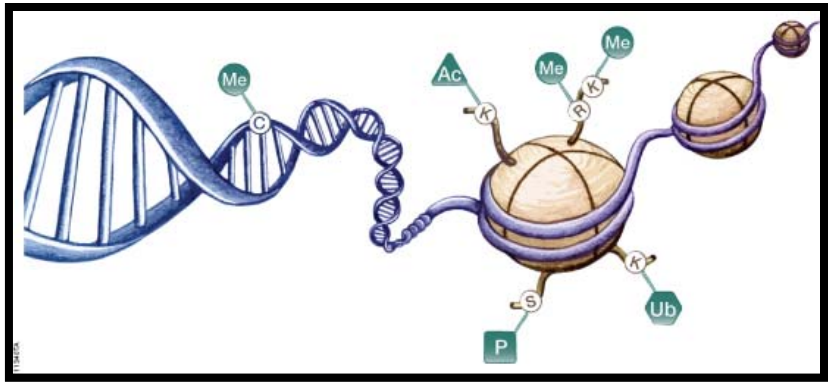
The King of Poisons: Arsenic - Latent Life Health Impacts



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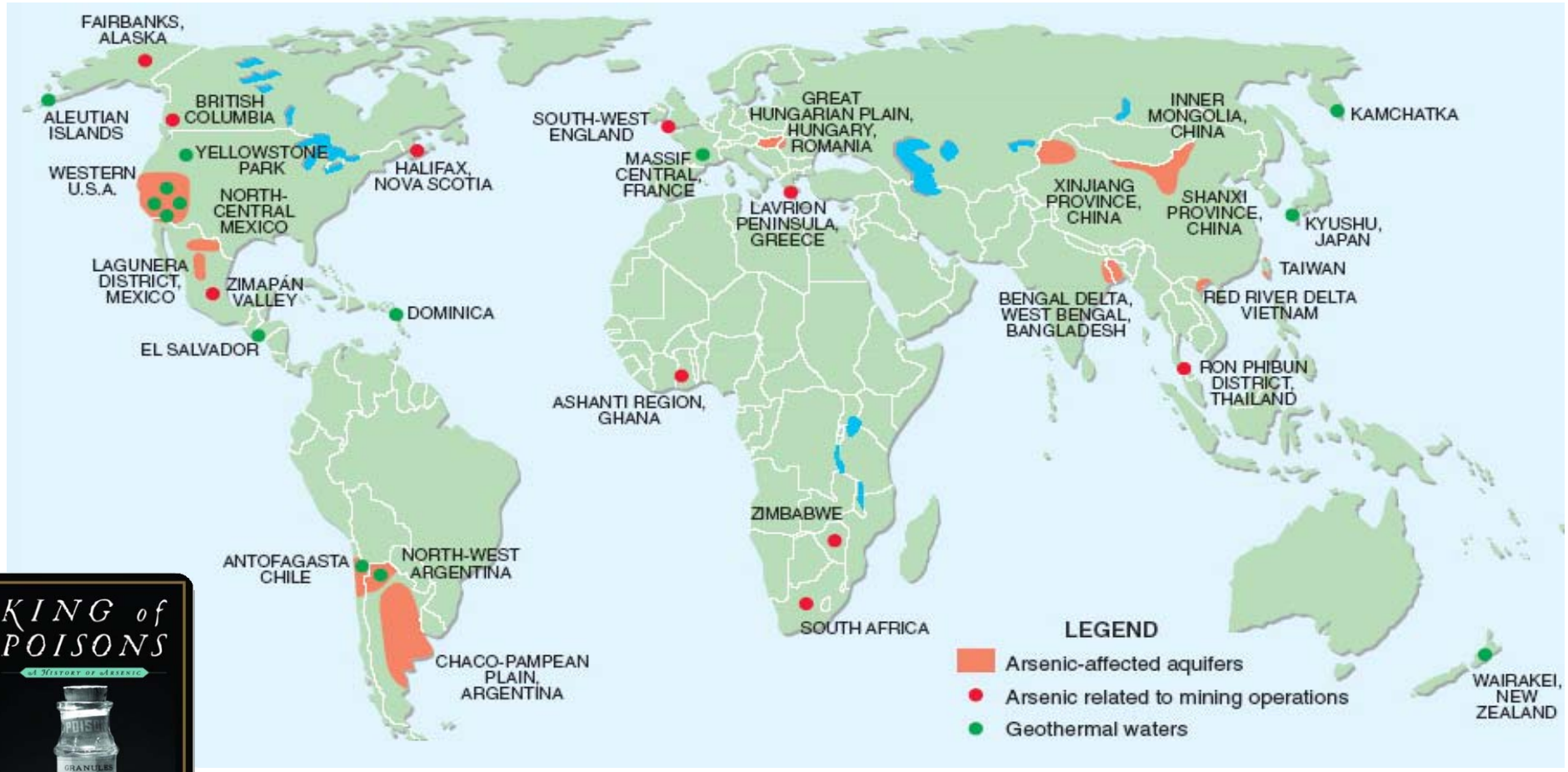
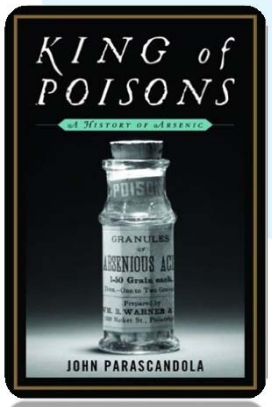
Arsenic, the king of poisons, contaminates the water of millions around the globe





