
- What are the roles of citizen and indigenous science in EH research?
- What have we learned from these community-based collaborations?

L-R: Cameron Farm assessment, 2019; Chris Nez at Claim 28 “Prius Rock”, 2014; Red Water Pond Road Community, 2007; soil and plant sampling, Pueblo of Laguna, 2020
Models underlying our community-partnered research: Western and Indigenous Commonalities

Data collection
- Population
- Biospecimen
- Animal studies
- Cells

Analysis and Review
- Exposure
- Association (population studies)
- Mechanisms (laboratory studies)

Core Community Questions, Concerns

Observation; Hypothesis generation

Reevaluation Intervention?
<table>
<thead>
<tr>
<th>Project Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiNEH Project (RO1) (2001 – 2012)</td>
<td>First research to examine community impacts on health in partnership with and at request of 20 chapters in and adjacent to Eastern Agency of Navajo Nation (NIEHS)</td>
</tr>
<tr>
<td>NBCS &amp; NBCS/ECHO (2010 – ongoing)</td>
<td>Responsive to congressional mandate to community concerns from DiNEH Project: “What is exposure doing to the health of future generations?” (CDC, NIH-OD)</td>
</tr>
<tr>
<td>Center for Native Environmental Health Research Equity (2015 – ongoing)</td>
<td>Comparative community partnered study with Navajo, Sioux, and Apsaloóke to examine ecosystem and health effects in tribes from distinct language groups and cultures impacted by mine waste, combined effects of microplastics and organic emissions from waste combustion. (NIEHS, USEPA, NIMHD)</td>
</tr>
<tr>
<td>UNM METALS Superfund Research and Training Center (2017-2022, 2022-2027)</td>
<td>Multidisciplinary and transdisciplinary team science research partnership with Navajo and Pueblo communities to examine environmental and health risks from mine waste to communities and design interventions to reduce and reverse impacts (NIEHS)</td>
</tr>
</tbody>
</table>
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?
• Population: 1,304 in 20 chapters; 267 in biomonitoring

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?
• Population: >1,000 families totaling ~1,800 mothers, fathers, children; ongoing

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?
• Populations: Diné, Laguna across four communities
How have impacted tribal communities participated in EH research?

Red Water Pond Road residents played active role in CRUMP (2002-‘07), DiNEH Project (2006-2007) and EPA removal actions (2007-‘12)

RWPRC residents helped measure gamma radiation rates and collect soil samples around homes next to the Northeast Church Rock Mine, leading to a USEPA-mandated RSE in 2006-2007 and three removal actions (below).

Three USEPA-ordered “interim removal actions” removed 18” to 25’ of radium- and uranium-contaminated soils (~136,000 cy) from around homes, mine-water arroyo. Residents were “relocated” to hotels in Gallup for 3 to 7 months each time.
Blue Gap-Tachee residents joined field studies on effects of exposure to mine dusts

1. Some residences close to mine wastes

2. C. Nez identifies U ore, Claim 28

3. T. Shirley operates PM sampler

4. Microscopy identifies U-V complex (C) in sub-micron particles

5. Most toxic metals in smaller particle sizes

6. Mouse aspiration of mine-dust in solution indicate toxicity to lungs, autoimmune response

7. 2014 Metals Monograph 1; 2015 Blake ES&T paper; 2018 Zychowski SOT
How have Diné communities participated in EH research? Cameron residents collaborated with METALS to assess contaminants in soils, plants on farmlands near AUMS.

### Preliminary findings:
Most metals at or below crustal averages on farmlands; little uptake of toxic metals in Camelthorn; good uptake of key nutrients.
Citizen and Indigenous Science: Community Action Posters Describe Impacts


R: Metals Assessments on Laguna Pueblo agricultural lands, 2022

Blue Gap-Tachee Chapter: Disruption of Life Cycles, 2018

A family’s uranium exposures in Waterfall Spring, 2018
What have we learned from Community-engaged Research around uranium mining impacts?

- Community members:
  - field staff (25+)
  - study designers
  - participants in studies
  - leaders in policy initiatives
- Common toxic substances (U, V, As, Ra, Pb, etc.), common conditions across mines
- Collaborations can reduce health risks from mine wastes
- Citizen and indigenous science is science: validated, informed by traditional values, multidisciplinary
- Eager to engage their communities, join the next generation of scientists
Mineralogic composition and nanoparticle matter in AUM wastes

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Associate Professor
Department of Civil, Construction & Environmental Engineering

October 4, 2021

Co-Authors: Melissa, Gonzales, Adrian Brearley, Joseph Galewsky, Carmen Velasco, Isabel Meza, Johanna Blake, Mehdi Ali, Sumant Avasarala, Adrian Brearley, Eliane El Hayek, Jorge Gonzalez, Juan Lezama

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OVERARCHING QUESTIONS

• How do U and other metals occur and behave in mine waste sites?

• What is the mineralogical composition and size of mine waste particles?
How do we answer this question?

