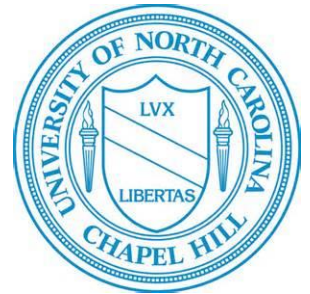


Epigenetic effects of arsenic and other toxic metals

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Curriculum in Toxicology



- What is known about toxic metals and their impact on the epigenome?
- Can we integrate epigenetic data into the risk assessment framework?
- What research gaps exist related to our understanding of toxic metal-epigenome relationships?

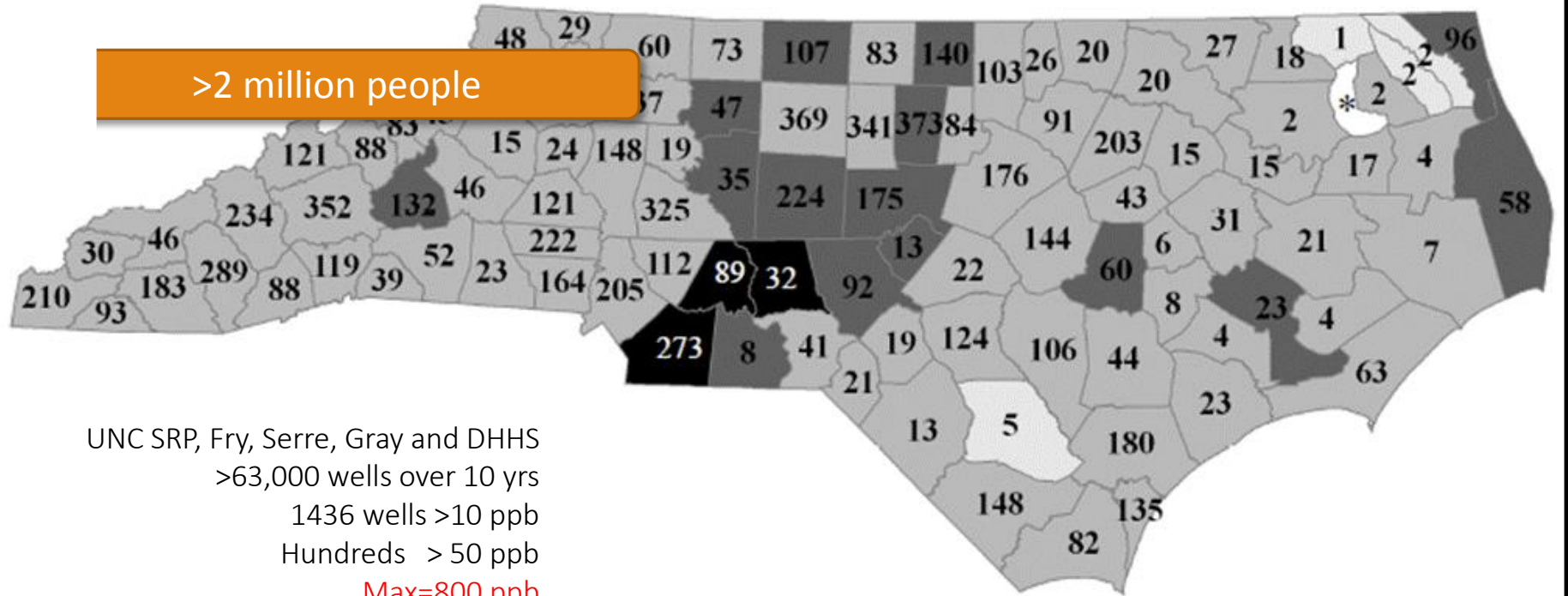
Arsenic: continues to poison the water of millions around the globe