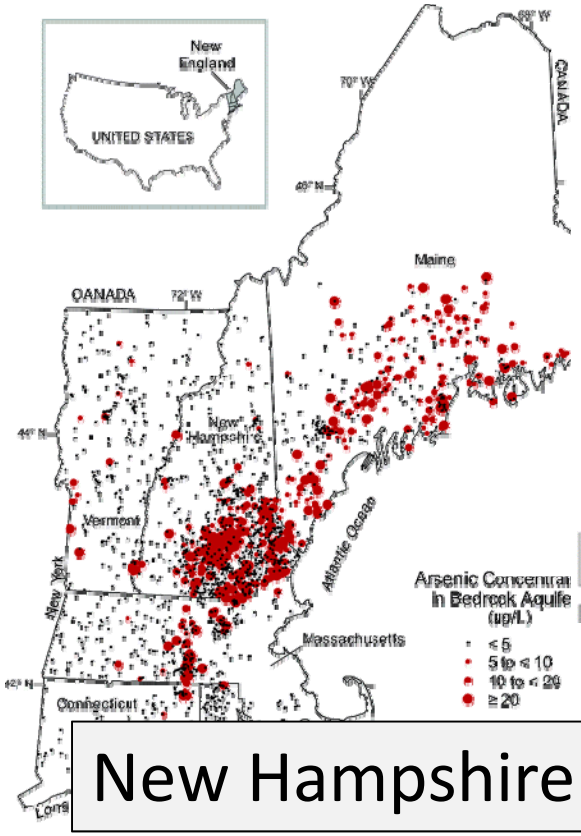
Arsenic, the king of poisons, contaminates the water of millions around the globe

A Sluggish Response to Humanity's Biggest Mass Poisoning

Arsenic-laced water has sickened thousands in South Asia. After delays and false starts, India is addressing the problem with a $500 million safe-water initiative

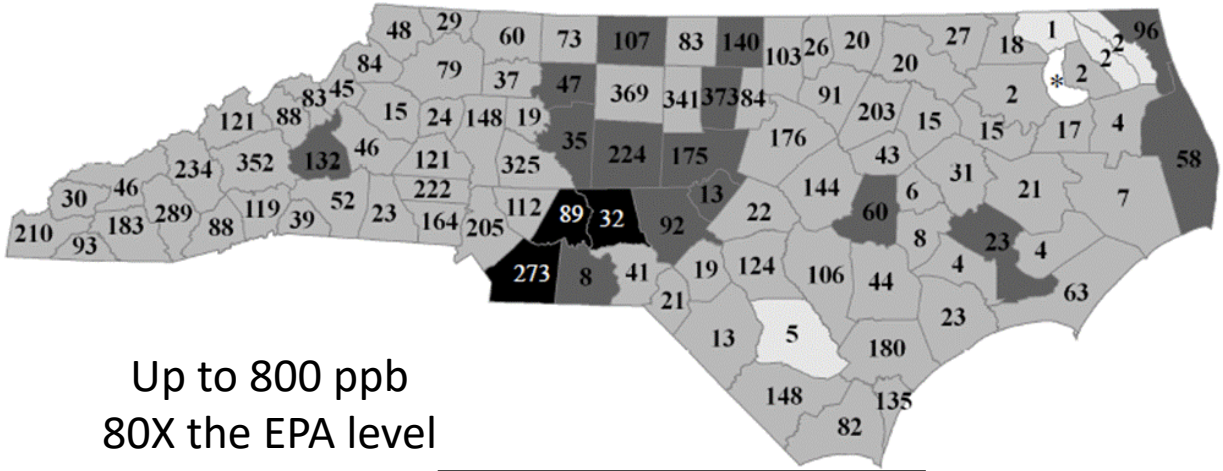
Elevated levels of arsenic in private US drinking wells