Analytical Facilities & Training

• Aqueous Chemistry Analyses:
  Inductively coupled plasma (ICP)
  a) Optical emission spectrometry (ICP-OES)
  b) Mass spectrometry (ICP-MS)
  c) Ion chromatography (IC)

• Solid Analyses

Postdoc, Graduate, Undergraduate, and High School Level Training!
Use of Spectroscopy and Microscopy Methods

X-ray Spectroscopy

Electron Microscopy
RESULTS: Uranium, Arsenic, and pH in Water around Claim 28 Mine in Blue Gap

<table>
<thead>
<tr>
<th>Sample</th>
<th>Parameter</th>
<th>U (µg/L)</th>
<th>As (µg/L)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue Gap Tachee Spring</td>
<td></td>
<td>163.2</td>
<td>5.7</td>
<td>7.4</td>
</tr>
<tr>
<td>Blue Gap Tachee Seep</td>
<td></td>
<td>135.4</td>
<td>9.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Blue Gap Tachee Well</td>
<td></td>
<td>2.1</td>
<td>36.7</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Blake et al. 2015
Blake et al. 2019
## RESULTS: Solid Elemental Composition

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Uranium (mg/kg)</th>
<th>Vanadium (mg/kg)</th>
<th>Arsenic (mg/kg)</th>
<th>Iron (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue Gap Tachee (Mine Waste 1)</td>
<td>3118</td>
<td>3082</td>
<td>30</td>
<td>4371</td>
</tr>
<tr>
<td>Blue Gap Tachee (Mine Waste 2)</td>
<td>7345</td>
<td>919</td>
<td>9</td>
<td>77006</td>
</tr>
<tr>
<td>BRS</td>
<td>BDL</td>
<td>BDL</td>
<td>BDL</td>
<td>24013</td>
</tr>
</tbody>
</table>

*BRS* – Baseline reference soil: control from Blue Gap Tachee (Navajo)
RESULTS

• Discovery of previously unrecognized nanoparticles of U-bearing minerals (metals mixtures) in:
  • AUM mine waste samples and associated soils.
  • Legacy accumulation of airborne dust in church attic (Laguna Pueblo).
  • Weathering products of U-bearing strata from Jackpile mine – Laguna Pueblo.

• U-V-bearing minerals in nanoparticles are exclusively in respirable PM 2.5 fraction.

• BGT mine waste samples exhibit high toxicity.

Electron microscopy shows that Blue Gap/Tachee Claim 28 mine waste contains clusters (<1 um) of carnotite $(\text{K}_2(\text{UO}_2)_2(\text{VO}_4)_2\cdot2\text{H}_2\text{O})$ nanoparticles that are dispersing into individual nanoparticles that adhere to surfaces of other mineral grains.
HOW CAN YOU USE THESE FINDINGS?

- Knowledge of mineralogical composition provides insights about metal mobility for understanding risks to human health and identifying remediation strategies.
- Important to recognize exposure to hazardous metals mixtures carried by nanoparticles can occur by multiple pathways. Metals toxicity is key.
- Inhalation and ingestion of nanoparticulates are exposure pathways for humans and livestock.

Findings used to document community concerns; engage community members; bring community members into STEAM studies; apply indigenous values to air monitoring.
The role of biogeochemistry in metals bioavailability and cytotoxicity

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October 4, 2021

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OVERARCHING QUESTIONS

- How water chemistry affects the bioavailability of metals in plants?

- Can fungi help enhancing metals (arsenic) uptake and bioaccumulation in plants?

- How cytotoxicity can change with respect to the chemical physical form of metal in the environment?
How do we answer these questions?
Greenhouse experiments to study metals in plants
How do we answer these questions? Greenhouse experiments to study metals in plants

<table>
<thead>
<tr>
<th>Experiment on U uptake</th>
<th>Experiment on As uptake</th>
</tr>
</thead>
</table>
| **Hyperaccumulator model plant**  
*Brassica juncea* (mustard)  
\[ \text{pH} = 7.5 \]  
\[ \text{HCO}_3^- = 1 \text{mM} \]  
\[ \text{Ca}^{2+} = 0, 0.3\text{ and } 6 \text{ mM} \] | **Native grass**  
*Schizachyrium scoparium*  
(little bluestem)  
\[ \text{pH} = 7.5 \]  
\[ \text{HCO}_3^- = 5 \text{ mM} \]  
\[ \text{Ca}^{2+} = 3 \text{ mM} \]  
\[ \text{PO}_4^{3-} = 0.12 \text{ mM} \] |
RESULTS: Water chemistry effects on U bioavailability

Plants exposed to U concentrations (30-700 µg/L) in carbonate solutions at circumneutral pH over a range of Ca concentrations:

- Fast U Removal within 24 h
- % of removed U from water

Plants exposed to high U concentrations (19.04 mg/L)

- At low Ca (<0.3 mM), U can still be immobilized in the roots of the plant.
- High Ca (6 mM) helps U enter deeply into root structures and go up to the stem and the leaves of the plant.
RESULTS: Water chemistry and fungi effects on As bioavailability and toxicity

Growth of plants in the presence of fungi

<table>
<thead>
<tr>
<th>Plant without fungi</th>
<th>Plant inoculated with fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>132% longer plant roots</td>
</tr>
<tr>
<td></td>
<td>71% longer plant stems</td>
</tr>
<tr>
<td></td>
<td>1800% larger plants</td>
</tr>
</tbody>
</table>

Integration of spectroscopy to identify sites of accumulation in the plant

As content in the plants

- **Plant without fungi**: Significantly lower As content in both roots and shoots compared to inoculated plants.
- **Plant inoculated with fungi**: Significant increase in As accumulation in the shoots (P<0.05) and significant decrease in As accumulation in the roots (P<0.05).
RESULTS: How the chemical physical form of metal affects its cytotoxicity?

The toxicity of Carbon-rich U-bearing particles were used as a solid particulate phase of U and compared to soluble U salts in airway epithelial cell model (A549).

U: aqueous uranium
NS: narrow size distribution particles < 1 µm
WS: wide size distribution particles < 10 µm

The particulate form of U in carbon-rich particles enhances its bioavailability and toxicity in comparison to aqueous uranium.
Effects of the chemical physical form of uranium on its cellular toxicity

Understanding environmental health risks needs understanding bioavailability and toxicity which depend not only on the level of metals concentration but also their chemical physical forms in their surrounding environment.
How we involved community members in the process?