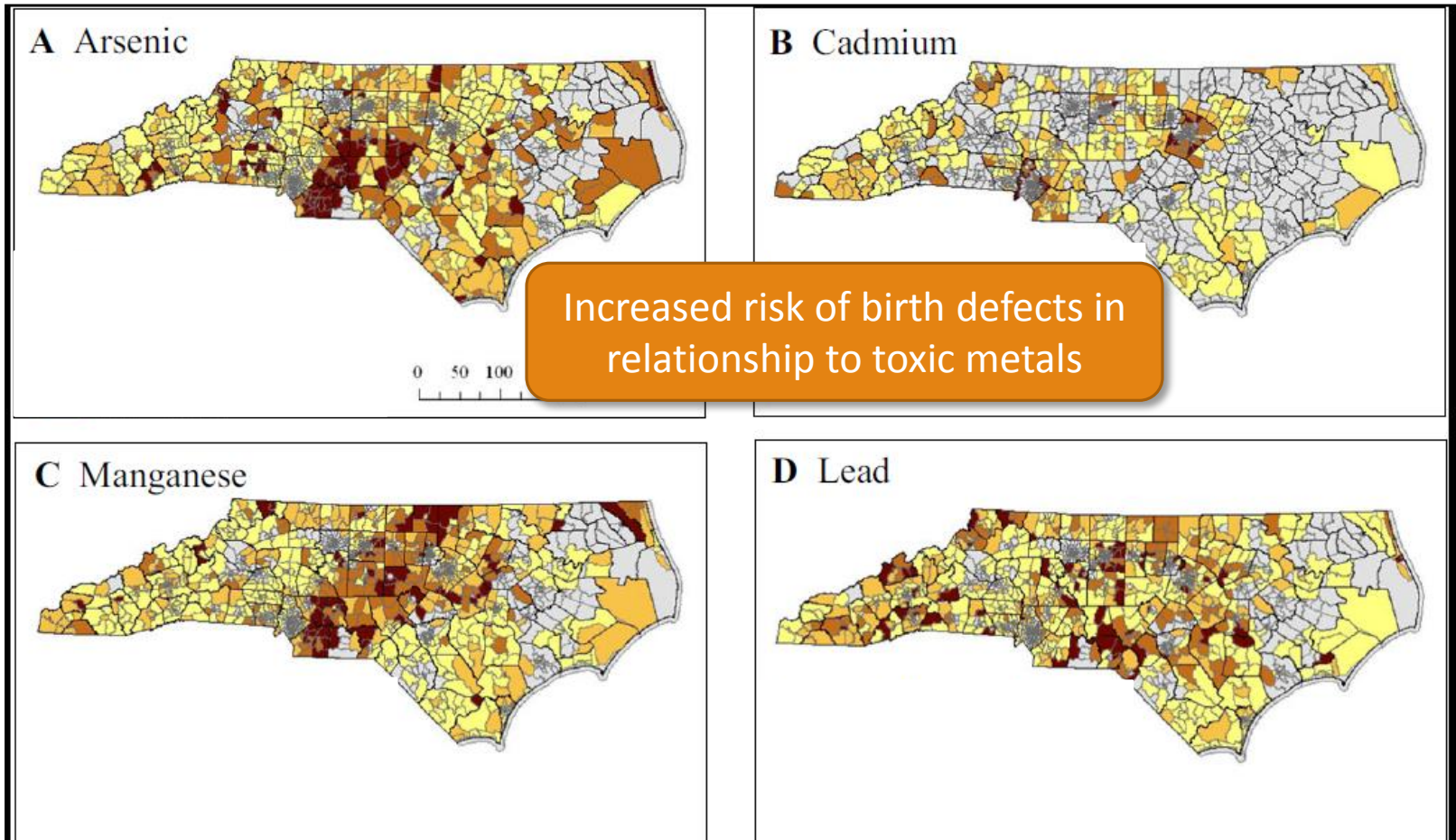
Smedley, Pauline L.. 2008 Sources and distribution of arsenic in groundwater and aquifers. In: Appelo, Tony, (ed.) *Arsenic in Groundwater : a World Problem*. British Geological Survey
EPA limit 10 ppb

Arsenic and other toxic metals are contaminating the water of residents in North Carolina

>2 million people



Arsenic and other toxic metals are contaminating the water of residents in North Carolina



Sanders et al. BMC Public Health 2014

Arsenic: continues to poison the water of millions around the globe

Research | Children's Health

A Section 508–conformant HTML version of this article is available at <http://dx.doi.org/10.1289/ehp.1307476>.

Maternal Arsenic Exposure, Arsenic Methylation Efficiency, and Birth Outcomes in the Biomarkers of Exposure to ARsenic (BEAR) Pregnancy Cohort in Mexico

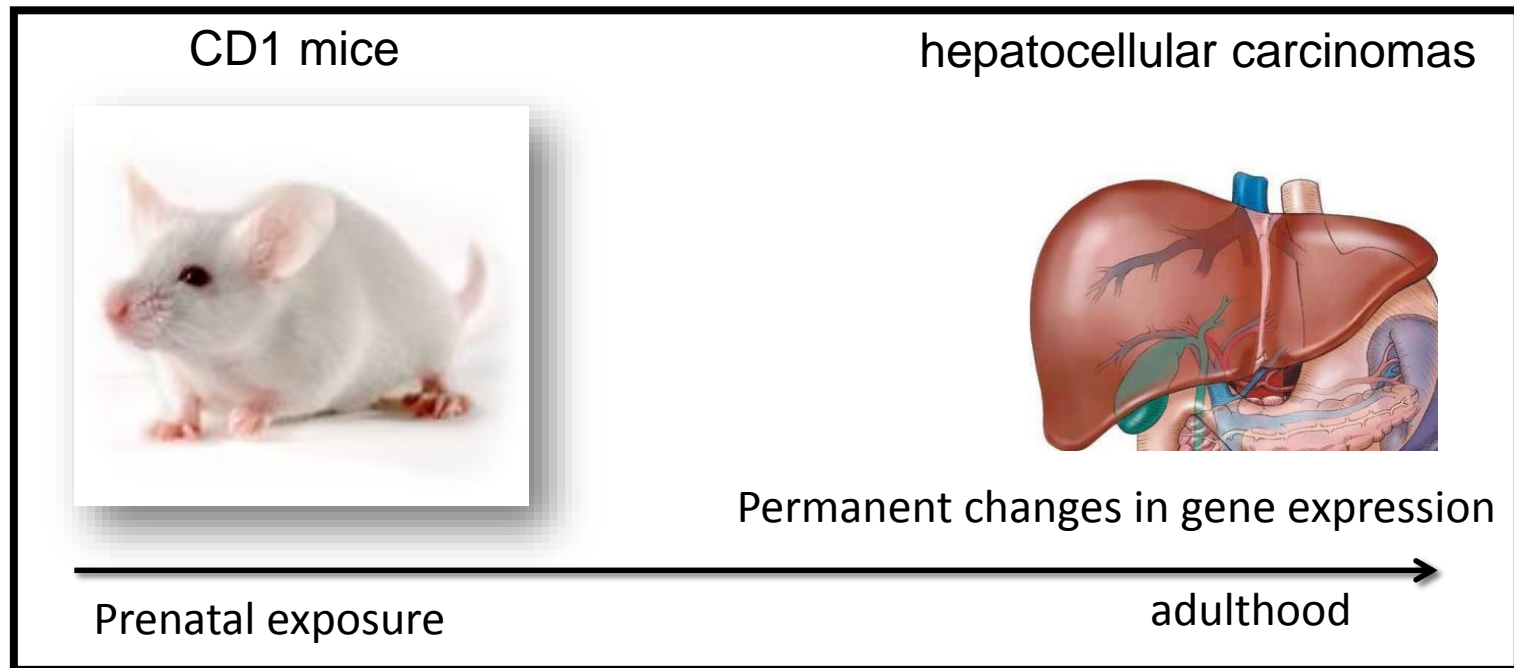
Jessica E. Laine,¹ Kathryn A. Bailey,² Marisela Rubio-Andrade,³ Andrew F. Olshan,^{1,4} Lisa Smeester,² Zuzana Drobná,⁵ Amy H. Herring,^{4,6} Miroslav Stýblo,^{2,5} Gonzalo G. García-Vargas,³ and Rebecca C. Fry²