50,000 on private wells



New Hampshire

2 million on private wells

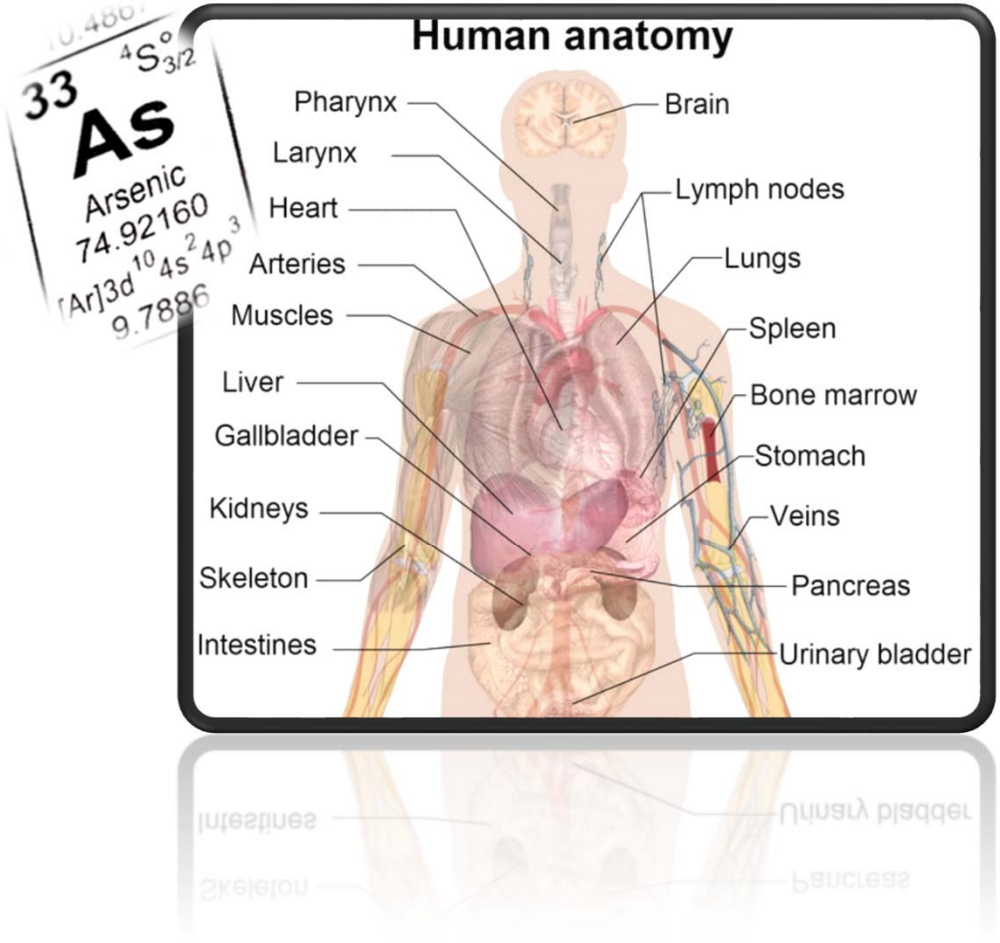


Up to 800 ppb
80X the EPA level

North Carolina

>13 million in US on private drinking wells

Arsenic is associated with both cancer and non-cancer endpoints



- Classified as Group 1 Carcinogen by the International Agency for Research on Cancer (IARC): Chronic exposure results in many cancers: **skin, bladder, lung, liver, prostate and kidney**

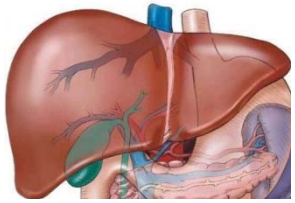
- Exposure is associated with non-cancer endpoints: neurological disorders, reproductive effects, cardiovascular disease, diabetes

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

Mice

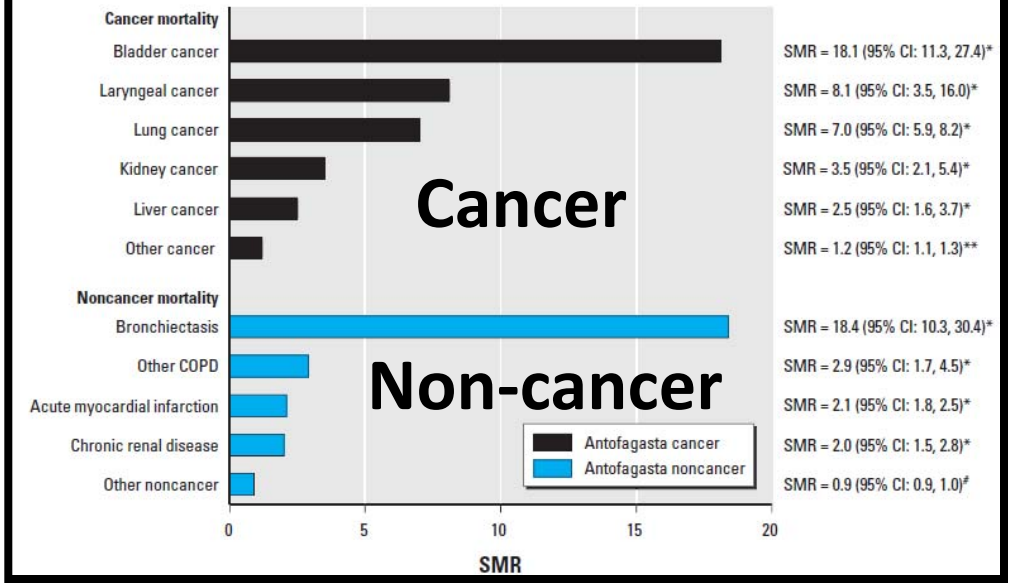
CD1 mice

hepatocellular carcinomas



Prenatal exposure → adulthood

Humans



Smith, A et al 20012

Permanent changes in gene expression

Waalkes, M. et al. Carcinogenesis 2004;
Xie, Y. et al TAP, 2007

Early life expo ort and long

Mice

CD1 mice

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Prenatal exposure

Permanent changes in

Waalkes, M. et al

Model contaminant for DOHAD hypothesis

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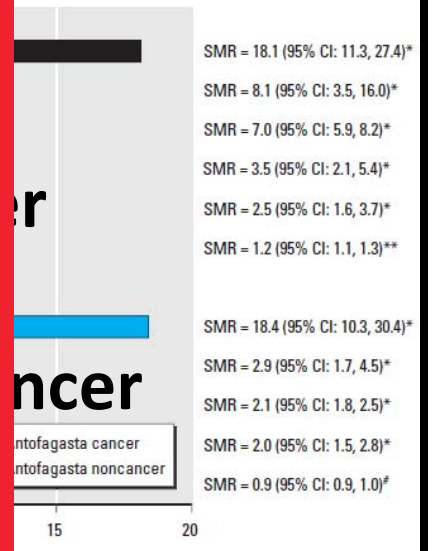