Gardening: Connecting Mother Earth to Human Health and Wellness

A research partnership with gardeners and farmers on the Pueblo of Laguna to look for metals on agricultural lands near legacy uranium mine sites
Local farmers, gardeners and growers volunteered to work with the scientists from the UNM METALS Superfund Research Center and the Pueblo of Laguna Environmental and Natural Resources Department (ENRD) to address a key community concern: Is my soil impacted with metals associated with mining?
### Sampling locations for data reported here

<table>
<thead>
<tr>
<th>Site No.</th>
<th>Village</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Paguat e</td>
<td>soil, pumpkin</td>
</tr>
<tr>
<td>7</td>
<td>Paguat e</td>
<td>soil, melon, grasses</td>
</tr>
<tr>
<td>9</td>
<td>Paguat e</td>
<td>soil, corn, squash, grasses</td>
</tr>
<tr>
<td>11</td>
<td>Mesita</td>
<td>soil, pumpkin</td>
</tr>
<tr>
<td>16</td>
<td>Laguna</td>
<td>soil, corn</td>
</tr>
<tr>
<td>18</td>
<td>Paguat e</td>
<td>Soil, corn, cucumber, grasses</td>
</tr>
<tr>
<td>Jackpile Mine</td>
<td>Paguat e</td>
<td>Soil, grasses, roots</td>
</tr>
</tbody>
</table>

![Map showing sampling locations](image-url)
Metals in soil

**U mg/kg (ppm)**

- **Mine**
- **Paguate east**
- **Paguate west**
- **Laguna west**

**V mg/kg**

- **Mine**
- **Paguate east**
- **Paguate west**
- **Laguna west**

**As mg/kg**

- **Mine**
- **Paguate east**
- **Paguate west**
- **Laguna west**

**Pb mg/kg**

- **Mine**
- **Paguate east**
- **Paguate west**
- **Laguna west**
Metals in crops

Pb (mg/kg) in corn and fruit detected below the international recommended values

Recommended level in cereal = 0.2 mg/kg
Recommended level in fruit vegetables = 0.1 mg/kg

As (mg/kg) in corn and fruit vegetables detected below the international recommended values

Recommended level in produce = 0.2 mg/kg

Pb mg/kg in roots detected higher than the recommended level for root vegetables

As mg/kg in roots detected higher than the recommended level
HOW CAN YOU USE THESE FINDINGS?

- Plants a pathway of exposure but a major player in understanding environmental chemistry and creating solutions

- Chemical parameters in the rhizosphere can enhance or decrease metals bioavailability and plants uptake; e.g., high U and Ca levels at circumneutral pH can increase U uptake to the shoots of the plant

- Studying bioavailability and toxicity is important to understand environmental health risks which depend not only on the level of metals concentration, but also on their chemical physical forms in their surrounding environment.

- Uranium and vanadium exceeding background were found ONLY in topsoil samples collected from the Jackpile Mine.

- Metals that are of potential human health concern, including U, V, As and Pb, were detected below health-based guidance in all fruit, vegetables and corn.

- Although the impact of mining legacy was not detectable in our sampling sites, we should note that these tests are limited to a certain number of locations; further studies are needed to understand the mobility of dust around the mine site.
Diné Network for Environmental Health (DiNEH) Project: Documenting exposures to legacy uranium mining wastes on the Navajo Nation
Esther Erdei, Ph.D.
Call for action to protect water sources

- Violation of Human Rights (UN 1948)
- Respect toward traditional knowledge, practices; support sustainability of all interactions w/ nature & non-human life
- Water is Life movement - Water is Life Blood of Mother Nature – human body is 73% H₂O
- Lack of USEPA risk assessment methodology for Tribal use – Animas River U contamination from CO, UNM CEHP & UoA collaboration
- Rural areas reviews – own works, 2 publications (Nov 2018 & Apr 2019) in Current Epidemiology Reviews
- Environmental justice, environmental racism, environmental privilege
Identifying Exposures: Pathways, Routes

**SOURCES:** Potentially harmful contaminants in the environment

**Exposure Pathways**
Air, water, plants, animals
(can be very simple or quite complex)

**Exposure Routes:**
How contaminants enter the body

**Inhalation (Breathing)**

**Ingestion**
(Eating, Drinking)

**Absorption**
(Skin Contact)

**Circulation:**
mother → placenta → baby

**Fetal Exposure Route:**
Placental transfer
DiNEH Project Risk Model

Sources of inputs to estimate each participant’s total exposure

Kidney Risk Model—Structure and Multiple Inputs

- **Kidney Disease**
  - Self report, medical records, clinical test

- **Biomarkers (SA2)**
  - Urine, lab analysis

- **Uranium exposure assessment**
  - Input from Core Exposure Assessment Model, Urine Confirmation

- **Other exposures**
  - Survey, GPS, Extant location

- **Co-morbidities**
  - Survey, medical records

- **Family history**
  - Survey

- **Tradition, culture, lifestyle**
  - Survey

- **SES factors**
  - Survey

- **Occupational Exposure**
  - Survey

- **Water Exposure**
  - Survey, lab analysis

- **Environmental Exposure**
  - Survey, mapping, modeling, field validation
DiNEH Survey Responses – Phase I

- High prevalence of cardiovascular disease and diabetes in DiNEH participants
- Do chronic exposures to U mine wastes exacerbate existing disparities in metabolic diseases?

