

US EPA ARCHIVE DOCUMENT

DiNEH Project Update: Survey → Clinic → Mechanisms

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With acknowledgement and thanks to the Team!

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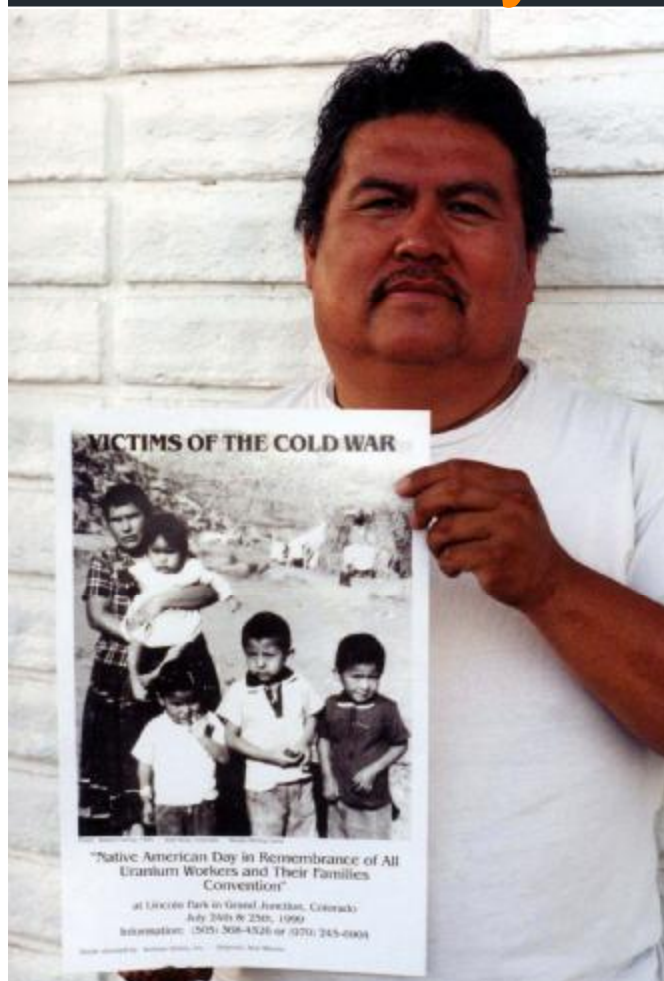
Navajo Nation Office
 of Vice-President,
 HEHS, AG

And to our
 funders:
 NIEHS (16 yrs)
 CDC (3 yrs)
 USEPA (4yrs)
 NIMHHD (2 yrs)

DiNEH and
 NBCS Research
 is reviewed and
 monitored by
 Navajo Nation
 Human
 Research
 Review Board

Community Health Concerns: 2000

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- Diabetes: 3-5x >> us as a whole
- CKD: 2.5x; ESRD: 3x;
- early onset: teens on dialysis
- >30% Navajo population lacks access to regulated water – use unregulated wells
- Anthropogenic and natural uranium surface exposures sources

DiNEH Iterative Assessment

Capacity Building – Multi-directional study design

Surveys



Medical Record Reviews



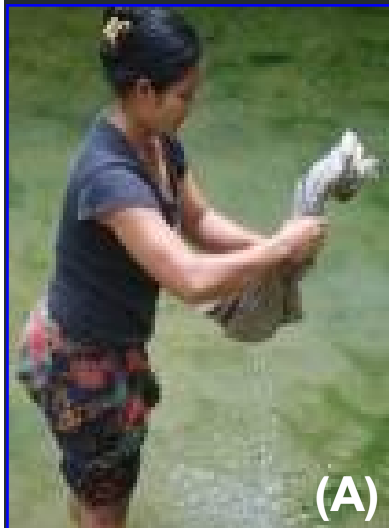
Clinical Assessments



Biomarker Analyses

DINER Project Results: Active-mining era exposures (workers and family) increased risk of kidney disease

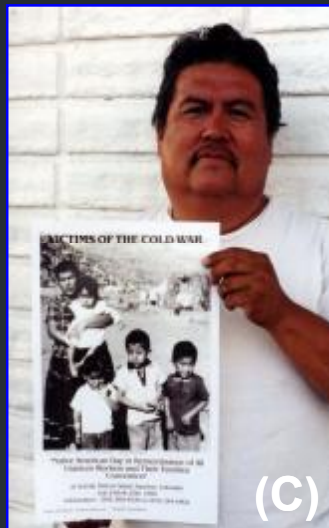
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(A)



(B)



(C)



(E)



Active-mining related exposures were estimated from self-reported survey data

- A: Washed the clothes of a uranium worker (22%)
- B: Worked in a uranium mine (10%)
- C: Lived in a mining camp (4%)
- D: Worked in a uranium mill (2%)
- E: Worked on a uranium mine or mill reclamation or hauled uranium ore or tailings in a pickup truck (2%)

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

DiNEH Results: Ongoing environmental legacy exposures → increased risk for hypertension, autoimmune disease, immune dysfunction

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Exposures estimated from two sources of data:

- 1) The proximity of each resident's home* to all of the abandoned uranium mine and mill waste features (100)
- 2) Reported activities that may result in exposure to uranium mine and mill wastes

- A: Used materials from abandoned uranium mine or mill (17%)
 B: Herded livestock next to uranium mine, mill or waste dump (13%)
 C: Drunk or contacted uranium mine waste water (13%)
 D: Played on a uranium tailings pile or waste dump (13%)
 E: Played outdoors near a uranium mine, mill, or waste dump (12%)
 F: Sheltered livestock in an abandoned uranium mine (2%)