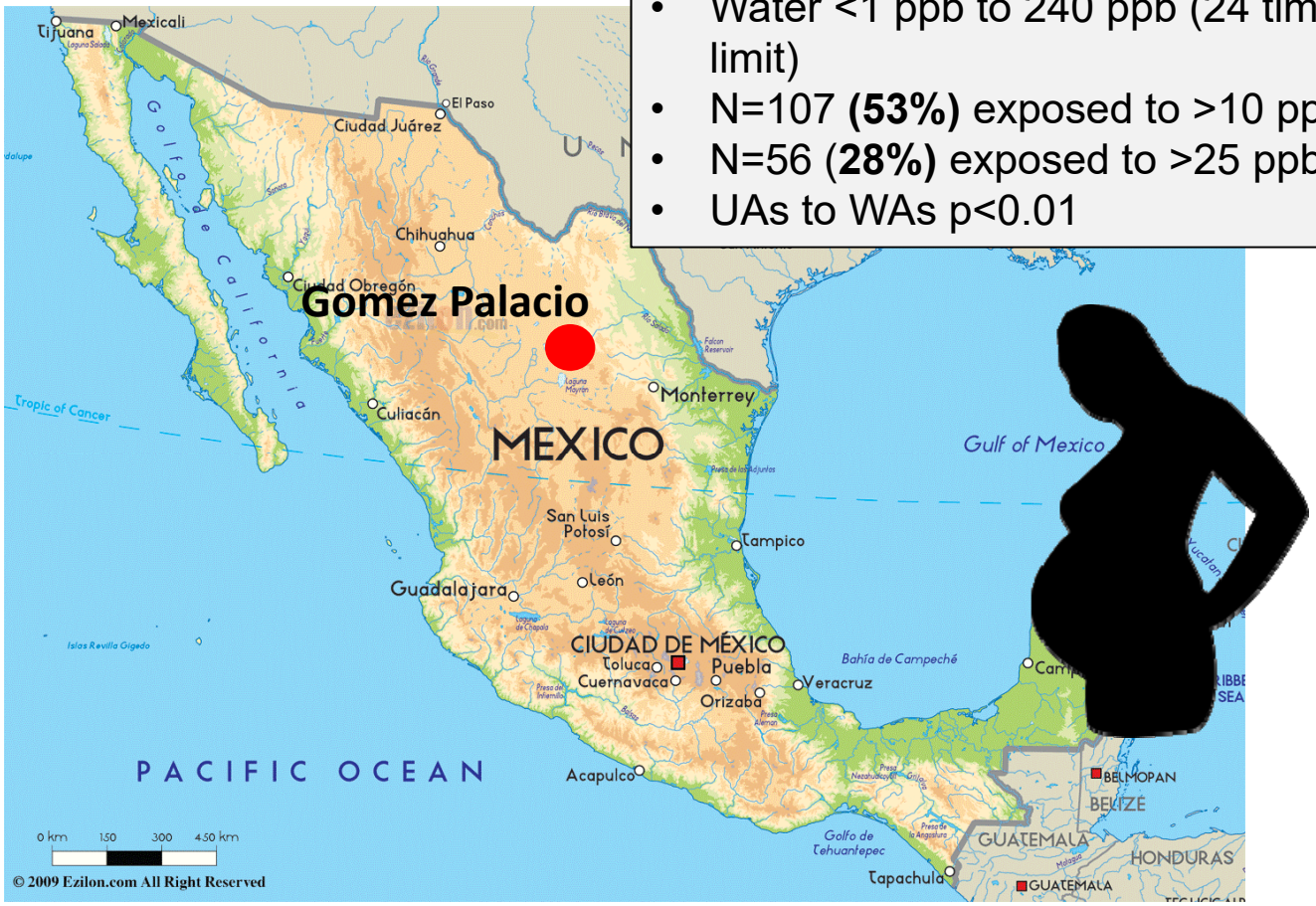
Smith, A et al 20012

What are the health effects of prenatal arsenic exposure and links to the epigenome?

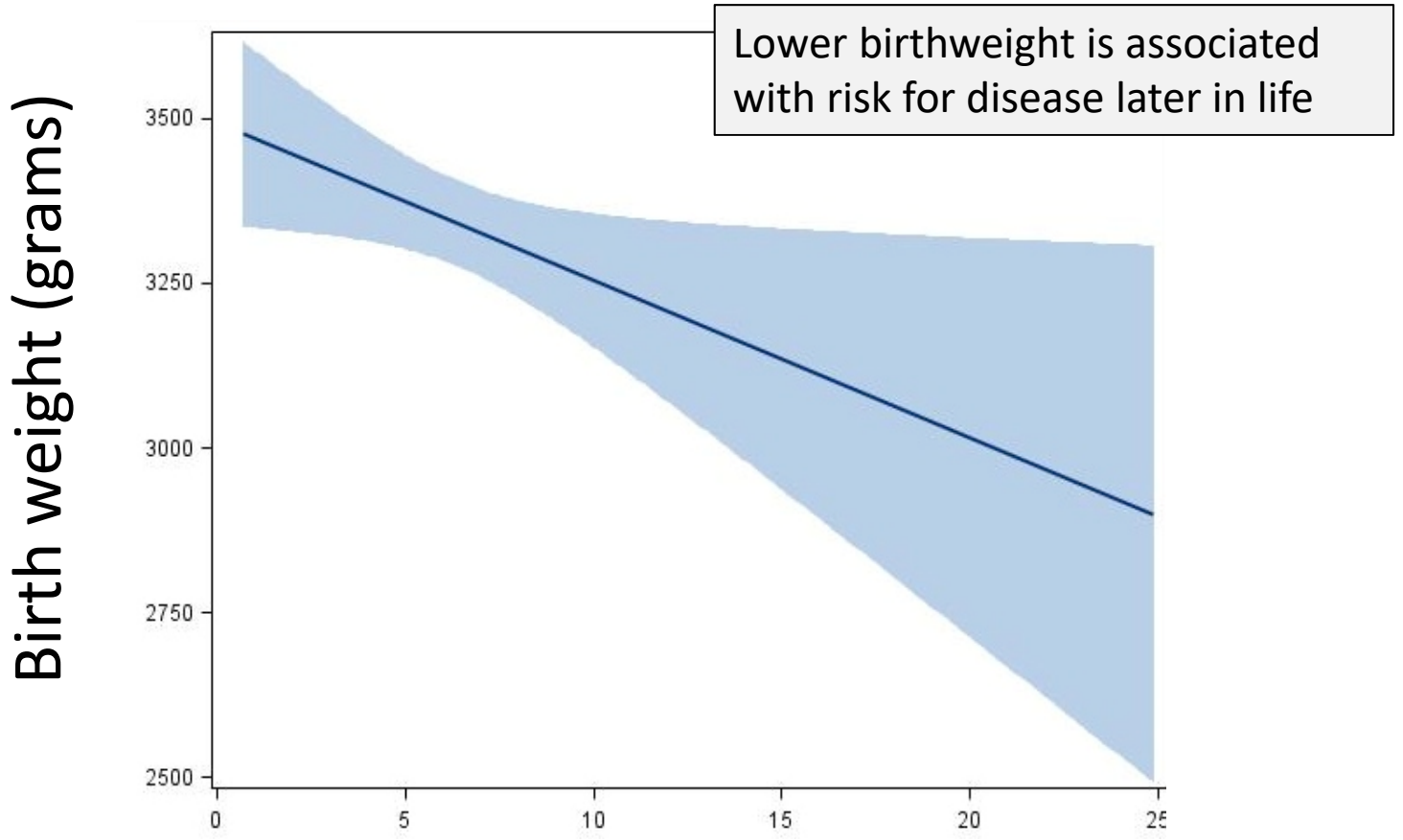
- Recruited 200 pregnant women
- Measured arsenic in drinking water and urine
- Collected cord blood for fetal DNA, RNA, protein isolation
- Measured a serious of birth outcomes