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Lower birthweight in relationship to prenatal arsenic exposure

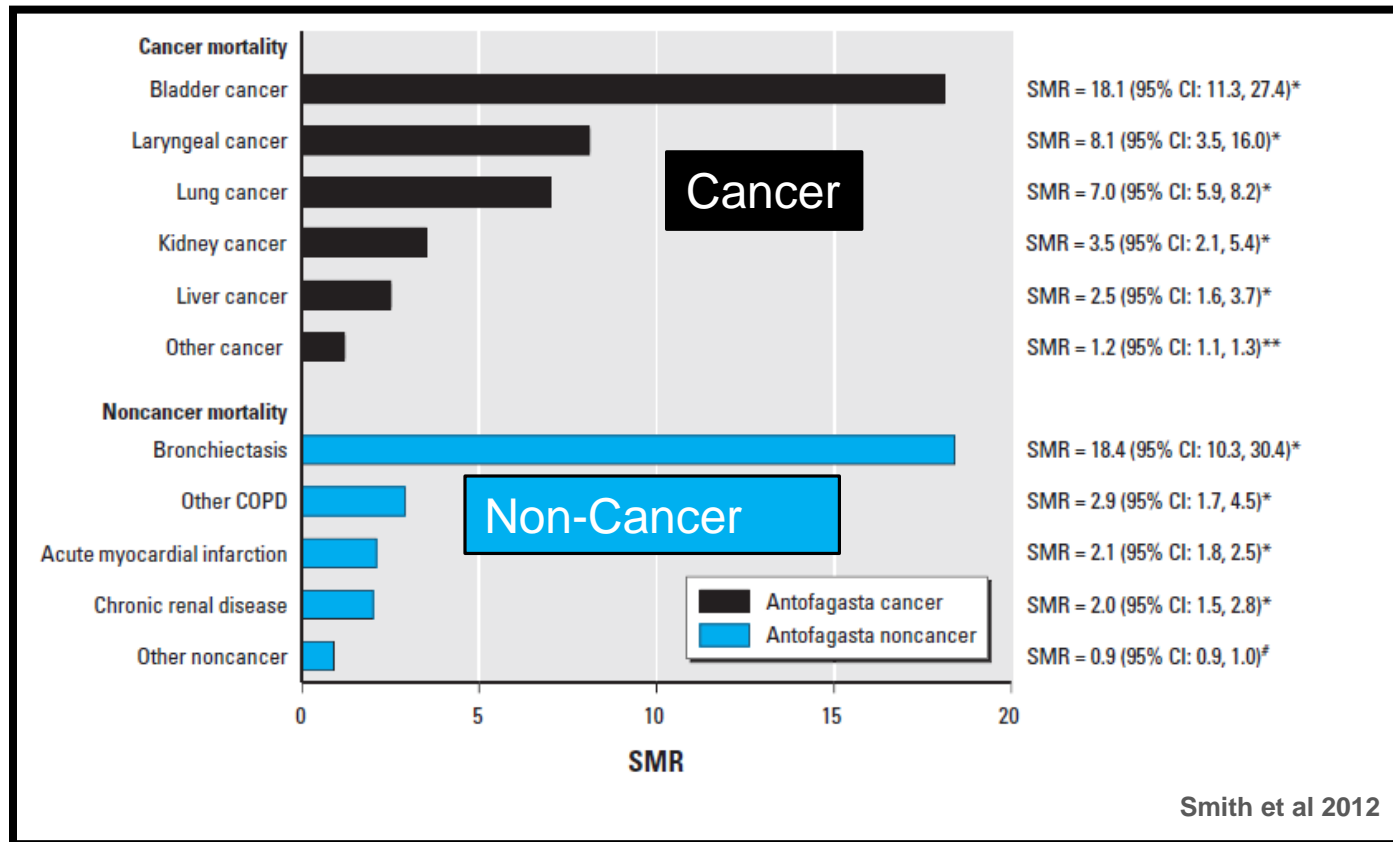


Early life exposures associated with both short and long term health effects



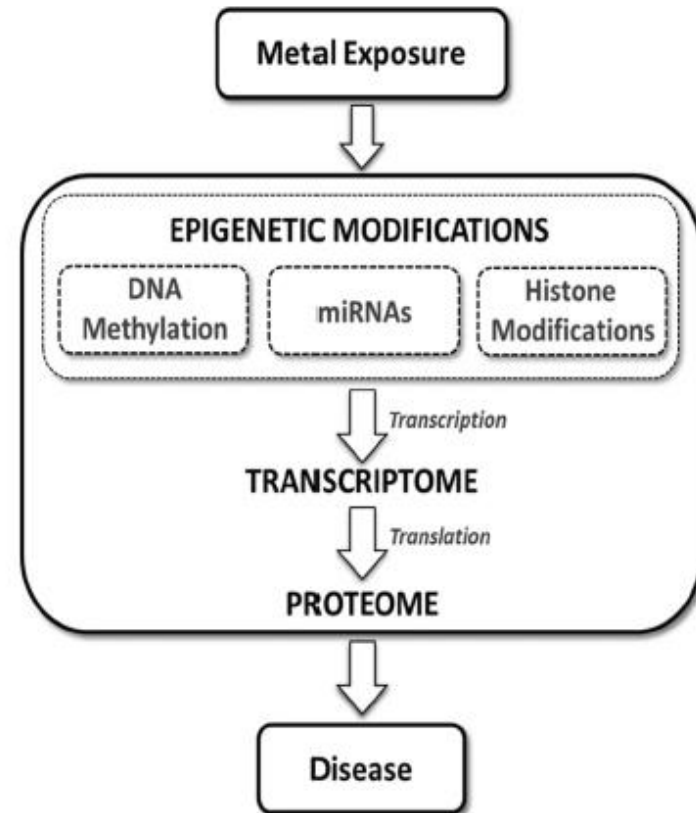
