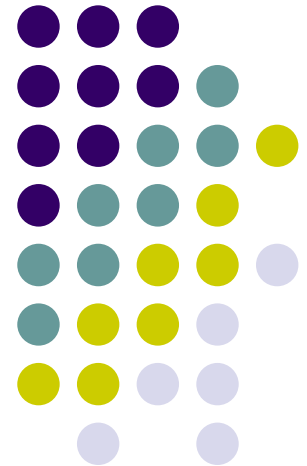
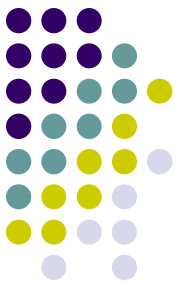


(Mouse) Strain dependence of lung responses to *in utero* arsenic exposure

Graeme R. Zosky, Kathryn A. Ramsey,
Peter D. Sly

*Telethon Institute for Child Health Research
Centre for Child Health Research, University of Western Australia*

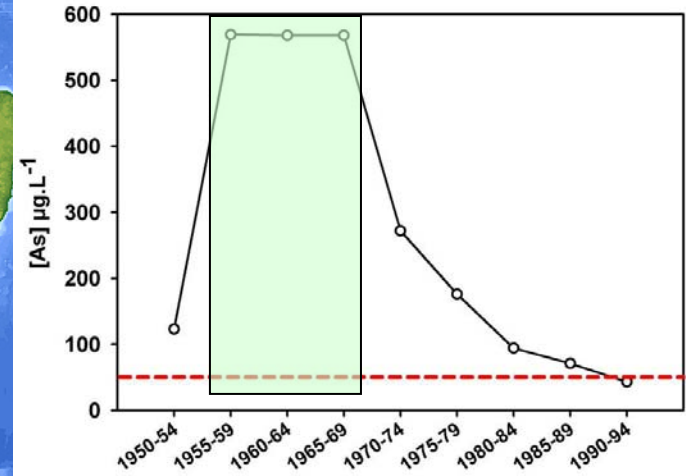
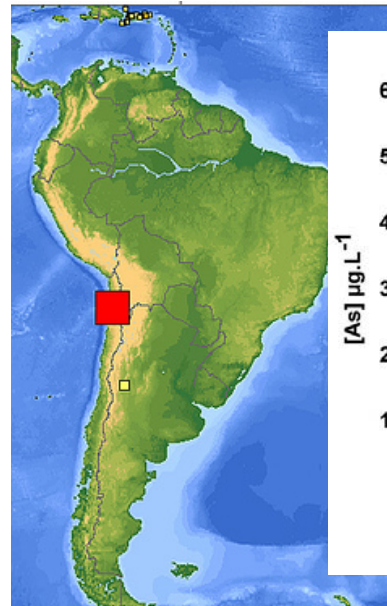
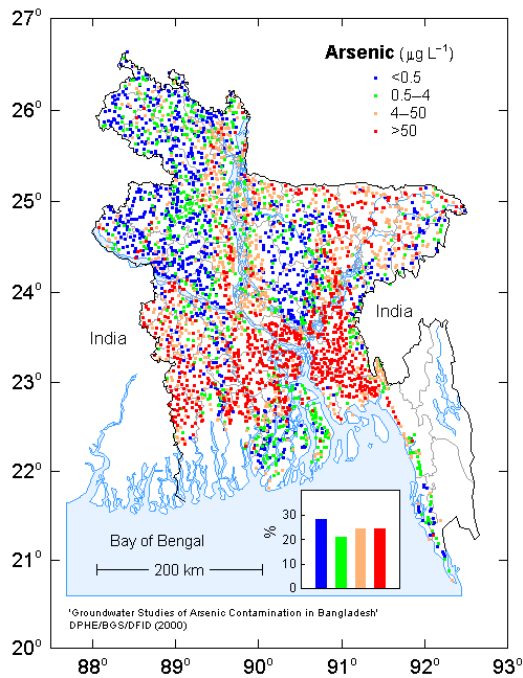




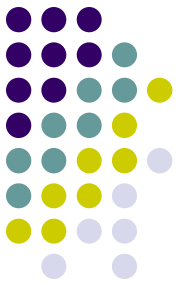
Arsenic in drinking water

- Global exposure to naturally occurring arsenic in drinking water is a public health catastrophe
- Chronic exposure to arsenic via drinking water has wide ranging health effects
 - Carcinogenic (skin, lung, liver, bladder)
 - Cardiovascular disease
 - Non-malignant lung disease?