Prevalence of Self-Reported Health Conditions Among 1,304 DiNEH Survey Participants
(*Cancer prevalence based on 1,011 participants surveyed)

- 35.9% HBP
- 25.1% Diabetes
- 17.1% Arthritis
- 6.2% Kidney Stone
- 5.4% Heart Disease
- 5.1% Kidney Disease
- 3.5% Stroke
- 3.1% Heart Attack
- 3.1% Autoimmune
- 2.5% Cancer
- None
## DINEH Survey Results for Casamero Lake Chapter: Health Problems

### Prevalence* of Self-reported Health Problems, Casamero Lake Chapter Participants Compared with Rates for U.S., All DiNEH Participants, and DiNEH Blood and Urine Participants

<table>
<thead>
<tr>
<th></th>
<th>US Prevalence</th>
<th>DiNEH self-reported (N=1304)</th>
<th>DiNEH B&amp;U (N=252)</th>
<th>Casamero Lake self-reported (N=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes II</strong></td>
<td>11%</td>
<td>25%</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>12%</td>
<td>25%</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Heart Disease</strong></td>
<td>3%</td>
<td>5%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

For further comparison: Navajo diabetes prevalence, 1991-1993 = 22% (all ages), 40% (> 40 yrs) (Navajo Nutrition Study, 1997).

*Prevalence = percentage of the population having a particular disease or condition at any given time.
C-Lake had lowest rates of Diabetes (14%), Kidney Disease (1.4%) and Cancer (0%)…

…but the highest rate of heart disease (8.6%)
Goal of the DiNEH Phase II sub-study

• Direct response to community members’ requests for research on immune system function during the capacity building and environmental risk evaluation work

• Address possible pathways within the human body in association with environmental uranium and other heavy metal (V, Pb, Hg, Ni, Cu, and As) exposures

• Find early indicators of health effects from legacy exposures
DiNEH Project Phase II
Biological sample collection

- Samples collected from 267 individuals, evenly distributed across 20 chapters (chart)
- 14 community-based collection events
- IHS collaboration through CUE-JTH Program
- Early markers, showing alterations in immune cell distribution and activity
- Biomonitoring to determine urinary metals/metalloids – U, total As, Ni, Cu, V

<table>
<thead>
<tr>
<th>Chapter</th>
<th># DiNEH Survey Participants (1,304)</th>
<th># DiNEH Participants in B&amp;U Collections (267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baca-Prewitt</td>
<td>96</td>
<td>32</td>
</tr>
<tr>
<td>Becenti</td>
<td>60</td>
<td>22</td>
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<tr>
<td>Casamero Lake</td>
<td>70</td>
<td>14</td>
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<tr>
<td>Church Rock</td>
<td>69</td>
<td>13</td>
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<tr>
<td>Coyote Canyon</td>
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<td>18</td>
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<td>Crownpoint</td>
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<td>20</td>
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<td>Iyanbito</td>
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<td>17</td>
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<td>Lake Valley</td>
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<tr>
<td>Littlewater</td>
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<td>Mariano Lake</td>
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<td>White Rock</td>
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<td>Whitehorse Lake</td>
<td>63</td>
<td>6</td>
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</table>
DINEH PROJECT RESULTS
(AVERAGE AGE 55)

ACTIVE-MINING ERA EXPOSURES
(WORKERS* AND FAMILIES) ➔
INCREASED KIDNEY DISEASE,
ADD TO OTHER KNOWN RISKS

* Many workers had already died from lung cancer,
more family members than workers

ONGOING ENVIRONMENTAL LEGACY
EXPOSURES ➔ INCREASED RISK
FOR HYPERTENSION, AUTOIMMUNITY,
AND MULTIPLE CHRONIC DISEASES

Based on proximity to waste and self-reported activities
creating contact with waste
Autoimmunity also linked to uranium in drinking water

Erdei et al., 2019, Journal of Autoimmunity
Evidence of immune dysregulation in Diné adults – uranium associated increase in autoantibodies

- Self-reported autoimmune disease diagnosis -- associated with proximity to AUM (n=1,304).
- Prevalence = 3.1% in both phases, lower than published national rates (3.0%-7.5%)
- Aggregation of AID cases – increased in Chapter with abandoned U mines/milling sites (map)
Autoantibody production and detection

• 239 samples analyzed at IHS LabCorp in Phoenix, AZ
  • (CLIA certified clinical diagnostic laboratory)

• Antinuclear antibody (ANA) testing using flow cytometry-based microbead assay

• Fluorescence staining and microscopy (traditional method; figure, top right) vs. new faster technique by IHS LabCorp

• Microbeads – special panel of autoantigens tested; positive response to specific autoantibodies may indicate connective tissue disease, Sjögren’s syndrome, all clinically relevant.

• ~27.2% of individuals (n=239; average age 55 ± 14 yrs) had detectable anti-nuclear antibodies

• ANA positivity associated with proximity to waste sites, certain metals in drinking water
Disruption of immune function $\rightarrow$ autoantibodies seen through the lens of a Native artist

Healthy immune cell – protections in place

Immune cell dysfunction – protections fighting each other

Paintings by Mallery Quetawki, Zuni Pueblo
Navajo Birth Cohort Study initiated in 2010 to address the impacts of uranium exposure on child health outcomes

Birth Outcomes, Child Development

- **Home Environmental Assessment**
  - Locations of nearly 600 homes
  - Indoor dust
  - Radon
  - Gamma survey indoors and outdoors
  - Drinking water

- **Enrollment Survey**
  - Occupational history
  - Activity Survey
  - Family history of exposures