*Note: Median length of residence in current homes was 33 years





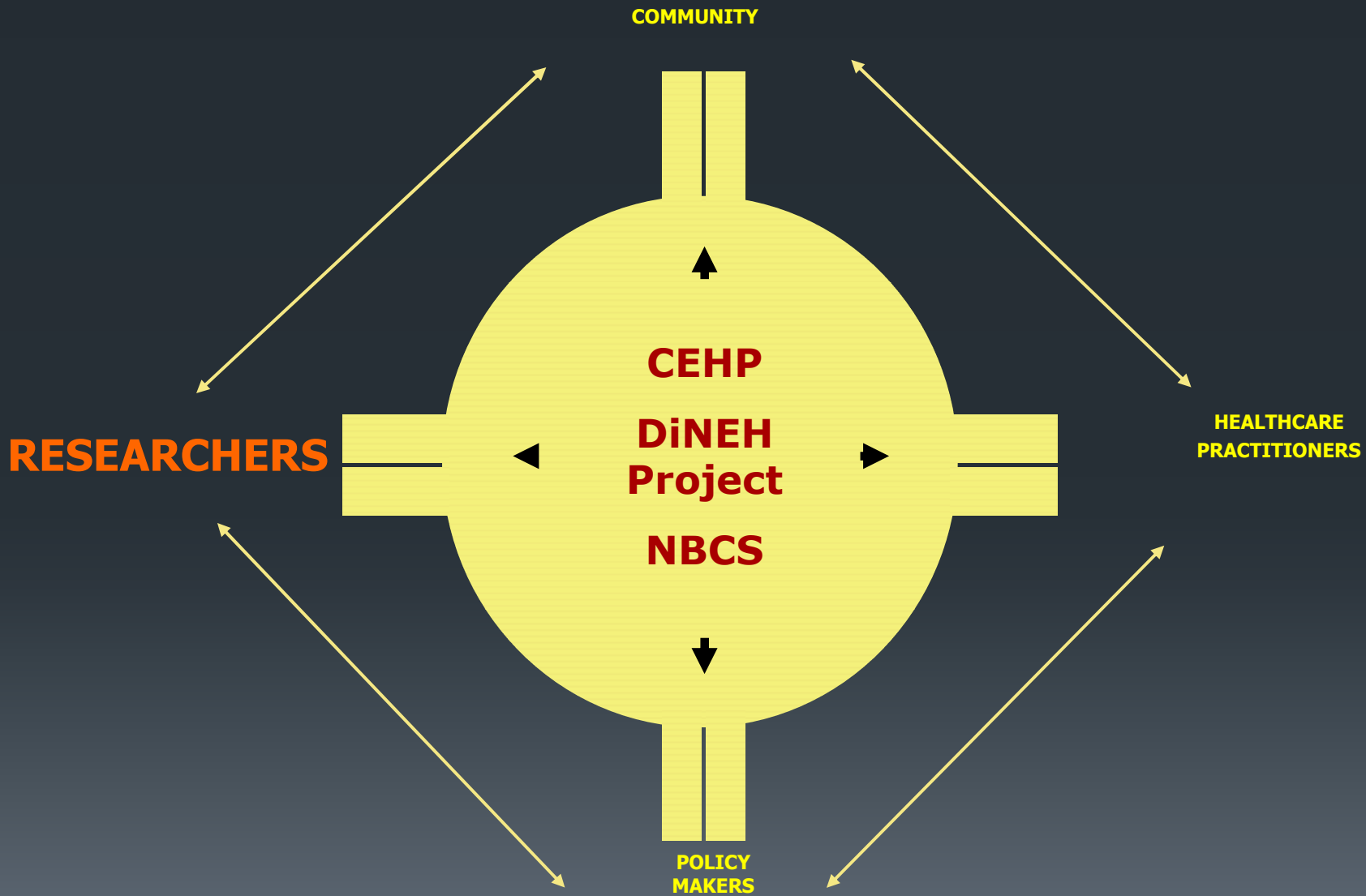
About 90 community members participated in a DiNEH-CUEJTH screening and collection day at Baca Chapter in August 2011.



DiNEH work with NAIHS CUE-JTH

- Design of long-term surveillance
- Assessments began July 2010; 270 DiNEH participants through 2011
- Standard clinical assessments by CUE-JTH
 - UNM Biomarker analyses for kidney function, immune function, cardiovascular damage
- Validation of survey self-report
- CUE-JTH continuing across Navajo Nation – now >900

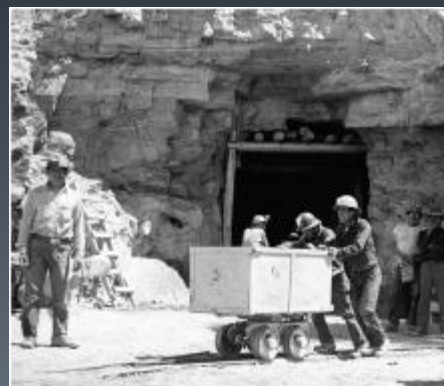
Mechanisms of Toxicity



Goal of DiNEH Phase II



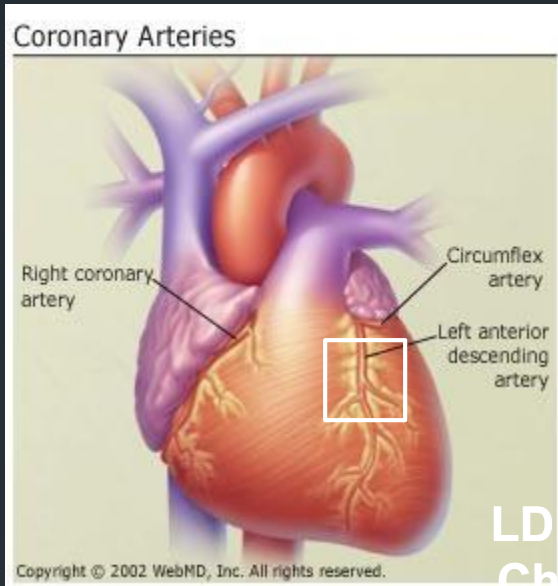
- Direct response to community members' requests for research on mechanisms underlying health effects.
- Find early indicators of exposure-related health effects
- Understand mechanisms to develop intervention, prevention