Arsenic in drinking water



Arsenic *in utero*



Research | Children's Health

Increased Mortality from Lung Cancer and Bronchiectasis in Young Adults after Exposure to Arsenic *in Utero* and in Early Childhood

Allan H. Smith,¹ Guillermo Marshall,² Yan Yuan,¹ Catterina Ferreccio,² Jane Liaw,¹ Ondine von Ehrenstein,¹ Craig Steinmaus,^{1,3} Michael N. Bates,⁴ and Steve Selvin⁴

¹Arsenic Health Effects Research Program, University of California, Berkeley, California, USA; ²Pontificia Universidad Católica de Chile, Santiago, Chile; ³Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, California, USA; ⁴School of Public Health, University of California, Berkeley, California, USA

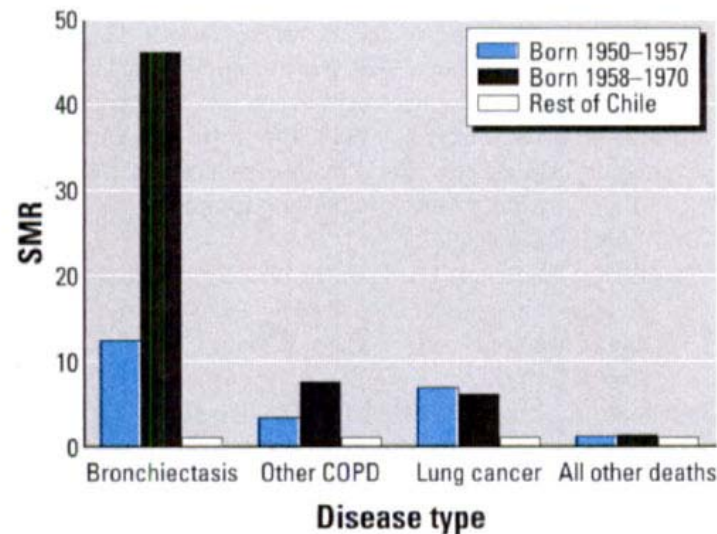
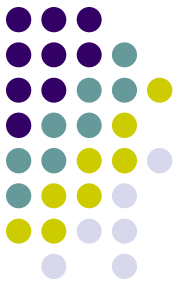


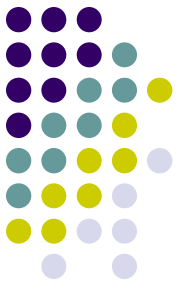
Figure 2. COPD SMRs for Antofagasta/Mejillones for individuals 30–49 years of age, pooled.

Arsenic and respiratory disease



- Dose dependent increase in the prevalence of chronic bronchitis (Milton and Rahman, 2002)
- Increased odds of bronchiectasis in patients with arsenic related skin lesions (Mazumder *et al.*, 2005)
- Correlation between arsenic exposure and FEV_1 (De *et al.*, 2004)

Mechanistic evidence for link between arsenic exposure and non-malignant lung disease



Toxicology and Applied Pharmacology 235 (2009) 105–113



In utero and postnatal exposure to arsenic alters pulmonary structure and function

R. Clark Lantz^{a,b,c,*}, Binh Chau^a, Priyanka Sarihan^a, Mark L. Witten^{b,d}, Vadim I. Pivniouk^{a,e}, Guan Jie Chen^a

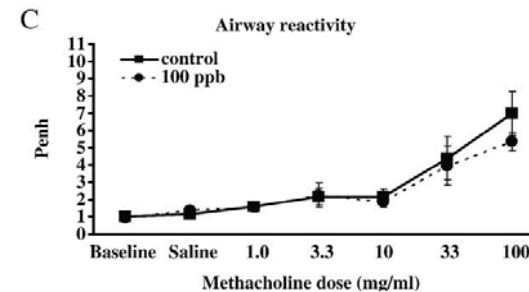
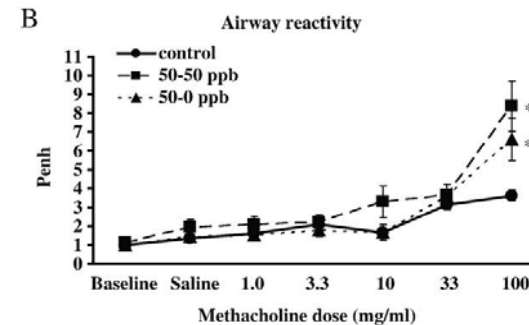
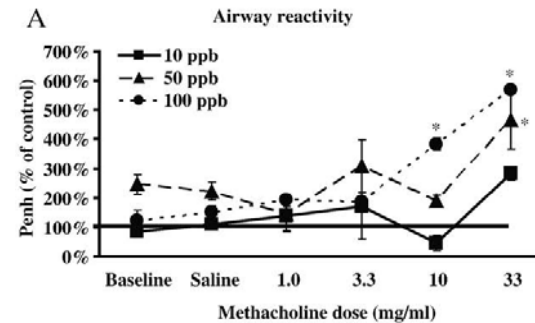
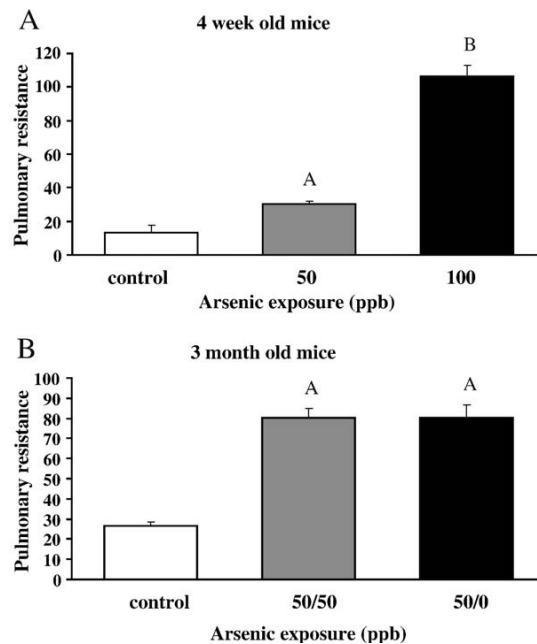
^a Department of Cell Biology and Anatomy, University of Arizona, Tucson, AZ 85724, USA