What are the health effects of prenatal arsenic exposure and links to the epigenome?

- Water <1 ppb to 240 ppb (24 times EPA limit)
- N=107 **(53%)** exposed to >10 ppb
- N=56 (**28%**) exposed to >25 ppb
- UAs to WAs p<0.01



Prenatal arsenic exposure is associated with lower birthweight in infants



Laine *et al.* EHP 2015

Huyck *et al.,* JOEM, 2007 (Bangladesh); Kile *et al.* Epidemiology, 2016 (Bangladesh); Fei *et al.* EH, 2013 (US); Hopenhayn *et al.* Epidemiology, 2003 (Chile)

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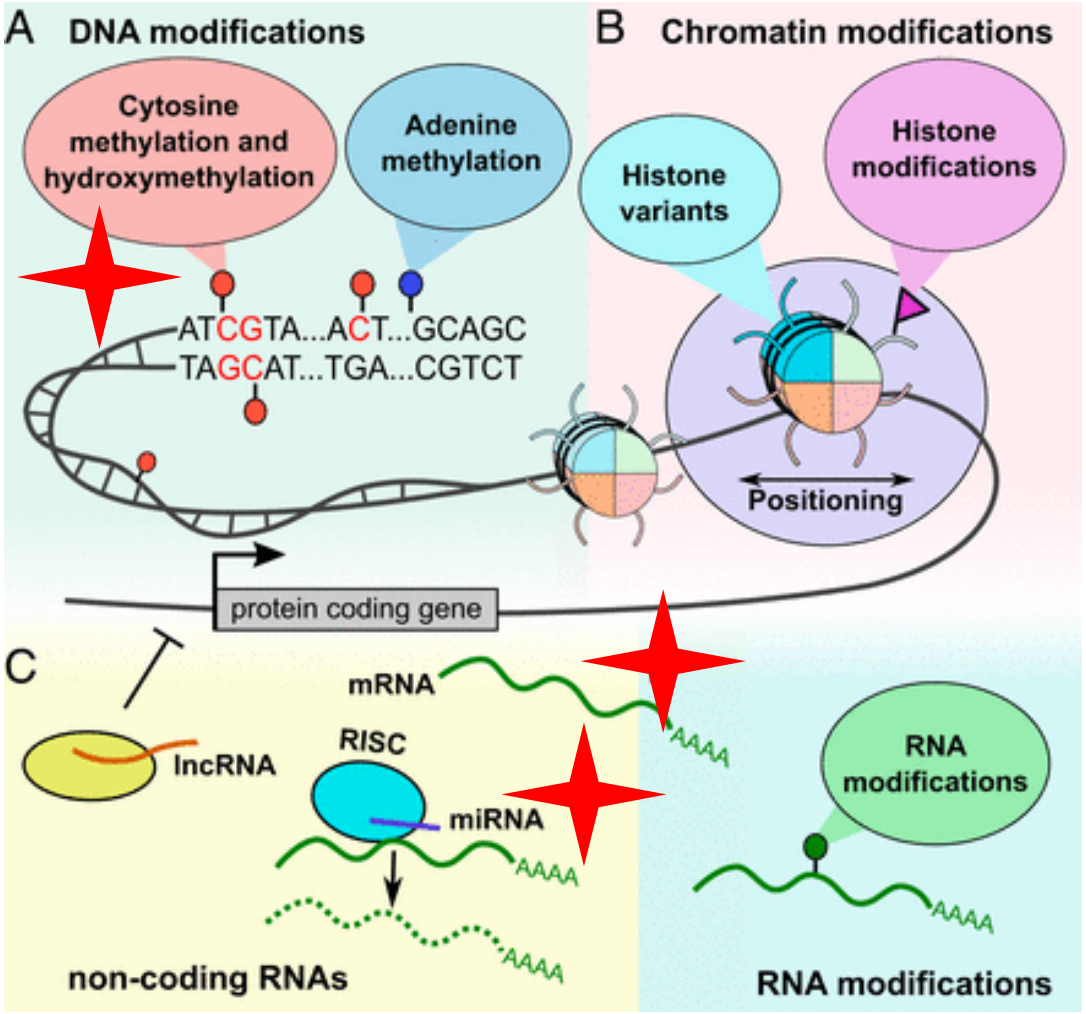