- **Biomonitoring (mom, baby)**
  - Urine metals (36-element panel)
  - Whole blood (Pb, Cd, total Hg)
  - Serum (Cu, Se, Zn)

Assess birth outcomes and child development from birth to age 9.
NBCS (2010-2018)

Enrolled 780 women during pregnancy, exposure assessment, assessment of child development through 1 year of age

NBCS/ECHO

Enrolled 481 (179 pregnant mothers and 302 children from NBCS)

NBCS-ECHO Plus – 2019-2024

• Continue enrollment to 1200 (345 children and 60 new pregnant mothers)
• Add common elements developed by ECHO consortium (allows us to compare exposures/outcomes with national sample)
• Assessment continues through the age of 9
ECHO (Environmental influences on Child Health Outcomes) Funded by NIH Office of the Director

MISSION:
To enhance the health of children for generations to come

VISION:
To become one of our nation’s pre-eminent research programs in child health

LONG-TERM GOALS:
Scientific: To inform high-impact programs, policies, and practices that improve child health
Strategic: To establish best practices for how to conduct Team Science in the 21st century

Focus on key pediatric outcomes
Data Collection

Pregnancy
• Surveys and questionnaires
• Blood and urine for metals

At delivery:
• Collect blood and urine for metals

From birth through 9 years of age:
• Collect data from surveys and questionnaires
• Collect biospecimens every year
• Annual ASQ assessment
• Between the ages of 3-5 and again between the ages of 6-8 we conduct physical and neurodevelopmental assessments.

Art by Mallery Quetawki
Exposures seen from biomonitoring of key metals

**Uranium (kidney toxicity; estrogen mimicker)**

- Black vertical line represents the 50th percentile for US population
- NBCS median urinary uranium concentrations exceed the US median (36% of men and 26% of women have urine uranium above national norms)

**Arsenic (cancer, immunotoxicity)**

- Distribution of urine total arsenic in NBCS females and males
- NBCS median urinary total arsenic concentrations are similar to the US median
- Exposure sources very different – in US, population exposures primarily seafood, rice
NBCS/ECHO: Exposures begin in childhood
By age 4, children are reaching adult concentrations

- Median concentration for urine uranium in the US adult population from NHANES (2015-16) = (0.005 μg/L)
- NBCS children birth to age 4 = 0.0035 – 0.013 μg/L

- Median concentration for total arsenic in urine in the US adult population from NHANES (2015-16) = (5.41 μg/L)
- NBCS children birth to age 4 = 1.2 – 4.5 μg/L
Exposures reflect patterns of mixtures

- More than 20% of moms have low exposures
- Overall rate of preterm birth in cohort 7%
- ~45% have mixture exposures that create a 3-fold greater risk of preterm birth (clusters 5 & 6)
- Mercury modulates the risk downward—indicates complexity of metals toxicity and mixed metals effects

## Summary of mean posterior probability from the fully adjusted model and relative risk of preterm birth by exposure cluster

<table>
<thead>
<tr>
<th>Exposure Cluster</th>
<th>Group Size (N)</th>
<th>Empirical Probability</th>
<th>Mean Posterior Probability (95% CI)</th>
<th>Relative Risk (95% CI)</th>
<th>Probability EC&lt;EC1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>88</td>
<td>0.034</td>
<td>0.045 (0.018-0.081)</td>
<td>Reference Group</td>
<td>Reference Group</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>0.032</td>
<td>0.049 (0.012-0.109)</td>
<td>1.362 (0.25-3.638)</td>
<td>50.46</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>0.042</td>
<td>0.059 (0.023-0.108)</td>
<td>1.647 (0.44-3.936)</td>
<td>65.97</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>0.090</td>
<td>0.093 (0.049-0.148)</td>
<td>2.587 (0.9-5.678)</td>
<td>92.57</td>
</tr>
<tr>
<td>5</td>
<td>141</td>
<td>0.092</td>
<td>0.097 (0.065-0.134)</td>
<td>2.706 (1.059-5.768)</td>
<td>96.26</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>0.119</td>
<td>0.117 (0.058-0.19)</td>
<td>3.295 (1.046-7.437)</td>
<td>95.74</td>
</tr>
</tbody>
</table>

*Posterior probability >0.95 that EC is above 1 compared to reference cluster (EC2).
Potential immune dysregulation associated with metals

Table 4. Significant Associations of Cytokines with Metals in the NBCS

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Univariable model</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNα</td>
<td>tAs↑, DMA↑, MMA↑</td>
<td>DMA↑</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Hg↑</td>
<td>Hg↑</td>
</tr>
<tr>
<td>IL-4</td>
<td>AsIII↓</td>
<td>AsIII↓</td>
</tr>
<tr>
<td>IL-7</td>
<td>Mn↓</td>
<td>Mn↑, MMA↓</td>
</tr>
<tr>
<td>IL-17A</td>
<td>U↑, Mn↑, AsIII↓</td>
<td>U↑, Mn↑, AsIII↓</td>
</tr>
<tr>
<td>IL-29</td>
<td>Mn↑, AsIII↓, DMA↓</td>
<td>Mn↑, AsIII↓, MMA↓</td>
</tr>
</tbody>
</table>

1 Significant (p<0.10) association with metal. 2 Significant metal predictors after variable selection. All metals were measured in urine. tAs=total arsenic; MMA and DMA are mono and dimethylated metabolites of As, respectively; Hg=mercury; AsIII=arsenite; Mn=manganese, U=uranium. Directionality: positive ↑; negative ↓ N=200