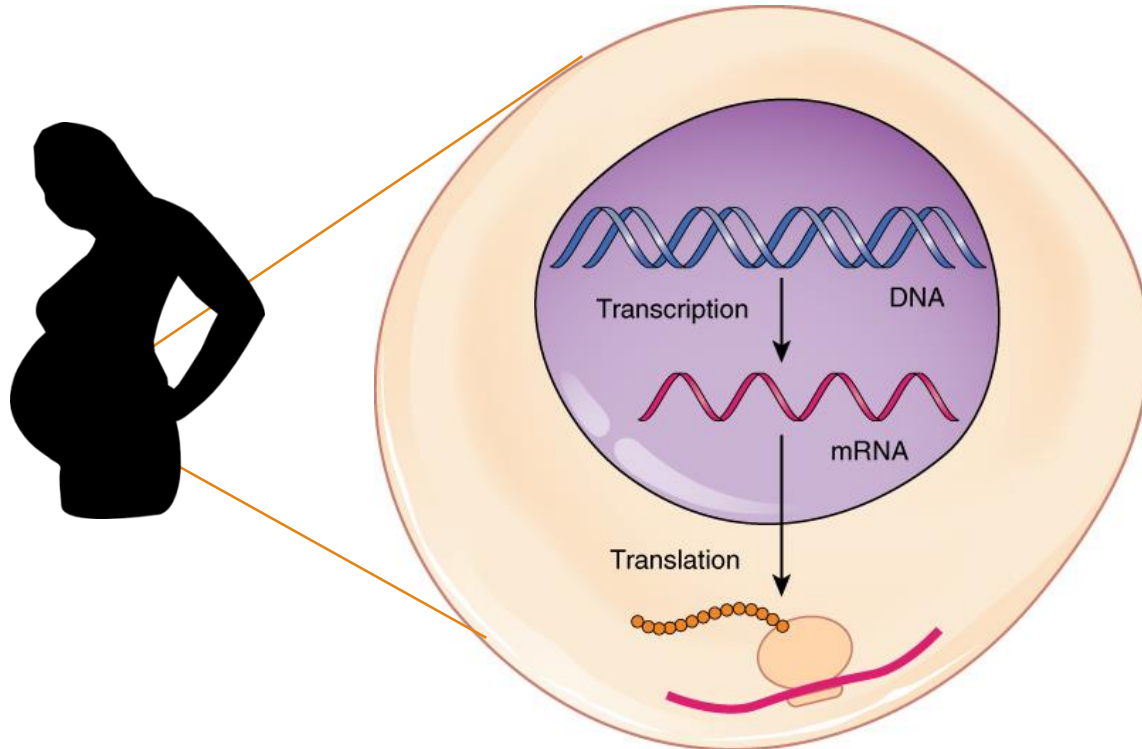
Waalkes, M. et al 2004. Xie, Y. et al, 2007.

Prenatal and early life exposure to inorganic arsenic is associated with adult onset disease



Does prenatal arsenic exposure alter the fetal epigenome?