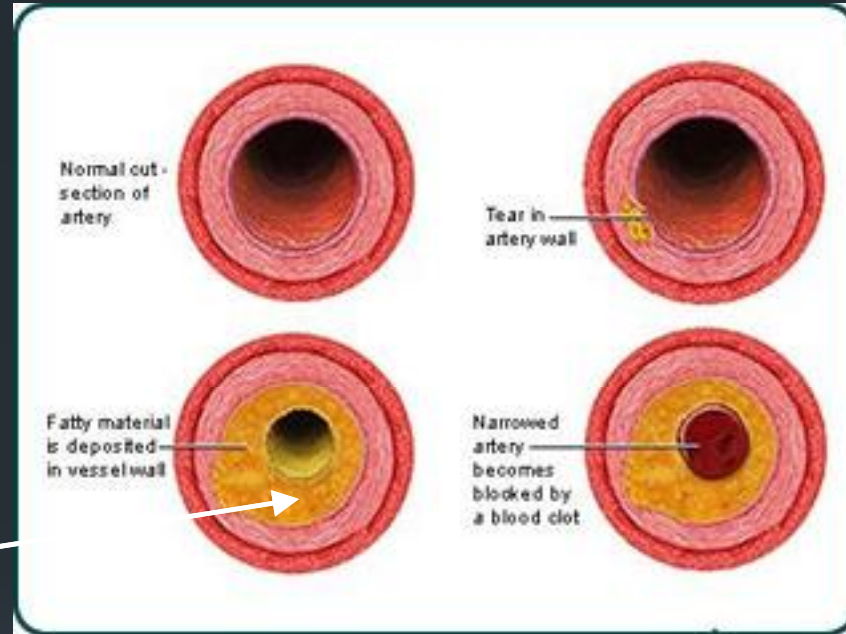
What do uranium mines have to do with Cardiovascular Disease (CVD) and Diabetes?

- CVD
 - Prevalence increasing in Navajo community
 - May be promoted or worsened by environmental exposure to heavy metal contaminants
- Diabetes
 - Diabetes also a risk factor for CVD
 - Prevalence increasing in Navajo community
 - Does diabetes increase susceptibility to metals?
 - mine wastes are mixtures of many metals

Cardiovascular Disease: Atherosclerosis

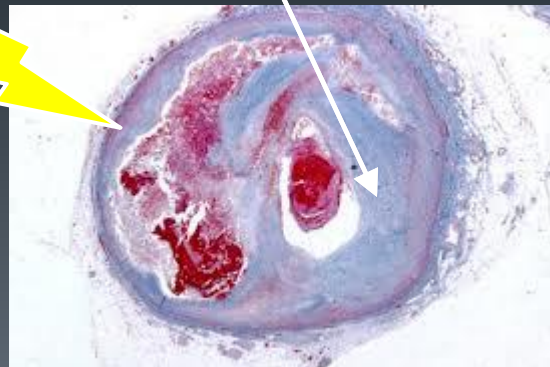


LDL ("Bad")
Cholesterol



Metals

oxLDL
marker for CVD



Vessel Dysfunction
Inflammation
Immune Responses
Oxidative Stress

Population Data

Health Condition (self report)	Prevalence in U.S. %	Navajo Cohort (n = 252) %
Type 2 Diabetes	11.3	26.2
Hypertension	25.0	38.1
Heart Disease	11.8	6.0
Stroke	2.7	5.2

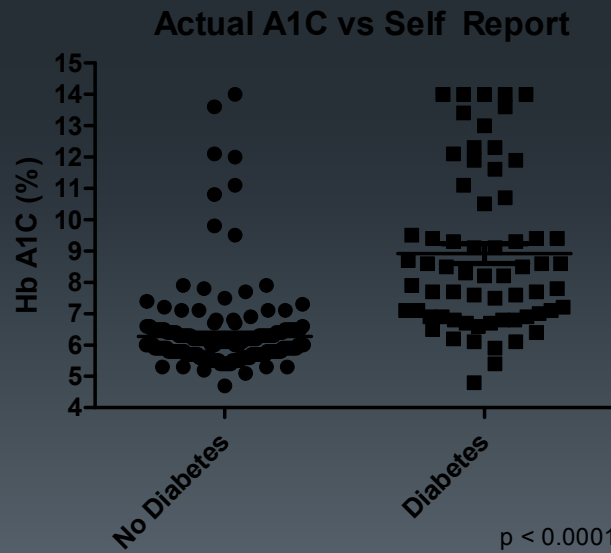
Navajo Cohort: BMI	
New Mexico Average	25.1
Navajo Cohort	30.4

Body Mass Index (BMI)	
Underweight	< 18.5
	18.5—
Normal	24.9
	25.0—
Overweight	29.9
Obese	> 30.0