Inflammatory marker levels vary by metal exposure clusters

Jennifer Ong PhD (dissertation)
Debra MacKenzie
Li Luo
**Detailed Neurodevelopmental Assessments**
(between ages of 3-5 and again at 7-8)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>DAS-II</td>
</tr>
<tr>
<td>Language</td>
<td>OWLS-2</td>
</tr>
<tr>
<td>Adaptive skills</td>
<td>Vineland</td>
</tr>
<tr>
<td>Social-Emotional</td>
<td>CBCL, SRS-2 (questionnaires)</td>
</tr>
<tr>
<td>Behavioral Observation</td>
<td>TOF, CARS-2</td>
</tr>
<tr>
<td>Medical</td>
<td>Medical and Developmental History, Physical Exam</td>
</tr>
<tr>
<td>Social cognitive functioning</td>
<td>Eye tracking measure</td>
</tr>
</tbody>
</table>
ND Assessment Summary

• Navajo preschoolers performed within the average ranges across multiple direct assessments and parent-report measures, except on the verbal domains across both modalities.

• High prevalence of language disorder independent of intellectual disability, general developmental delay, and autism spectrum disorder (validity of test instrument?, other reasons?)

• See Posters Nozadi, Lecke, Wegele, Rennie for NBCS related work
Outcomes of NBCS/ECHO Study

• Assess the relationship between exposures to environmental contaminants (metals, others) with ND trajectories and other health outcomes.

• Compare NBCS to national sample of over 50,000 children to increase our power to identify impacts of environmental exposures on child health as well as increasing our understanding of the influence of early life environmental exposures on health trajectory of Navajo children.

The presented data are solely the responsibility of the authors and do not necessarily represent the official views of the NIH, Centers for Disease Control and Prevention, or the Department of Health and Human Services.
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

And many others who have contributed to and supported this work!

Our funders:

NBCS/ECHO is funded by NIH/OD (2016-2023) UG3/UH3D023344.

Original Navajo Birth Cohort Study (2010-2018) was funded by the Centers for Disease Control and Prevention (U01 TS 000135).

Navajo Team Members

Other Native Team Members

Bold indicates Current Team
Non bold are former team members
Thinking Zinc: A nutritional intervention for metal toxicity

Debra MacKenzie, PhD and Erica Dashner-Titus, PhD

Laurie Hudson, PhD; Esther Erdei, PhD, MPH; Chris Shuey, MPH; David Begay, PhD; Sarah Henio-Adeky; Li Luo, PhD, Tamara Anderson-Daniels

Paintings by Mallery Quetawki, Zuni Pueblo

Funding: NIH/NIEHS P42 ES025589 (UNM METALS)

This material was developed in part under cited research awards to the University of New Mexico. It has not been formally reviewed by the funding agencies. The views expressed are solely those of the speakers and do not necessarily reflect those of the agencies. The funders do not endorse any products or commercial services mentioned in this presentation.
Experimental and Population Studies

As and U share mechanism of action

U less potent in tested activities

<table>
<thead>
<tr>
<th></th>
<th>ARSENIC</th>
<th>URANIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYTOTOXICITY</td>
<td>≥ 1 µM</td>
<td>&gt;&gt;10 µM</td>
</tr>
<tr>
<td>ROS GENERATION</td>
<td>Sustained</td>
<td>Transient, &lt; As</td>
</tr>
<tr>
<td>HO-1 induction</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>PARP-1 ZF PEPTIDE</td>
<td>Interaction</td>
<td>Interaction</td>
</tr>
<tr>
<td>PARP-1 ZINC LOSS</td>
<td>Yes</td>
<td>Yes, U &lt; As</td>
</tr>
<tr>
<td>PARP-1 INHIBITION</td>
<td>Yes</td>
<td>Yes, U &lt; As</td>
</tr>
<tr>
<td>DNA REPAIR INHIBITION</td>
<td>Yes</td>
<td>Yes, U &lt; As</td>
</tr>
<tr>
<td>PROTECTION BY ZINC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ZF TARGET SELECTIVITY</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Zinc-binding proteins are regulators of cell function.

Why Zinc?

Supplemental zinc is protective against As/U.

Zinc supplements have a good safety profile.

Low zinc status (<70 ug/dL) in many members of the Navajo Nation.

As target selectivity: C3H1 and C4 zinc fingers

>40 bench research publications by UNM METALS researchers

*other metals, including Cd

Zinc supplementation in elderly or zinc deficient subjects improves immune and DNA damage endpoints.
Zinc is protective

**Zinc is protective**

**Zinc**

**DNA Damage**


Ding et al. J. Biol Chem. 2009;
**Long Term Goal**: Determine whether dietary zinc supplementation reduces metal-induced human disease

**Project Goal**: Conduct clinical trial of dietary zinc supplementation to assess effects on biomarkers of metal-induced toxicity

**Immune Disorders**
- ANA-markers of autoimmunity
- Immune cell numbers and types
- Immune cell communication (cytokines)

**Cancers**
- DNA damage
- DNA repair protein activity
Thinking Zinc Study Design

0
Start of study

3 months later
(3rd to 4th month)

3 months later
(6th to 7th month)

3 months later
(9th to 10th month)

Baseline
- Enrollment and Consent
- Blood and Urine
- Gift card

Baseline
- Nutrition Survey
- Blood and Urine
- Receive Zinc (RDA)
- Gift card

Zinc
- Blood and Urine
- Receive Zinc (RDA)
- Gift card

Last visit
- Nutrition Survey
- Blood and Urine
- Gift card

We measure:
- Metal levels in urine and blood
- Markers of immune function
- DNA damage and DNA repair protein activity
- Zinc in diet (nutrition survey)