DNA methylation, miRNA and protein expression are altered, links to immune response and lower birthweight



Ray et al. Frontiers in Genetics 2014

Rojas et al. Tox Sci 2015

Laine et al. EHP 2015

Rager et al. Tox Sci 2014

Bailey et al. Tox Sci 2014



Incorporating epigenetic data into the risk assessment process for the toxic metals arsenic, cadmium, chromium, lead, and mercury: strategies and challenges

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Risk assessment process:

Defining associations between health outcomes and exposure.

To determine levels of exposure at which negative health outcomes associated with the exposure are minimized.

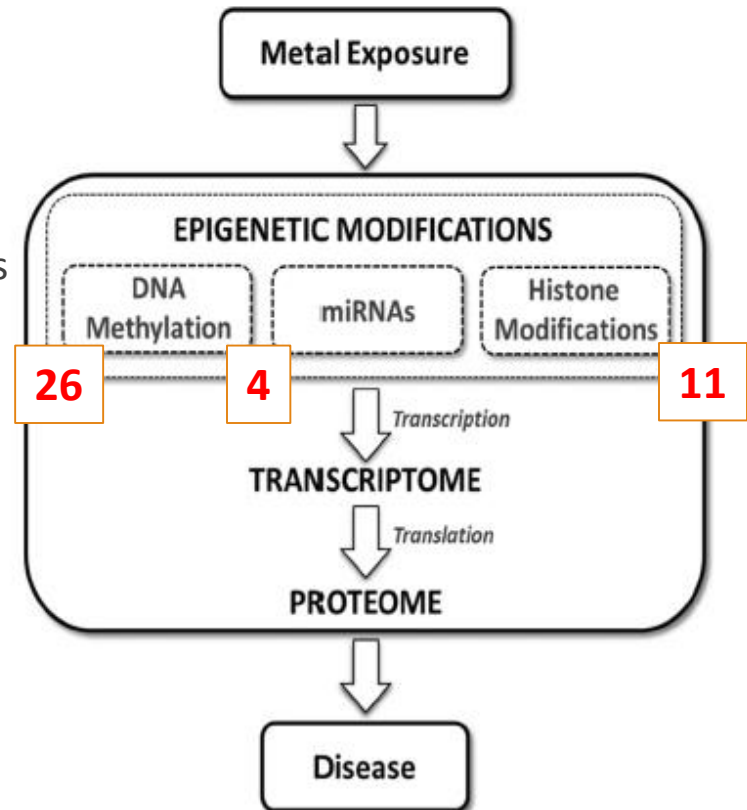
Epigenetics-Risk Assessment

- *Inform understanding of **biological mechanisms and mode of action** of contaminant-disease relationships
- *Include epigenetic modification in **dose-response estimates** between contaminant and disease
- *Potential to be used as both **biomarkers of exposure and effect**
- *Predict inter-individual differences in outcomes **responders and non-responders** to exposure