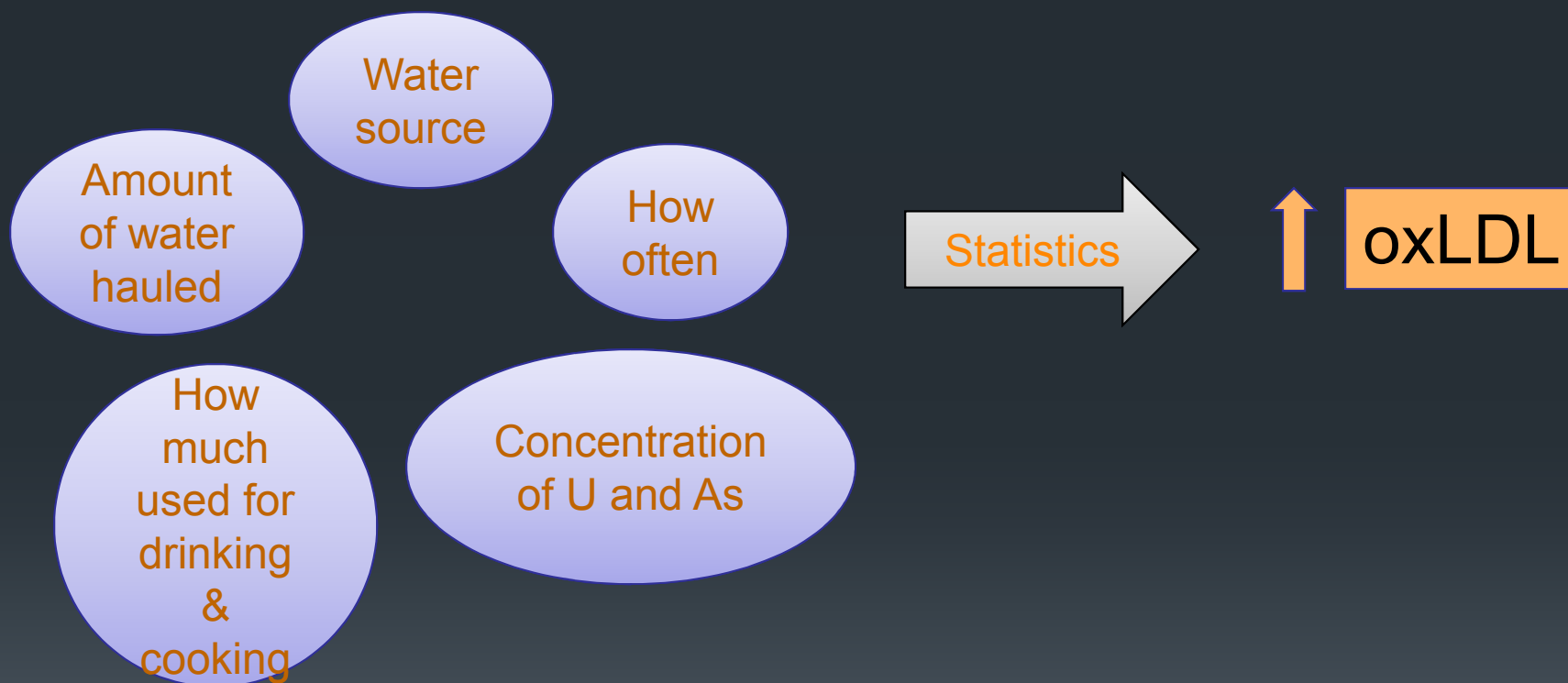
http://www.cdc.gov/nchs/data/series/sr_10/sr10_252.pdf
<http://www.cdc.gov/nchs/data/nhanes/databriefs/adultweight.pdf>
http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

Population Data

Self-Reported Presence/Absence of Diabetes	Navajo Cohort: A1C	A1C Classification	
No Diabetes	6.3%	Healthy	<5.7%
Diabetes	8.9%	Pre-Diabetes	5.7-6.4%
		Diabetes	>6.5%



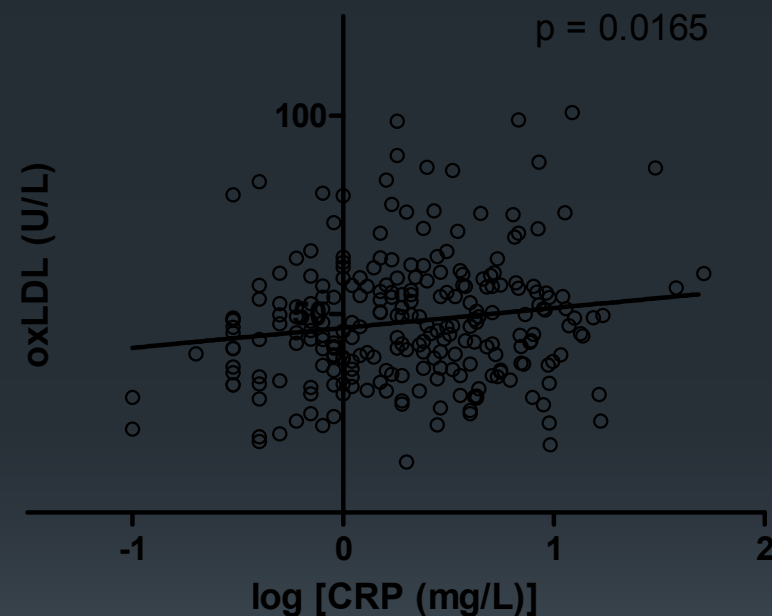
Water as an exposure source for uranium and arsenic



