Thinking Zinc: A Study of Zinc Supplements on the Navajo Nation

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Abstract

Research themes in the *Thinking Zinc* clinical trial

Paintings by Mallery Quetawki, Zuni Pueblo

DNA Damage by Uranium

DNA Repair

Functional Immune System

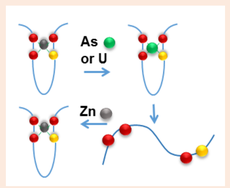
Communities living in proximity to abandoned uranium mines have documented exposures to metals in drinking water, soil and dust. The objective of this study is to characterize and compare metal exposures in "Thinking Zinc" participants of the Navajo Nation. Thinking Zinc is an intervention trial to assess the effect of dietary zinc supplementation to mitigate the toxicity of metal exposures. Urinary metal analysis finds Thinking Zinc study participants with elevated levels of uranium approximately 4-fold greater than those detected in the general US population. Of 15 metals tested, 4 had at least 10% of the participants above the National Health and Nutrition Examination Survey (NHANES) 95th percentile. Interestingly, the median values of multiple metals were lower in the Thinking Zinc group compared to the Navajo Birth Cohort Study. Urinary metals differences were observed between the two study locations, Red Water Pond Road and Blue Gap/Tachee. Many metals show substantial fluctuations over time, with greater differences detected in urinary versus serum metals. Median total urinary arsenic concentrations in Thinking Zinc participants are similar to values in NHANES, although there are distinct differences in arsenic forms suggesting changes in metabolic outcomes for arsenic in the Navajo population. These findings highlight that certain metals exposures related to legacy uranium mine waste are elevated compared to NHANES in studies conducted on the Navajo Nation and that specific metals exposures may differ between Navajo communities. The finding of toxic metal fluctuations over time may ultimately inform additional strategies to reduce exposures through behavioral interventions.

Why Zinc?

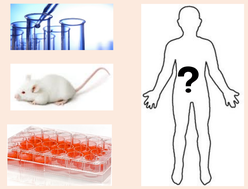
Zinc-binding proteins regulate many aspects of cell function.

"Zinc Finger" Mallery Quetawki

Certain metals displace zinc in proteins*.

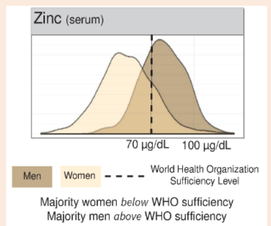


Zinc is protective in peptide, protein, cell and animal models*.



*>40 bench research publications by UNM METALS researchers.

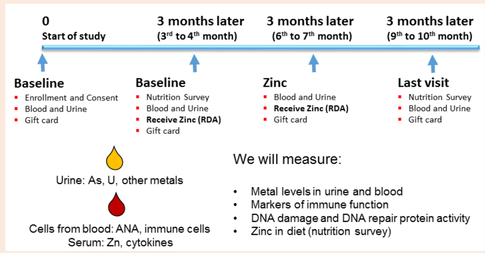
Range of serum zinc levels in NBCS population



- Low serum zinc is associated with increased DNA damage increased inflammatory cytokines in non-indigenous populations[1-4].
- Higher urinary arsenic is associated with increased oxidative stress which induces DNA damage [6].

Overall Question and Study Design

Question: Will findings of zinc benefit from experimental models be applicable to an human population with environmental metal exposures?



Inclusion criteria:
- Men or women between the ages of 21-64
- Current resident of the Navajo Nation.
- Willing to provide blood and urine samples on scheduled study dates.
- Willing to take a daily zinc supplement.

Exclusion criteria:
- Women who are pregnant or nursing or women who plan to become pregnant .
- Diagnosed diabetes.
- Known or suspected allergy to zinc.
- Diagnosed syndrome of copper homeostasis.
- Individuals consuming zinc supplements or multivitamins and are unwilling to stop for the duration of the study.

Table 1. Demographic Data for Thinking Zinc

	Total study	Red Water Pond Road	Blue Gap/Tachee
Number of participants	52	37	15
Male	18	12	6
Female	34	25	9
Median Age	54.5	51	56
Range	21-64	21-64	23-62

Preliminary Biomonitoring Results

Urinary metals concentrations for several metals, including uranium are higher than national averages (i.e. NHANES) and higher than observed for Navajo Birth Cohort Study