Arsenic

In vitro: lung, liver, colon, prostate, skin, urothelial cells

Human samples: bladder tumors, blood

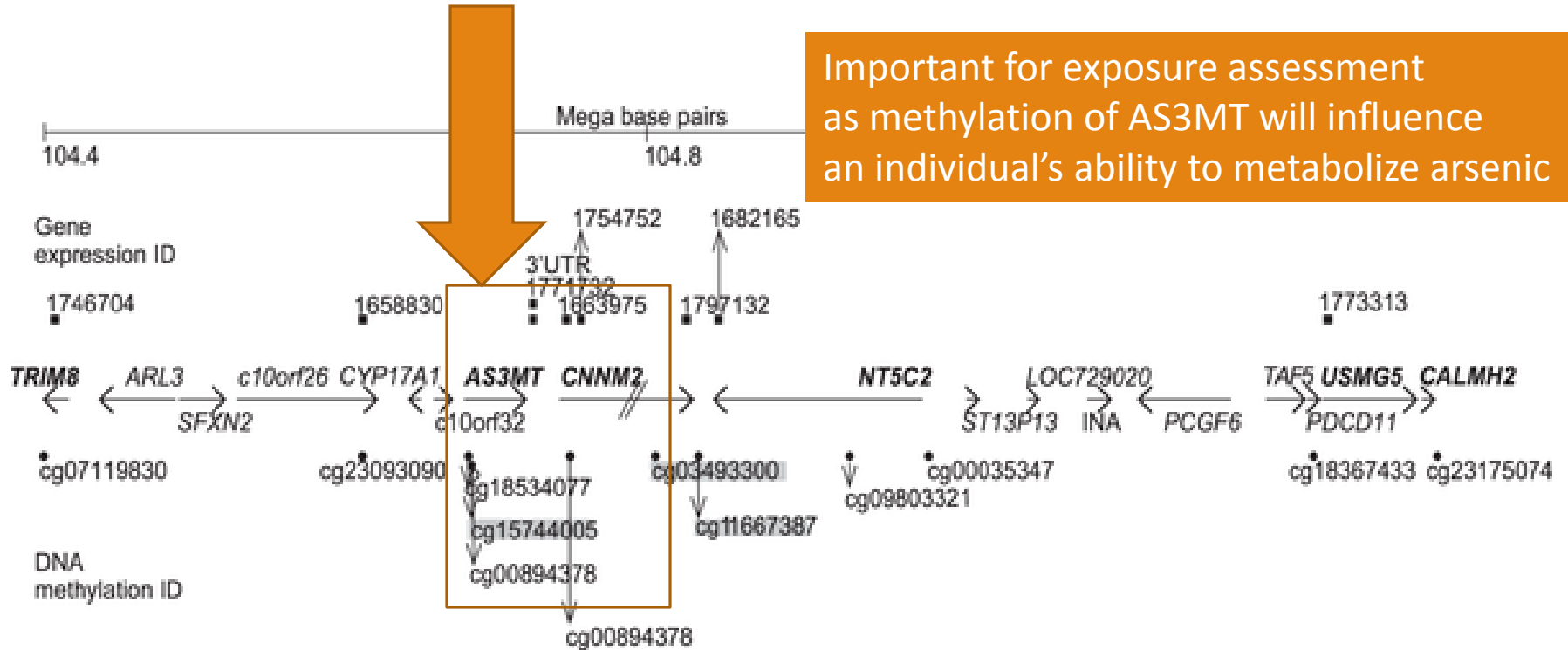


Key genes with altered functionality associated with epigenetic modifications:

Tumor suppressors: **P53, P16, RASSF1A**

Are there genes with altered CpG methylation that play a role in contaminant metabolism?

AS3MT methylation: Associated with gene expression



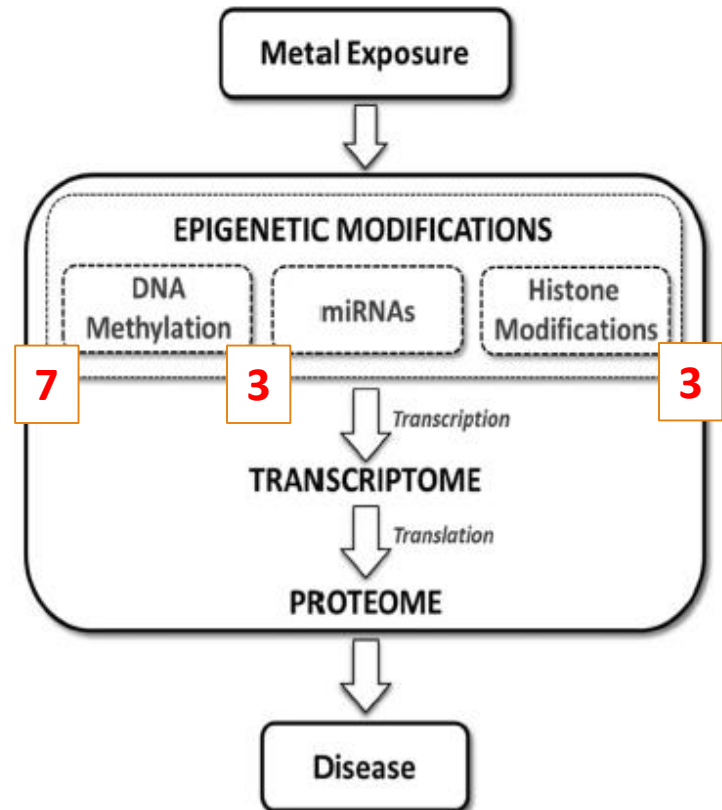
Engström KS, Hossain MB, Lauss M, Ahmed S, Raqib R, et al. (2013) Efficient Arsenic Metabolism — The AS3MT Haplotype Is Associated with DNA Methylation and Expression of Multiple Genes Around AS3MT. PLoS ONE 8(1): e53732. doi:10.1371/journal.pone.0053732

<http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0053732>

Cadmium

In vitro: prostate, leukemia, lung, prostate

Human samples: blood



Key genes with altered functionality associated with epigenetic modifications:

Tumor suppressors and DNA repair: **P16, RASSF1A, MSH2**

Can we identify biological mechanisms that explain how contaminants target specific genes for altered CpG methylation ?

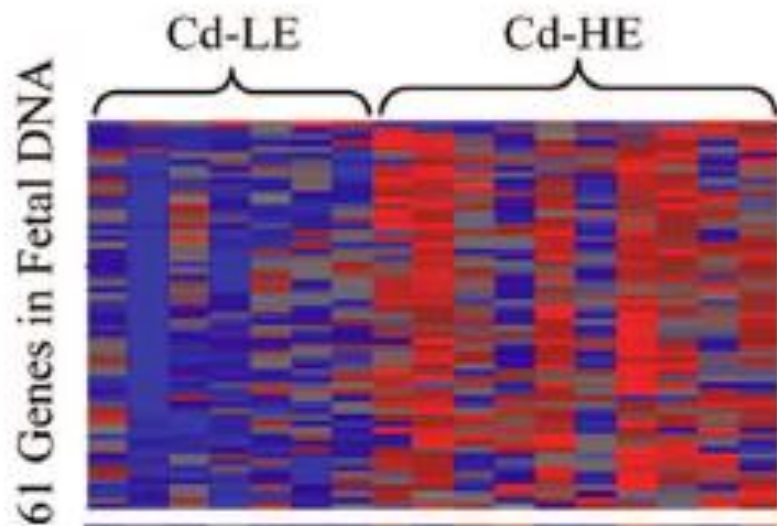
Cadmium exposure and the epigenome

Exposure-associated patterns of DNA methylation in leukocytes from mother-baby pairs