Total consumption of arsenic and uranium was estimated from several factors

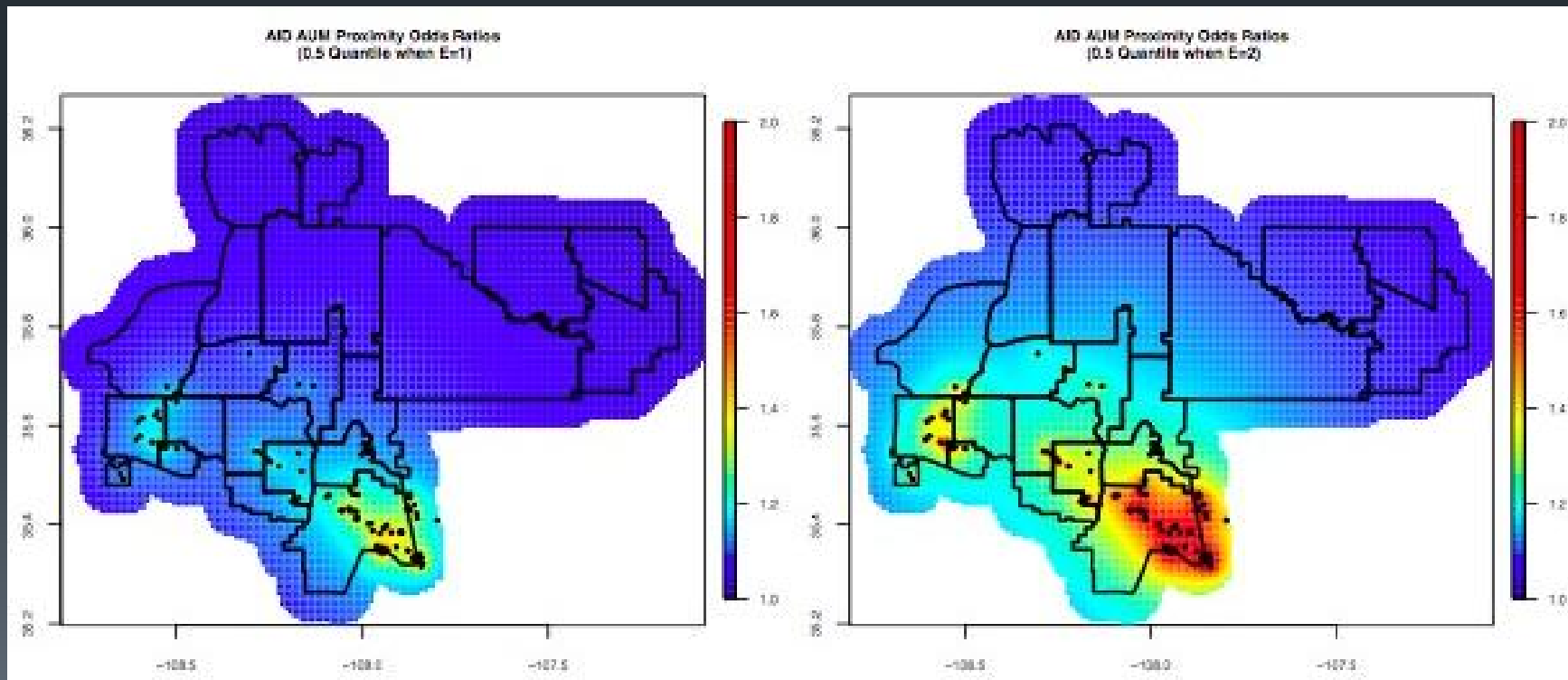
Inflammation & oxLDL

- C-Reactive Protein (CRP) increases in response to inflammation
- Inflammation is common in CVD and diabetes
- CRP level is a risk factor for atherosclerosis



Environmental Legacy Exposures Also Increase the Likelihood *Autoimmune Disease*

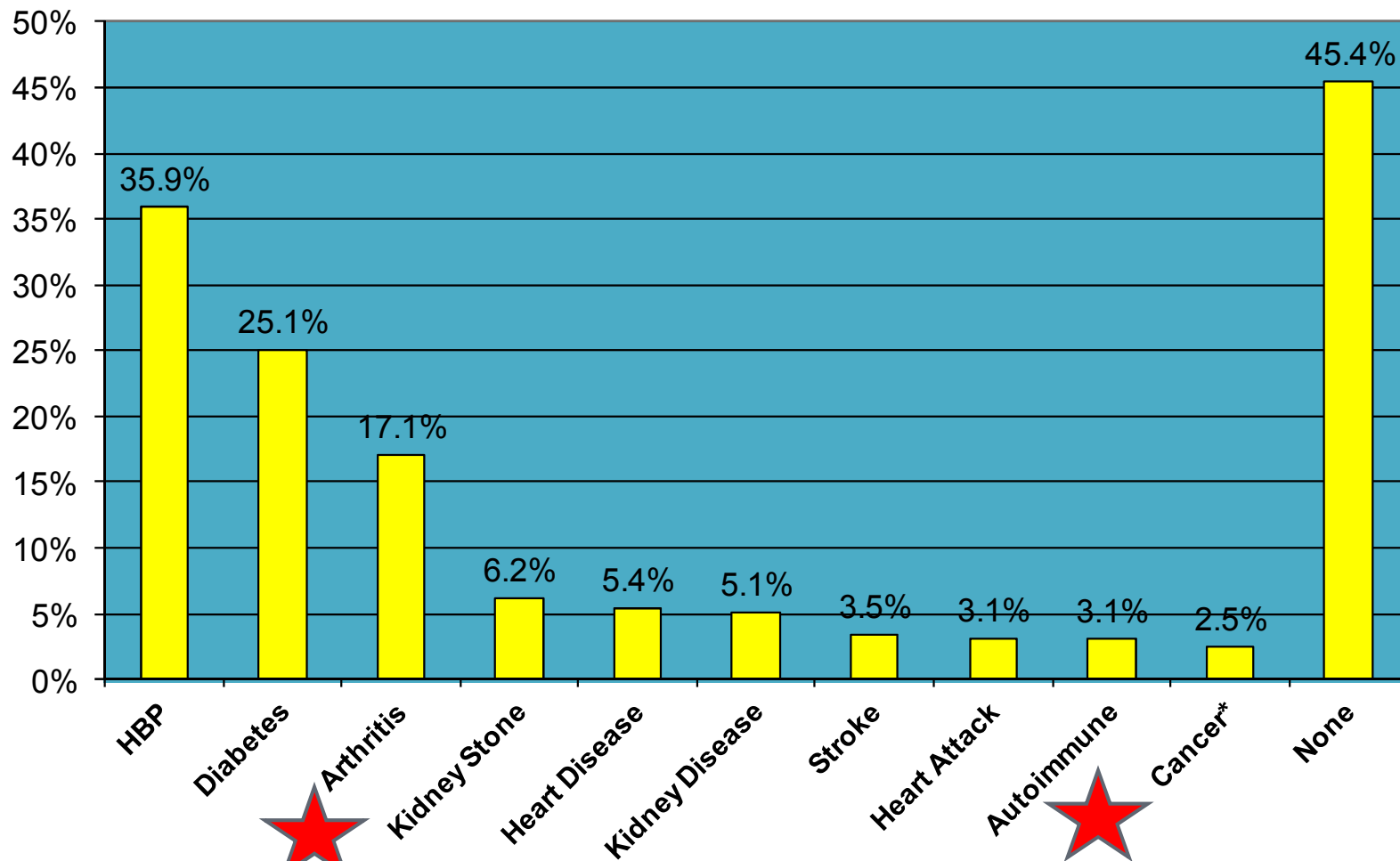
Figures below show increases in risks for *autoimmune disease* (self-reported) based on an increase from 1 to 2 types of exposure activities