Table 2. Thinking Zinc Participant Pre-Zinc Urinary Metal Levels

Metal	Median	Range	%>95th percentile NHANES/NBCS	NHANES 50th	NHANES 95th	NBCS 50th	NBCS 95th
Antimony	0.059	0.006 – 1.540	10%/1.1%	0.046	0.151	0.077	0.964
Arsenic	4.305	0.893 – 135.014	2.22%/3.33%	5.62	56.2	5.392	16.81
Barium	1.012	0.025 – 437.227	3.3%/1.1%	1.24	4.83	3.903	27.9
Beryllium	0.002	0.000 – 0.047	NA/4.4%	<LOD	<LOD	0.011	0.014
Cadmium	0.137	0.009 – 1.207	3.3%/12.2%	0.188	0.882	0.096	0.44
Cesium	2.994	0.055 – 25.151	4.4%/1.1%	4.22	10.4	4.675	16.771
Cobalt	0.292	0.019 – 4.794	5.6%/2.2%	0.404	1.2	1.012	2.522
Lead	0.156	0.003 – 3.605	6.7%/3.3%	0.315	1.14	0.306	1.884
Manganese	0.096	0.002 – 2.33	8.9%/0%	0.209	0.487	0.244	6.89
Molybdenum	18.345	0.363 – 130.684	1.1%/0%	36.3	94.7	55.193	245
Platinum	0.0149	0.000 – 0.398	22.2%/26.7%	<LOD	0.035	0.007	0.03
Strontium	75.711	0.961 – 3100.765	7.8%/2.2%	101	266	185	696.056
Tin	0.741	0.010 – 14.605	10%/0%	0.431	3.06	2.07	20.975
Tungsten	0.027	0.002 – 0.193	0%/0%	0.061	0.279	0.137	1.276
Uranium	0.022	0.002 – 19.162	39%/10%	0.005	0.026	0.016	0.109
Vanadium*	0.137	0.019 – 28.837					

Median metal levels are shown for Visit 1 and Visit 2 samples (n = 90) 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

Preliminary Results (cont.)

Table 3. Metals comparisons between cohorts

	Red Water Pond Road (n=67)		Blue Gap/Tachee (n=23)	
Metal	**Median**	**Range**	**Median**	**Range**
Urinary µg/g creatinine (n=90)				
Antimony	0.073	0.020 – 1.540	0.02	0.006 – 0.080
Arsenic	4.31	1.235 – 135.014	4.275	0.893 – 10.573
Cadmium	0.163	0.031 – 1.207	0.057	0.009 – 0.359
Cobalt	0.393	0.040 – 4.794	0.169	0.019 – 1.327
Manganese	0.091	0.002 – 2.328	0.099	0.003 – 0.752
Platinum	0.014	0.000 – 0.398	0.015	0.007 – 0.128
Uranium	0.02	0.002 – 19.162	0.041	.003 – 0.376
Vanadium*				

Metals levels are shown for Visit 1 and 2 samples collected before zinc supplementation.
*Measurement of metal level is incomplete so cohort comparison is not possible at this time.

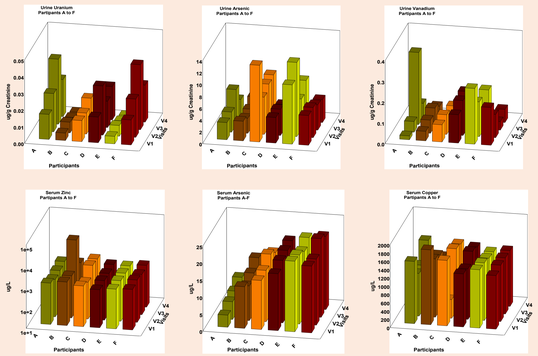


Figure 1: Biomonitoring data reveals fluctuations in urinary levels of uranium, vanadium and arsenic exposure. Thinking Zinc participants showed variability in urinary metal levels over longitudinal biomonitoring with episodic higher dose exposures. Less fluctuations are seen in serum metals levels.

Table 4. Urinary Arsenic and Metabolites in Thinking Zinc Participants

	Pre-Zinc		*Post-Zinc*		NHANES Median
As Form	N	Median (ug/L) [IQR]	N	Median (ug/L) [IQR]	
Total As	32	6.470 [4.322 - 10.562]	28	4.447 [3.385 - 6.042]	5.74
AsIII	32	0.401 [0.299 - 0.690]	28	0.346 [0.274 - 0.588]	0.12
MMA	32	0.987 [0.603 - 1.30]	28	0.889 [0.661 - 1.571]	0.28
DMA	32	3.864 [2.313 - 5.680]	28	2.477 [1.879 - 3.385]	2.95

Legend: Values for urinary arsenic species and metabolites were determined though ICP-MS analysis conducted at the Arizona Laboratory for Emerging Contaminants for a subset of participants enrolled in Thinking Zinc. AsIII (arsenite); MMA (monomethyl-arsinic acid); DMA (dimethylarsinic acid).

Acknowledgements

We thank the communities contributing to and supporting this work!
Navajo communities of Red Water Pond Road Blue Gap-Tachee Chapter
Tachee Uranium Concerns Committee & Laguna Pueblo

Approvals: The study Thinking Zinc is approved by the University of New Mexico Institutional Review Board (#18-381) in December 2018 and by the Navajo Nation Human Research Review Board (# NNR 18-330) in January 2019
Funding: NIEHS P42 ES025589
Additional Funding from: CDC U01 TS000135 (NBCS), NIEHS & NIMHD P50ES026102 (Native EH Equity), USEPA 83615701 (Native EH Equity Center)
UNM Comprehensive Cancer Center NCI P30CA11810
UNM College of Pharmacy

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