Alison P Sanders^{1,†,‡}, Lisa Smeester^{1,†,‡}, Daniel Rojas², Tristan DeBussycher³, Michael C Wu⁴, Fred A Wright⁴, Yi-Hui Zhou⁴, Jessica E Laine⁵, Julia E Rager¹, Geeta K Swamy⁶, Allison Ashley-Koch⁷, Marie Lynn Miranda⁸, and Rebecca C Fry^{1,2}

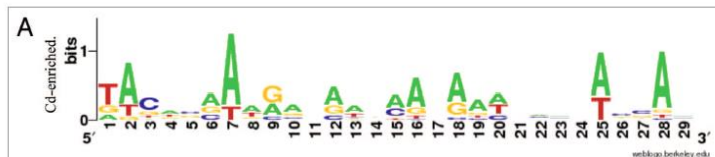
¹Department of Environmental Sciences and Engineering; Gillings School of Global Public Health; University of North Carolina; Chapel Hill, NC USA; ²Curriculum in Toxicology; School of Medicine; University of North Carolina; Chapel Hill, NC USA; ³Center for Bioinformatics; University of North Carolina; Chapel Hill, NC USA; ⁴Department of Biostatistics; Gillings School of Global Public Health; University of North Carolina; Chapel Hill, NC USA; ⁵Department of Epidemiology; Gillings School of Global Public Health; University of North Carolina; Chapel Hill, NC USA; ⁶Department of Obstetrics and Gynecology; Duke University; Durham, NC USA; ⁷Center for Human Genetics; Duke University Medical Center; Durham, NC USA; ⁸School of Natural Resources and Environment; Department of Pediatrics; University of Michigan; Ann Arbor, MI USA

Cd-associated genes with altered CpG methylation are enriched for MTF binding sites



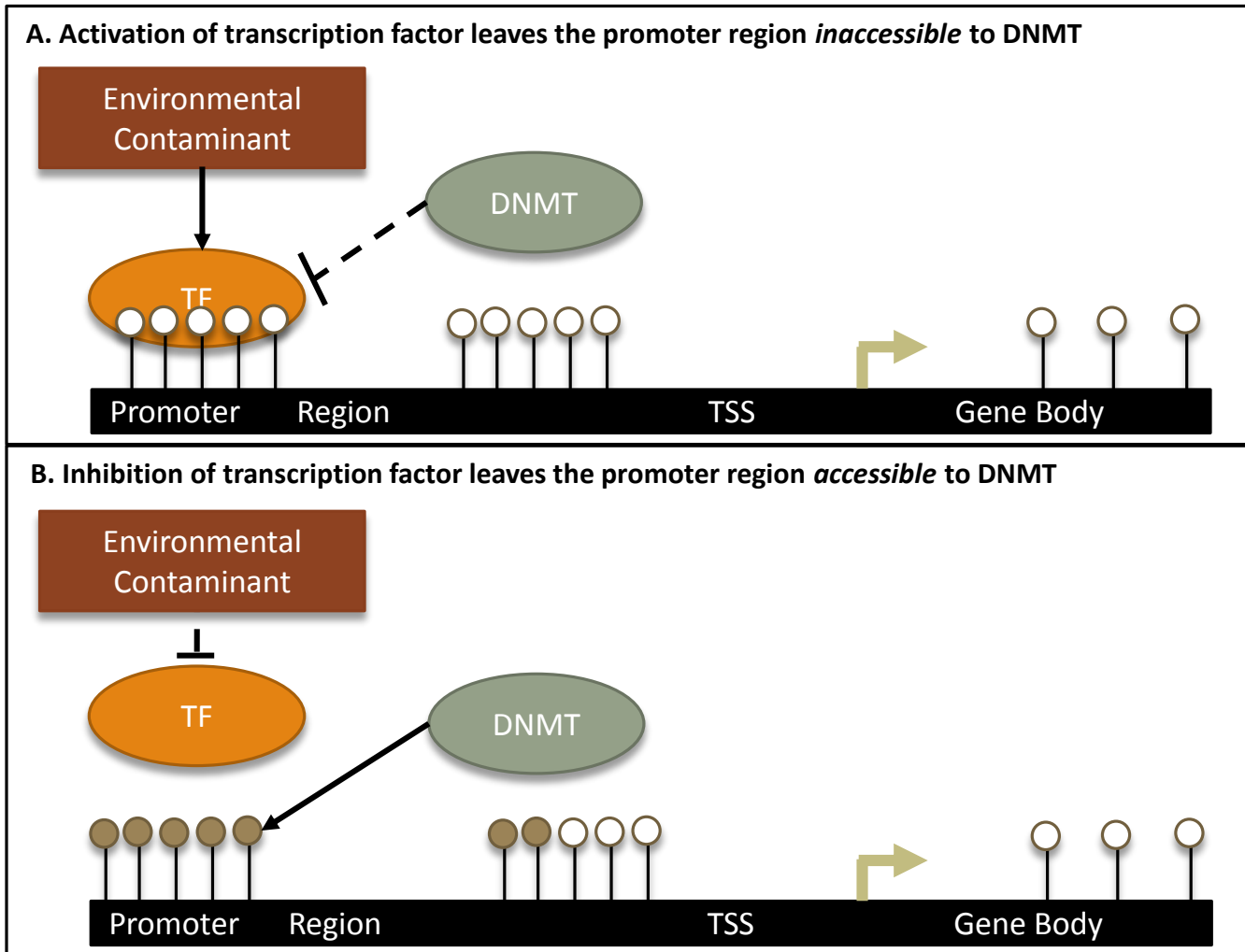
Important for understanding a mechanism by which contaminants may impact specific genes