CpG methylation
miRNA expression
mRNA expression
Protein expression
Disease

Aristizabal et al., PNAS 2019

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

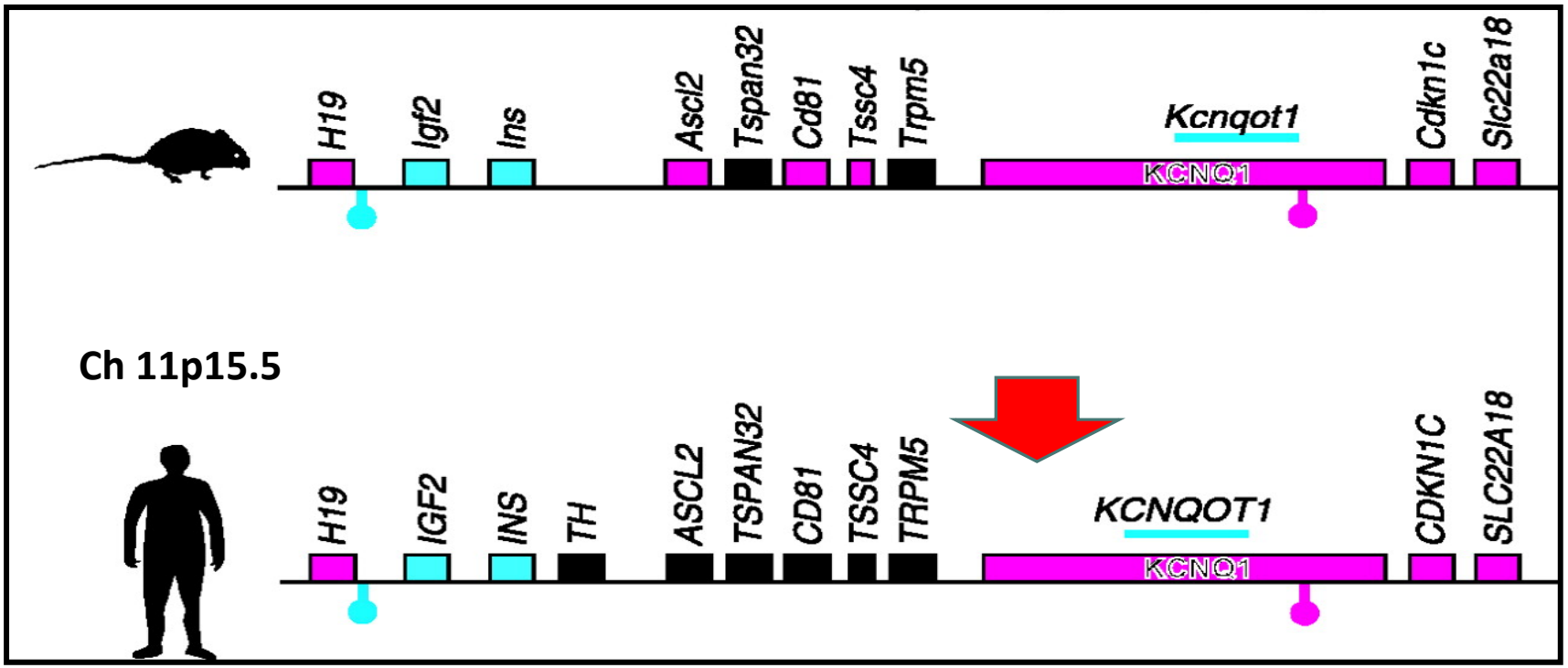
Prenatal Arsenic Exposure and the Epigenome: Identifying Sites of 5-methylcytosine Alterations that Predict Functional Changes in Gene Expression in Newborn Cord Blood and Subsequent Birth Outcomes

Daniel Rojas*, Julia E. Rager†, Lisa Smeester†, Kathryn A. Bailey†, Zuzana Drobná‡, Marisela Rubio-Andrade¶, Miroslav Stýblo*,‡, Gonzalo García-Vargas¶, and Rebecca C. Fry*,†,1

*Curriculum in Toxicology, †Department of Environmental Sciences and Engineering, ‡Department of Nutrition and §Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina and ¶Facultad de Medicina, Universidad Juárez del Estado de Durango, Gómez Palacio, Durango, Mexico

TOXICOLOGICAL SCIENCES, 143(1), 2015, 97–106

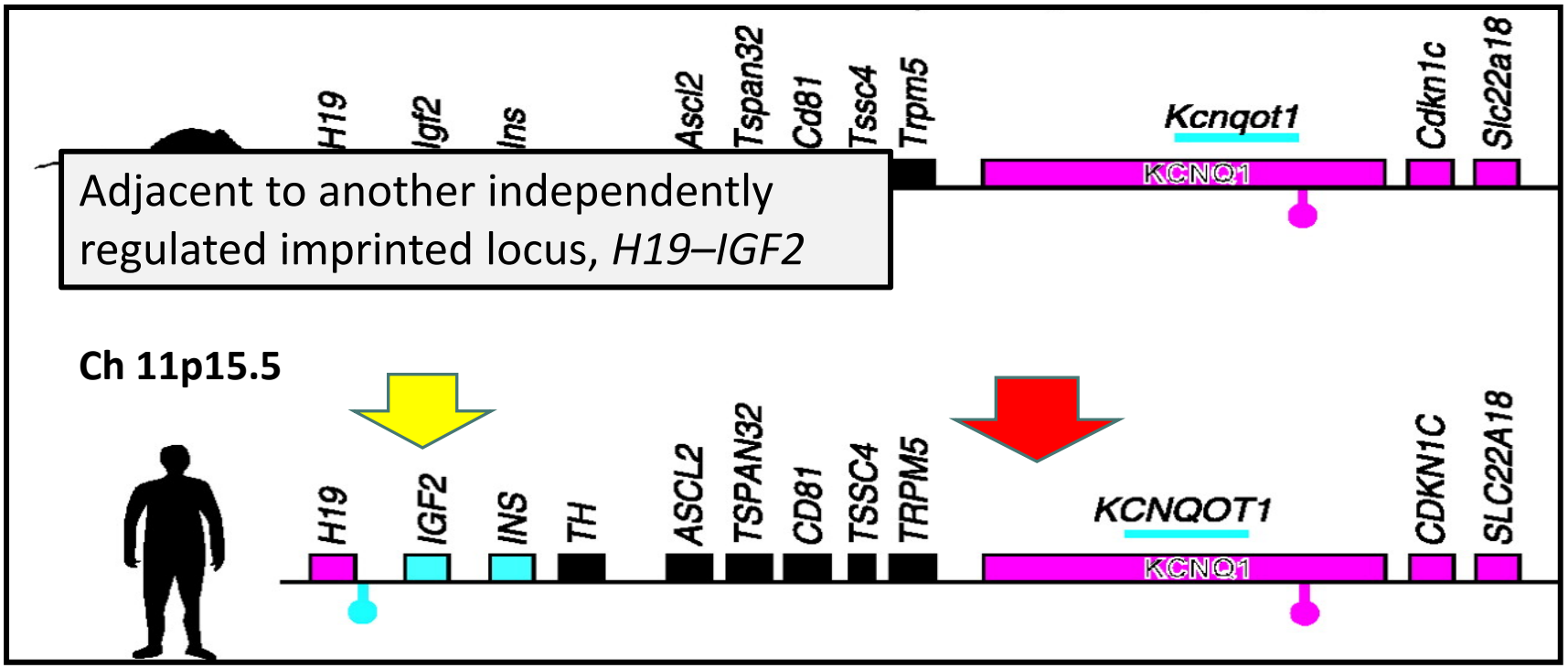
KCNQ1 is an imprinted gene on the short arm of Ch11