Urine: As, U, other metals

Cells from blood: ANA, immune cells

Serum: Zn, cytokines
Status/Progress

Approvals
• Navajo HRRB January 2019
• Registration Clinicaltrials.gov NCT03908736

Continued Community Engagement (CEC/SRIC)
• >50 community activities (i.e. chapter meetings and booths at events)

Enrollment (52 of 80 goal as of March 2022)
34 women, 18 men ages 21-64, median ~59
• RWPR Community Completed in April 2022
• Blue Gap Community – ongoing

Retention—71+%  

Sample and Data Analysis—in progress
Initial findings from RWPRC Participants

Red Water Pond Road Community
### Thinking Zinc Participant Pre-Zinc Urinary Metal Levels

<table>
<thead>
<tr>
<th>Metal</th>
<th>Median</th>
<th>Range</th>
<th>%&gt;95th percentile NHANES/NBCS</th>
<th>NHANES 50th</th>
<th>NHANES 95th</th>
<th>NBCS 50th</th>
<th>NBCS 95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony</td>
<td>0.077</td>
<td>0.020 – 1.540</td>
<td>15%/1.7%</td>
<td>0.046</td>
<td>0.151</td>
<td>0.077</td>
<td>0.964</td>
</tr>
<tr>
<td>Arsenic</td>
<td>4.392</td>
<td>1.495 – 135.014</td>
<td>3.3%/4.9%</td>
<td>5.62</td>
<td>56.2</td>
<td>5.392</td>
<td>16.81</td>
</tr>
<tr>
<td>Barium</td>
<td>1.201</td>
<td>0.058 – 437.227</td>
<td>5%/1.7%</td>
<td>1.24</td>
<td>4.83</td>
<td>3.903</td>
<td>27.9</td>
</tr>
<tr>
<td>Beryllium</td>
<td>0.002</td>
<td>0.000 – 0.047</td>
<td>NA/6.7%</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>0.011</td>
<td>0.014</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.163</td>
<td>0.031 – 1.207</td>
<td>5%/16.7%</td>
<td>0.188</td>
<td>0.882</td>
<td>0.096</td>
<td>0.44</td>
</tr>
<tr>
<td>Cesium</td>
<td>3.199</td>
<td>0.921 – 25.151</td>
<td>6.7%/1.7%</td>
<td>4.22</td>
<td>10.4</td>
<td>4.675</td>
<td>16.771</td>
</tr>
<tr>
<td>Cobalt</td>
<td>0.416</td>
<td>0.106 – 4.794</td>
<td>6.7%/3.3%</td>
<td>0.404</td>
<td>1.2</td>
<td>1.012</td>
<td>2.522</td>
</tr>
<tr>
<td>Lead</td>
<td>0.129</td>
<td>0.016 – 2.706</td>
<td>1.7%/1.7%</td>
<td>0.315</td>
<td>1.14</td>
<td>0.306</td>
<td>1.884</td>
</tr>
<tr>
<td>Manganese</td>
<td>0.092</td>
<td>0.002 – 1.963</td>
<td>8.3%/0%</td>
<td>0.209</td>
<td>0.487</td>
<td>0.244</td>
<td>6.89</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>24.148</td>
<td>1.728 – 130.684</td>
<td>1.7%/0%</td>
<td>36.3</td>
<td>94.7</td>
<td>55.193</td>
<td>245</td>
</tr>
<tr>
<td>Platinum</td>
<td>0.013</td>
<td>0.000 – 0.398</td>
<td>28.3%/30%</td>
<td>&lt;LOD</td>
<td>0.035</td>
<td>0.007</td>
<td>0.03</td>
</tr>
<tr>
<td>Strontium</td>
<td>101.669</td>
<td>10.867 – 3100.765</td>
<td>11.7%/3.3%</td>
<td>101</td>
<td>266</td>
<td>185</td>
<td>696.056</td>
</tr>
<tr>
<td>Tin</td>
<td>0.954</td>
<td>0.116 – 14.605</td>
<td>11.7%/0%</td>
<td>0.431</td>
<td>3.06</td>
<td>2.07</td>
<td>20.975</td>
</tr>
<tr>
<td>Tungsten</td>
<td>0.030</td>
<td>0.002 – 0.193</td>
<td>0%/0%</td>
<td>0.061</td>
<td>0.279</td>
<td>0.137</td>
<td>1.276</td>
</tr>
<tr>
<td>Uranium</td>
<td>0.019</td>
<td>0.002 – 19.162</td>
<td>31.7%/6.7%</td>
<td>0.005</td>
<td>0.026</td>
<td>0.016</td>
<td>0.109</td>
</tr>
<tr>
<td>Vanadium*</td>
<td>0.156</td>
<td>0.019 – 28.837</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median metal levels are shown for Visit 1 and Visit 2 samples collected before zinc supplementation. Values are corrected for urinary creatinine and reported as micrograms per gram creatinine (µg/g creatinine). For reference, the 50th and 95th percentile levels are provided for the 2019 (January) National Health and Nutrition Examination Survey (NHANES) values and participants in the Navajo Birth Cohort Study including women, men and babies (N=1661-1782 for each metal). Metals results highlighted in blue represent those where more than 10% of samples had levels in excess of the NHANES 95th percentile values. *Urine levels for vanadium are not included in NHANES reporting. NA – Not available due to measurements below the level of detection of the instrument.