DiNEH Survey Responses

Prevalence of Self-Reported Health Conditions Among 1,304 DiNEH Survey Participants

(*Cancer prevalence based on 1,011 participants surveyed)



DiNEH biological sample collection

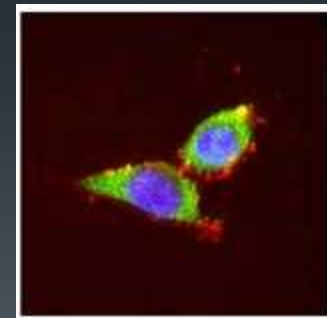
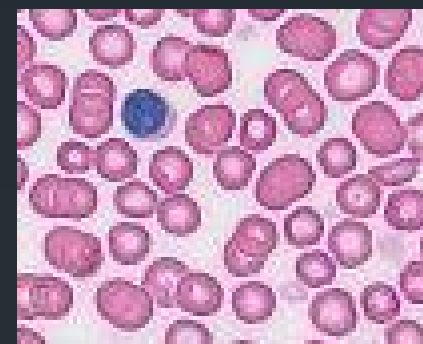


- DiNEH project participants from 20 chapters
- Blood and urine samples were collected from 267 individuals
- A subset has been analyzed for immune biomarkers (N=69)



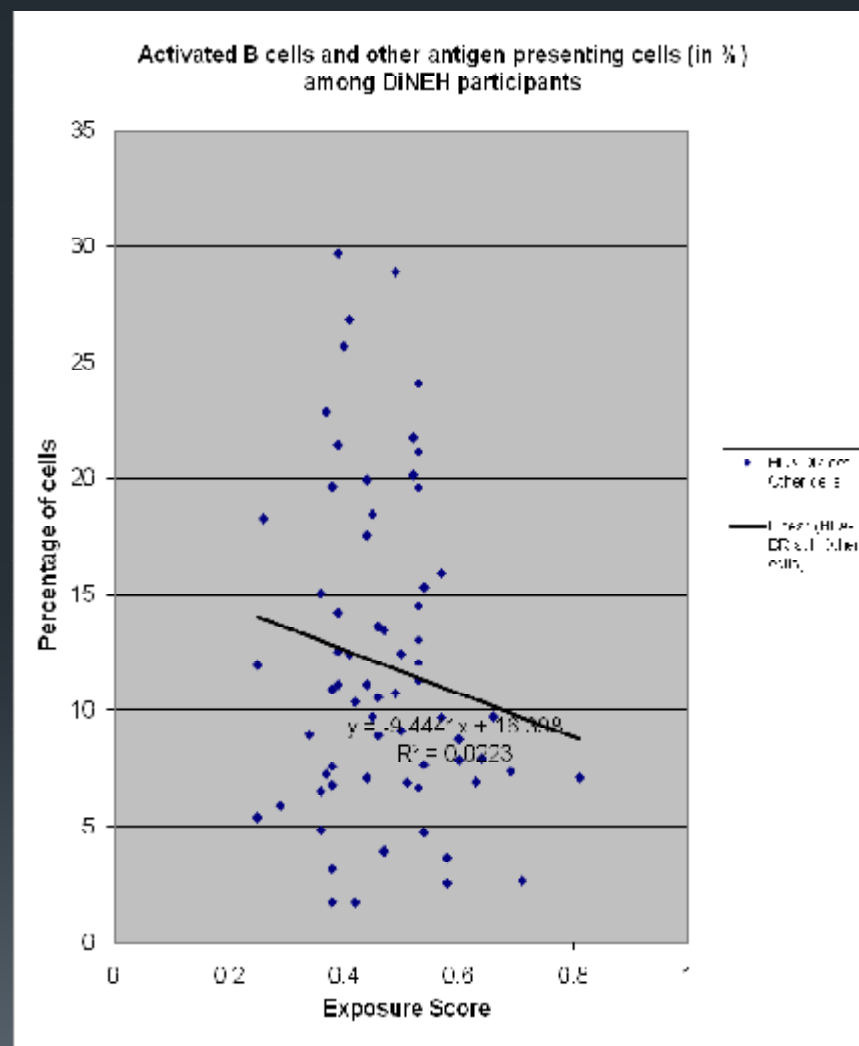
Flow cytometry measurements (n=69)

- Lymphocyte subpopulations from whole blood samples..
- 6 cell populations were measured:
 - T cells (CD3+), T helpers (CD4+), T suppressors (CD8+);
 - B cells (CD19+);
 - HLA-DR+ cell activation in T cells and
 - B cells and other cell types; NK cells (CD3-/CD16+/CD56+).



Flow cytometry results II.

- Increased percentage of activated T cells
- Decreased percentage of activated B cells
- Decoupling of T cell and B cell activities suggest altered immune response among this subset of participants
- Can lead to lower production of protective antibodies



Serum cytokine measurements



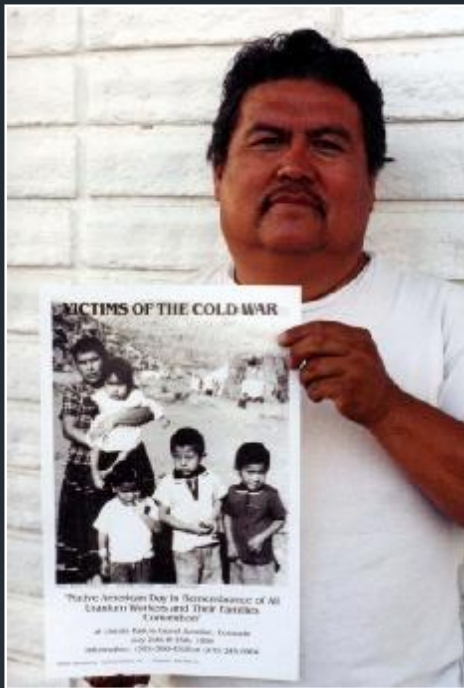
- Detection of 10 human serum cytokines (IL-1 β , IL-2, IL-8, IL-10, INF- γ , TNF- α , and GM-CSF) high sensitivity assay
- Uses only 50 μ l of serum sample/participant
- Complex task: cytokine production indicative of the presence of an inflammatory response
- Work in progress
- Metal-induced chronic inflammation could be common pathway to both immune and cardiovascular results