Blue=paternally expressed alleles
Pink=maternally expressed alleles
black indicates non-imprinted genes

DNA methylation of *KCNQ1* (potassium channel protein) is negatively associated with gene expression and birthweight

KCNQ1 is an imprinted gene on the short arm of Ch11



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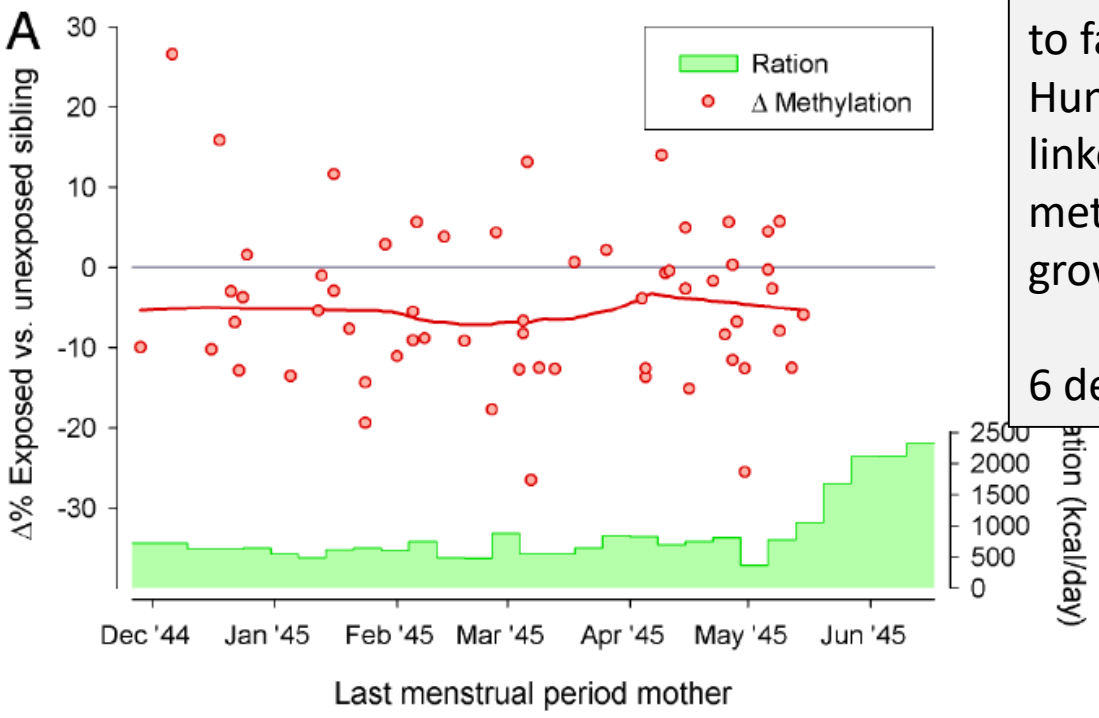
IGF2 is an imprinted gene on Ch 11p15.5, susceptible to prenatal famine-induced changes in DNA methylation



Periconceptual exposure to famine during the Dutch Hunger Winter (1944-45) linked to decreased methylation of Insulin-like growth factor 2

6 decades later!

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans[a,1,2], Elmar W. Tobi[a,2], Aryeh D. Stein[b], Hein Putter[c], Gerard J. Blauw[d], Ezra S. Susser[e,f], P. Eline Slagboom[a], and L. H. Lumey[e,1]

17046–17049 | PNAS | November 4, 2008 | vol. 105 | no. 44

KCNQ1 is associated with weight at birth, later life growth and metabolism

J Assist Reprod Genet (2014) 31:1361–1368
DOI 10.1007/s10815-014-0278-0

EPIGENETICS

Relevance of genomic imprinting in intrauterine human growth expression of *CDKN1C*, *H19*, *IGF2*, *KCNQ1* and *PHLDA2* imprinted genes

Amilcar Cordeiro · Ana Paula Neto · Filipa Carvalho · Carla Ramalho · Sofia Dória

Nat Genet. 2013 January ; 45(1): 76–82. doi:10.1038/ng.2477.