^b Southwest Environmental Health Science Center, University of Arizona, Tucson, AZ 85721, USA

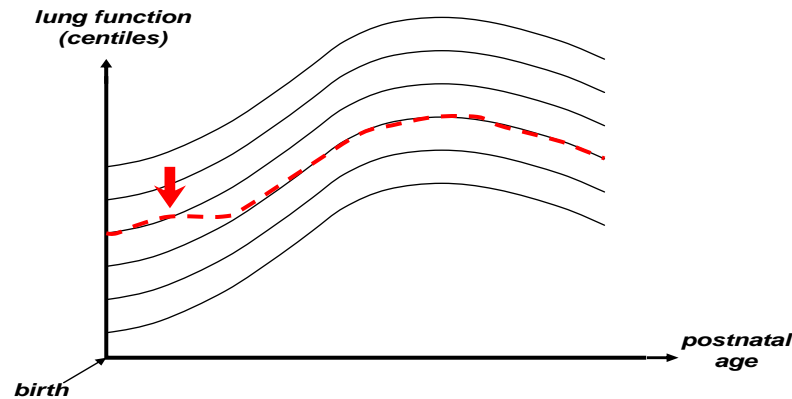
^c BIOS Institute, University of Arizona, Tucson, AZ 85721, USA

^d Department of Pediatrics, University of Arizona, Tucson, AZ 85724, USA

^e Arizona Respiratory Center, University of Arizona, Tucson, AZ 85724, USA



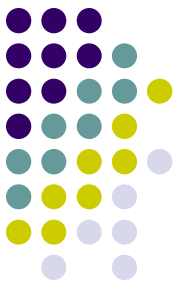
Linking As exposure to lung function and growth



Somatic growth (organism)

Lung growth (organ)

Lung structure (within organ)