Results of autoantibody production

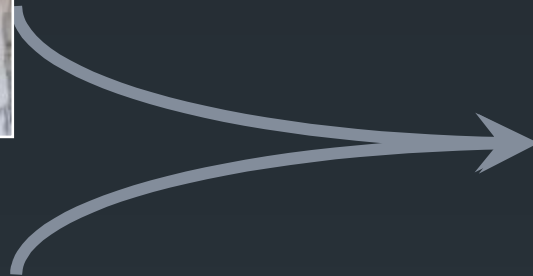


(IHS LabCorp)

- ANA positivity was 52%, higher than national average (13%)
- Techniques used to detect ANA differ widely between labs
- ANA positivity is known to increase with age
- High titer indicates that connective tissue disease is likely if clinical findings are present.
- False-positive results occur in normal blood donors and in patients with chronic liver disease, neoplasms, or active chronic infections.
- Positive ANA, at least 1 positive disease specific Ab result was also obtained.



Community Concerns



Toward a mechanism-based intervention



Bench Research

Arsenic increases DNA damage

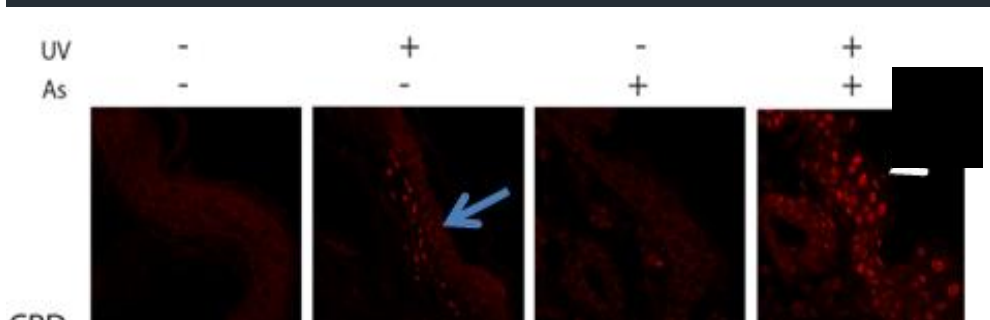


- Radiation also damages DNA

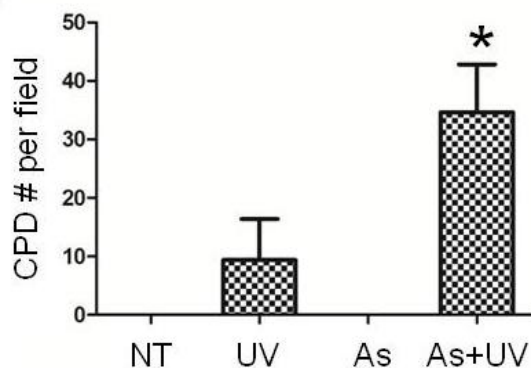
- If DNA damaged →

- Repaired, or
- Reproduce damaged cells, or

- If germ cell (sperm or egg), pass damage on to next generation



Blue arrow= UV alone
White arrow=UV+As



DNA damage (CPDs)

Karen Cooper
Brenee King

Arsenic inhibits DNA repair enzyme – also in immune cells

- Inhibits by knocking out zinc – (good metal)
- Lab studies indicate uranium acts in similar way
- Zinc in prenatal vitamins potentially sufficient to reverse
- Uranium + arsenic? Studies in progress



**Navajo Birth Cohort Study
2010 - present
Cooperating Organizations**

**Centers for Disease Control and
Prevention/Agency for Toxic
Substances and Disease Registry**

DiNEH Project Team

- UNM Community Environmental Health Program (CEHP)
- UNM Pediatrics Department, Center for Development and Disability
- Southwest Research and Information Center (SRIC)
- Consultants

Birth Cohort
Navajo mothers,
fathers and
babies; other
community
members;
chapters

**Navajo Area Indian
Health Service (NAIHS)**

**Navajo Nation
Division of Health**

With Help From

**Growing in Beauty
(developmental
disabilities services
provider)**

**PL93-638 Facilities
(Tséhootsooí, Tuba City)**

**Other Navajo Nation Agencies
(Environmental Protection Agency,
WIC, Health Education,
Office of Uranium Workers)**

**USEPA
Region 9**

NBCS Status

- Funded 2010
- 2.5 years to complete regulatory process
 - 4 IRBs (complete by August 2011)
 - OMB – delayed initial response by several months
 - Final approval not until mid-February 2013
- Recruitment began one-week later: Chinle
- Today, enrollment at Tsehootsooi, Tuba (Kayenta)
- Shiprock scheduled first week of May
- Gallup, Kayenta to follow
- Renewal in progress – May 13

Outcomes Model Structure

EXPOSURE INPUTS

Uranium

Proximity, dust, occupation, water, land use
 Survey, GPS, NURE data, Biomonitoring, Existing water quality, in-home dust, parent biomarker analyses

Radiation

Home scans
 Biomonitoring, Existing data

Radon

In-home
 Canister monitoring

MODIFIERS

Reproductive History

Mother and father
 Survey & Medical Records

Nutritional Status

Mother
 WIC, FFQ, Biomonitoring

Demographic Variables

Parental income, education, parental ages
 Survey

Alcohol, Substance Abuse

Surveys, Meconium, Medical Record

Co-Exposures

Other metals, PAHs, Particulates, Sulfur Compounds
 Biomonitoring, Surveys, Home Assessments

REPRODUCTIVE OUTCOMES

Reproductive Difficulty

Miscarriage, delivery complications
 Medical Record

Low Birth Weight

Medical Record Review

Congenital Malformation

Medical Record, Survey

DEVELOPMENTAL OUTCOMES

Development: Behavior

communication, gross & fine motor skills, problem solving and personal social skills
 ASQ-I & Mullen