New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism

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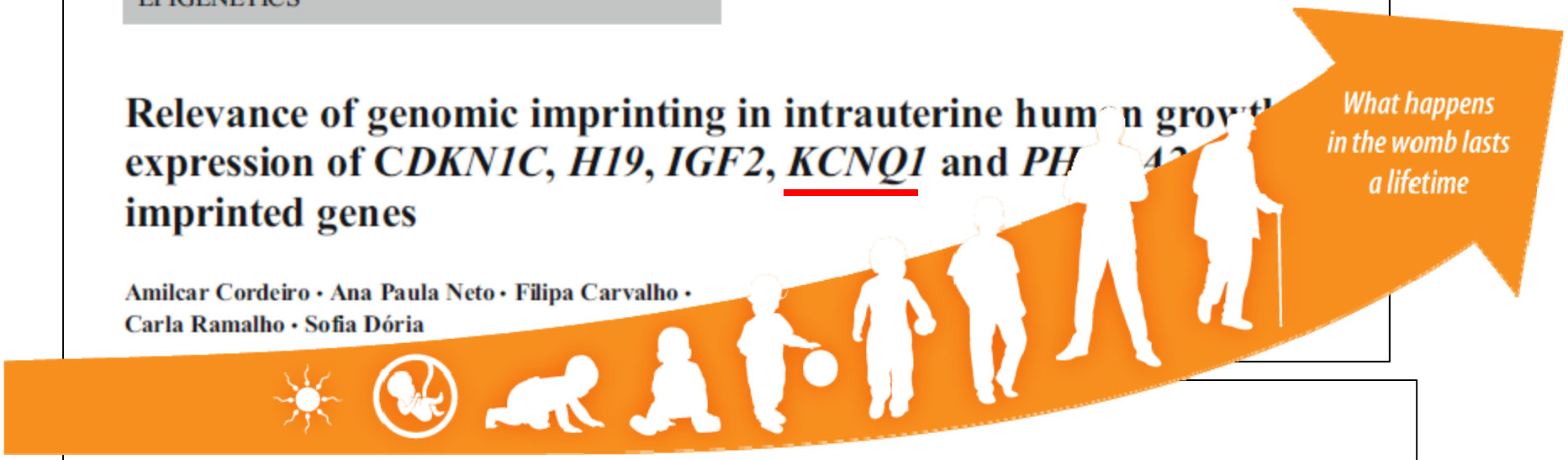

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KCNQ1 is associated with weight at birth, later life growth and metabolism

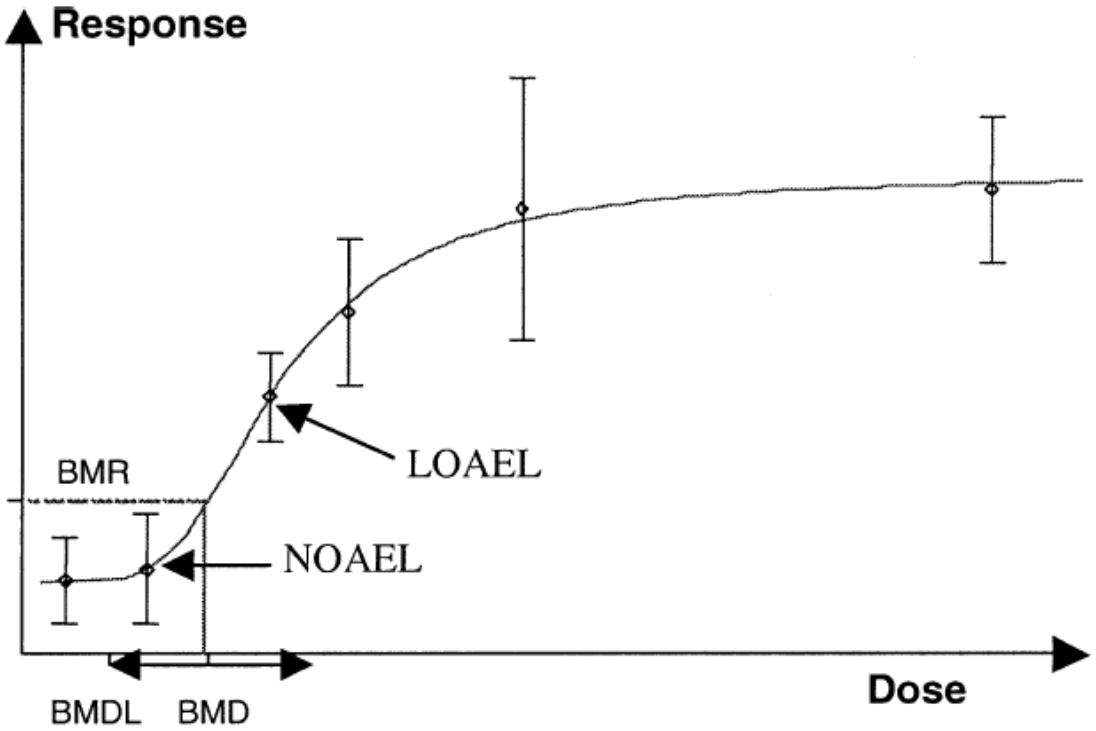
Mechanisms of action of arsenic:

critical genes that REGULATE <u>fetal growth and later life health</u> are targeted for arsenic-associated DNA methylation

happens
womb lasts
fetime

Benchmark Dose Modeling Estimates of the Concentrations of Inorganic Arsenic That Induce Changes to the Neonatal Transcriptome, Proteome, and Epigenome in a Pregnancy Cohort

Julia E. Rager[*†], Scott S. Auerbach[‡], Grace A. Chappell[†], Elizabeth Martin[§], Chad M. Thompson[∥] and Rebecca C. Fry[§]



55 ppb 86 ppb

Chem. Res. Toxicol. 2017, 30, 10, 1911-

- Inorganic arsenic continues to poison individuals around the globe
- Increasing evidence for the role of the epigenome in arsenic-induced disease
- Developing strategies to integrate epigenetic data into a risk assessment framework

Acknowledgements

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