Metal responsive transcription factor



Transcription Factor	Fetal DNA (p values)	
	Cd ^a	Cotinine ^a
TCFAP2E	$2.3 \times 10^{-5*}$	$9.2 \times 10^{-4*}$
TCF7L1	$6.7 \times 10^{-5*}$	$2.0 \times 10^{-5*}$
SRF	$2.2 \times 10^{-4*}$	$3.2 \times 10^{-4*}$
MTF1	$3.1 \times 10^{-4*}$	$1.6 \times 10^{-4*}$

Transcription factor occupancy theory



Research Gaps

- ❑ Need increased **samples sizes** for human cohort-based studies
- ❑ Need to compare results across different **tissues**, and assess **temporal stability** of changes
- ❑ Need to examine relationship between epigenetic modification and **functional changes in gene or protein expression**
- ❑ Need to examine relationship between epigenetic modifications and **disease**

Conclusions

- ❑ Strong evidence that toxic metals impact the epigenome
- ❑ In many cases these modifications are targeting critical cellular processes (DNA repair machinery, cell cycle control genes, tumor suppressors)
- ❑ The relationship between these changes and functional consequences (changes in gene or protein expression, or cellular response, or health endpoints) is not well established

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Jessica Laine

Sloane Miller

Daniel Rojas, MS

Julia Rager, PhD

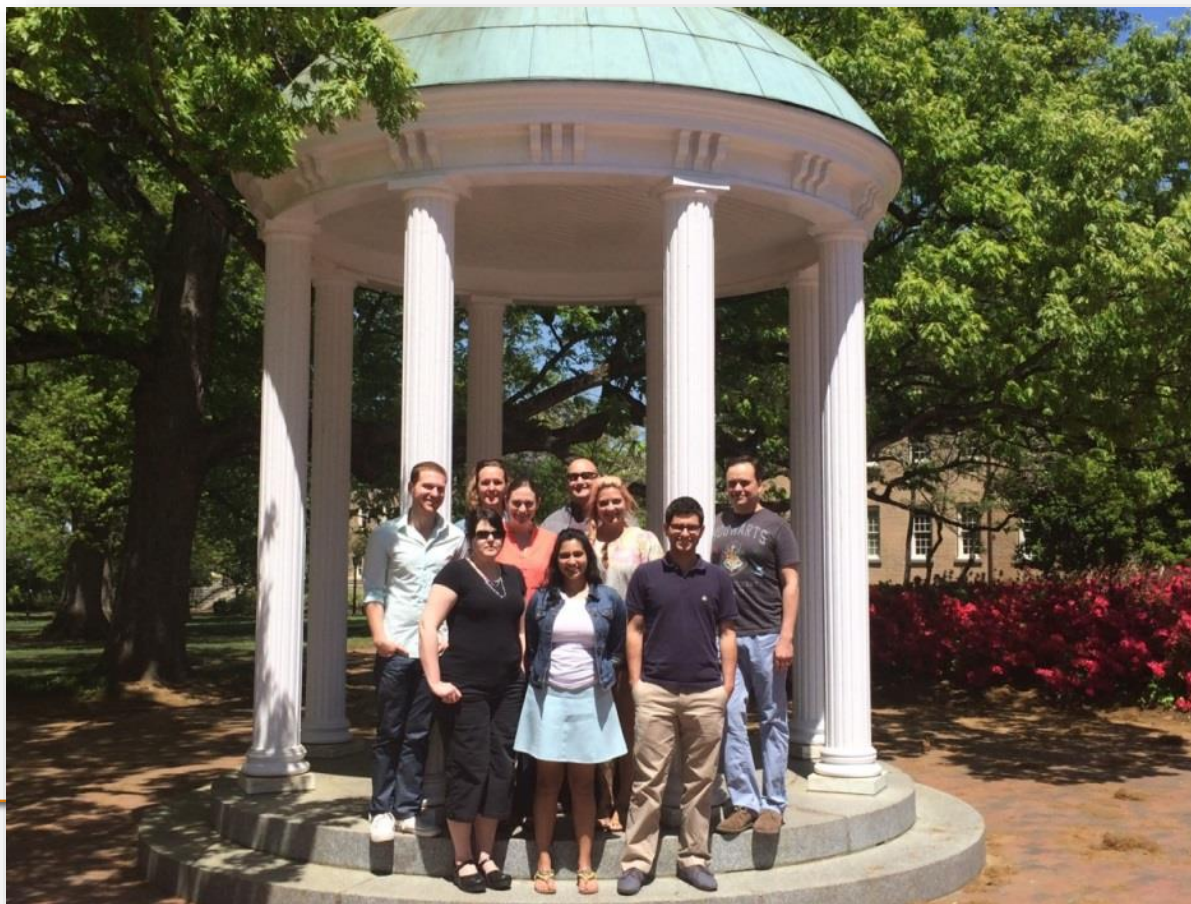
Paul Ray PhD

Alison Sanders, PhD

Elizabeth Martin

Lisa Smeester

Andrew Yosim



Funding

NIEHS Superfund: P42 ES005948

NIEHS (ONES): R01ES019315

NIEHS CEHS UNC: P30ES010126