Development: Physical

Length, weight, head circumference
 Anthropometry

Development: Medical Infections, Morbidity, Mortality

Medical Record Review

Development: Biomarker

Inflammation, Immune system
 Laboratory Analysis

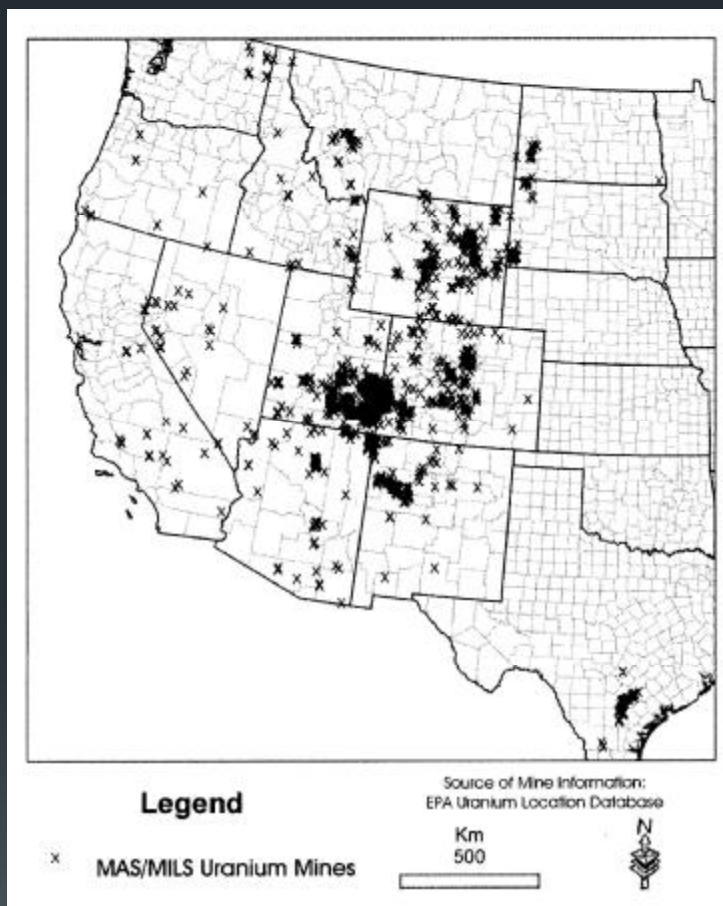
NBCS Participant Exposure Assessment

Exposure Source	Methods/Media/Locations	Data Source(s)/Laboratory
Environmental Monitoring – Existing Data + New Sampling		
Ambient air quality	Regional air monitoring stations	USEPA, NNEPA data
Gamma radiation	Screening surveys of indoor, outdoor environments at participant' s home using Ludlum-19 or equivalent meter (based on NNEPA SOPs)	De novo screenings with NBCS data sharing; existing data for homes previously screened by NNEPA-SF or USEPA
Indoor dust	Wipe or vacuum samples collected during in-home assessment	USEPA-9 laboratory
Indoor H ₂ S	Homes in oil & gas production areas and non-O&G areas (controls)	Hydrogen sulfide tape meters furnished by USEPA, ATSDR
Indoor radon	6-day canisters or E-PERMs placed in home in winter months	USEPA or private company for canisters; NNEPA-Air for electret reading; existing NNEPA data
Proximity to AUMs	Existing electronic dataset of AUM locations, surface areas	USEPA/USACE atlases (w/ metafiles in DVDs)
Water (regulated, unregulated)	Survey responses for water use, water sources	USEPA, NNEPA existing water quality data for previously tested sources; new testing
Personal Historical Exposures – Survey self report		
Historic & current activity patterns of participants contacting wastes, contaminants	Survey questions on land use, water use	Intake surveys of mother, father (NBCS)
Occupations, work-related	Survey questions on work history	Intake surveys of mother, father (NBCS)
Confirmation Biomonitoring – Measurement of toxic materials in biological samples		
Metals, metalloids	Blood and urine samples	CDC Environmental Health Lab; UNM Earth & Planetary Sciences ICP-MS
Alcohol metabolites	Meconium	Contract laboratory or Emory U.
Uranium decay chain isotopes	Meconium	UNM nuclear chemistry laboratory
Polycyclic Aromatic Hydrocarbons	Blood and urine samples	CDC Laboratories

Future of Partnership: Navajo Birth Cohort Study (NBCS)

- Opportunity to confirm DiNEH results in younger population
 - *DiNEH cohort mean age ~55*
 - *NBCS – parents 14-45*
 - *Infants*
- Build research capacity on Navajo
- Model for translation of results
 - Integration with health care
 - Inform policy and regulations
- Incorporate outcomes from DiNEH – continue linkage to mechanistic studies → intervention

Legacy of Mining in the West



- More than 500,000 abandoned hardrock (excluding coal) mine features in US (Mineral Policy Center) (200,000 mines – EPA)
- Clean-up costs? \$22 mil/site (USEPA, 2001)
- USEPA estimates:
 - ~10,400 abandoned uranium “mine features” in 15 western states
- U.S. Bureau of Mines estimates:
 - ~4,100 discrete uranium mines
 - Source:
<http://www.epa.gov/rpdweb00/tenorm/uranium.html>
- *Many impact tribal lands (Laguna, Sioux – but also other rural communities (Bluewater Valley)*
- *Wastes are mixtures – synergy?*

Oversight, Review and Approval

- *All research presented here is reviewed and approved by Navajo Nation Human Research Review Board (NNHRRB) and UNM Human Research Review Committee*

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- *DHHS/NIH/NCRR: #1UL1RR031977;*
- *CDC/ATSDR U01 TS000135; and*
- *Contracts and in-kind support from USEPA Region 9; and Navajo Nation Environmental Protection Agency (NNEPA)*

Is this OK?????????



10.09.2009