- Certain metals had 10% of samples exceeding the NHANES 95th percentile (blue). Antimony, Platinum, Strontium, Tin, and Uranium.
- For Uranium 31.7% and 6.7% of samples exceeded the NHANES and Navajo Birth Cohort Study (NBCS) 95th percentile, respectively.
Longitudinal biomonitoring reveals fluctuations

**Uranium**

**Vanadium**

**Total Arsenic**

**NHANES Values**
* 50th percentile 0.005
** 95th percentile 0.031

Synchronized participant group for collections

**NHANES Values**
* 50th percentile 5.74
** 95th percentile 49.9
Post-zinc reduction in DNA damage marker 8-OHdG

- Preliminary population results from TZ demonstrate a reduction in oxidative DNA damage with zinc
  - (See Dasher-Titus, Poster on Thinking Zinc)

- Also see reductions in cytokines associated with inflammation and autoimmunity (GM-CSF, IFNγ, IL12-P70, IFNβ, IL29 and IFNα)

Emam et al. 2014
Paintings by Mallery Quetawki
Zuni Pueblo
Thinking Zinc built on Community Input
Sarah Henio-Adeky, Chris Shuey, MPH; David Begay, PhD

- Study Design: Single-arm cohort design, not placebo-controlled
- Study name from community input: Thinking Zinc — Beesh Dootł’izh Bantsáhákees
  [metal + blue (the one that is) + thinking about it]
- Expanded age inclusion criteria
- Community vetting of recruitment and outreach materials
- Translation of scientific language to Navajo for presentations and consenting

Painting by M. Quetawki
Creating a resource in Diné Bizaad (Navajo Language) for learners and speakers identified as a critical need for success of the UNM Thinking Zinc clinical trial.

Western scientific terminologies needed to be translated into Diné Bizaad to enhance understanding by Navajo community members.

Respects the fact that most elderly Diné speak their Native language, and that visuals and hands-on instruction improve their understanding of key concepts.
# Navajo Translations of Key Terms in the Thinking Zinc Study

<table>
<thead>
<tr>
<th>Terms*</th>
<th>Dine Language Translations (English literal translation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Terminology</strong></td>
<td></td>
</tr>
<tr>
<td>Thinking Zinc</td>
<td>Beesh Dootł’izh Bantsáhákees <em>(metal, blue, thinking about)</em></td>
</tr>
<tr>
<td>Blue Gap/Tachee</td>
<td>Bis Dootł’izh Nídeeshgiizh <em>(dirt, blue, spread apart)</em></td>
</tr>
<tr>
<td>Red Water Pond Road</td>
<td>Tólichíí’ Siká Atiin <em>(Red Water Pond Road)</em> Ahidaazdigai <em>(where the meadows meet)</em></td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Ats’ís baa’aháyaháádée’ k’ehgo nabóhwintaah. <em>(body, from where it is cared for, like it, try out)</em></td>
</tr>
<tr>
<td>Community Engagement</td>
<td>Diné t’áá kédahat’íídí bíl ahił na’anish naha’í’ígo na’aalkaah <em>(people, all those living there, with together, work, research conduct)</em></td>
</tr>
<tr>
<td>Zinc Study</td>
<td>Beéesh dootł’izh bóhoo’aah <em>(metal, blue, learn about)</em></td>
</tr>
</tbody>
</table>
# Navajo Translation of Scientific Terms

## Health Problems (Áądahas’á Bee anáhóó’t’íl’ígíi)

<table>
<thead>
<tr>
<th>Category</th>
<th>Navajo Translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers</td>
<td>Ats’íís bit’óól dahdiníséeh áádoóó ba’át’e’ hóló yileehgo (body, cell growth, thereafter, bad behavior, gets to be)</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>Ajeéh ba’áh dahaz’á yileehgo (heart, poor health, gets to be)</td>
</tr>
<tr>
<td>Immune Disorder</td>
<td>Ats’íís yich’ááh naabaah yeé doo hózhó naańnish da yileehgo (body, protect from, does not fully work, gets to be)</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>Hats’á’ashk’azhí ba’áh dahaz’á yileehgo (kidney, poor health, gets to be)</td>
</tr>
<tr>
<td>Skin Problems</td>
<td>Hakági yeenít’iłh (skin, affects)</td>
</tr>
</tbody>
</table>

## Health and Biological Terminology

<table>
<thead>
<tr>
<th>Category</th>
<th>Navajo Translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers</td>
<td>Ats’íís bee naalkaah bee íneel’ááh (Body, research on, with findings)</td>
</tr>
<tr>
<td>Cells</td>
<td>Ats’íís bitsésílíí bit’óó’ (Body, precede, seed)</td>
</tr>
<tr>
<td>DNA</td>
<td>Ats’íís bit’óó’ bits’ánee’ bit’óó’ yee ats’íís hada’neel’t’éé (Body, seed, growth, string, body develops)</td>
</tr>
</tbody>
</table>
Methods in Community Engagement

• Conducted eight work sessions with community members (2018)
• Vetted written and oral Navajo terms in a community outreach presentation
• Developed study name and eligibility requirements with community members
• Held five work sessions with six Navajo-speaking study staff (2019-2021)
• Used paintings (below) by Zuni artist Mallery Quetawki to illustrate DNA damage and repair by Zn

![Paintings illustrating DNA damage and repair by Zn](image-url)
Traditional Foods Used in Outreach

- Outreach and educational materials prepared in both English and Navajo.
- Community slide presentation given solely in Diné Bizaad.
- Uses images of traditional foodstuffs, like blue corn mush and lamb, to illustrate how community members can increase their zinc intake.
Conclusions

• Translating and interpreting English terms supports enhanced understanding among Diné speakers of the purpose, methods and future results of the study.

• Translations into Diné Bizaad also promote meaningful dialogue among researchers and Diné community members who are advisors to and participants in this and other studies.
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- Blue Gap-Tachee

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