Questions to address

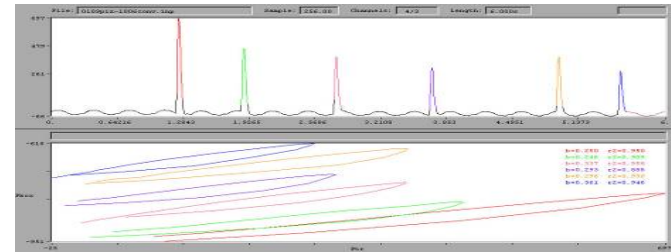
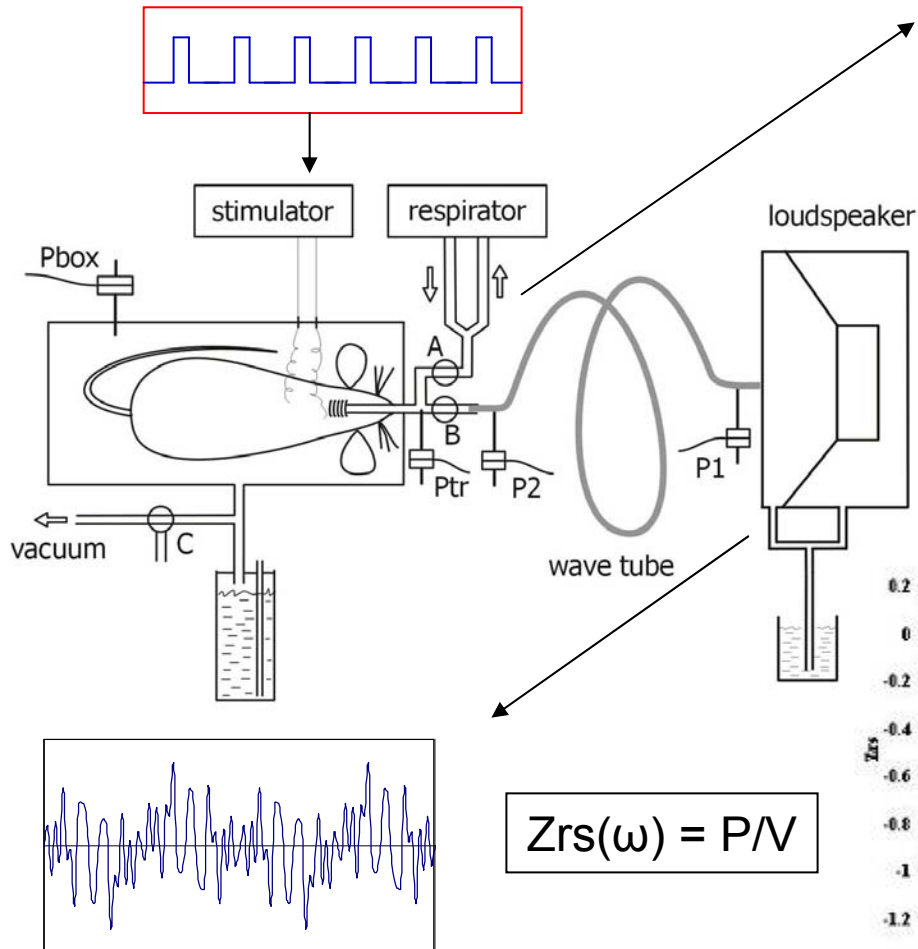
- Is *in utero* exposure to As alone sufficient to alter lung development/function?
 - adjusted for body size?
 - adjusted for lung volume?
- Which region/s of the lung are susceptible?
- How does genetic susceptibility to As alter lung response to arsenic exposure?

Exposure model



- 3 strains of mouse
 - BALB/c
 - C3H/HeARC
 - C57BL/6
- Pregnant dams given $100 \mu\text{g}\cdot\text{L}^{-1}$ As (NaAs_2O_3) in drinking water (or control water) from e8 to birth
- Growth and lung function of offspring studied at 2 weeks of age

Measuring lung function in mice



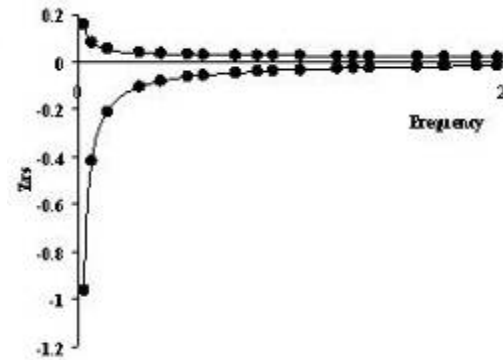
$$TGV \propto \Delta P_{\text{box}} / \Delta P_{\text{trachea}}$$

(Lung volume)

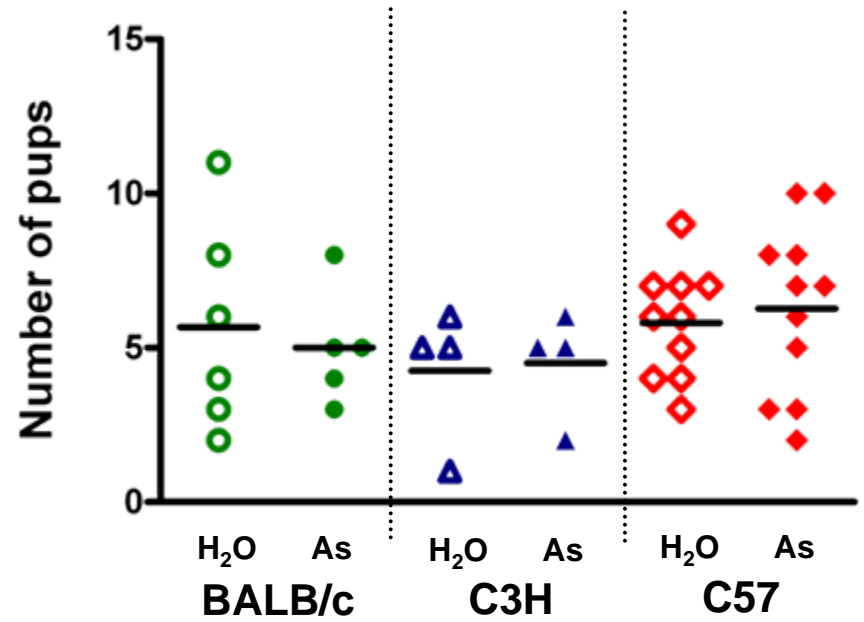
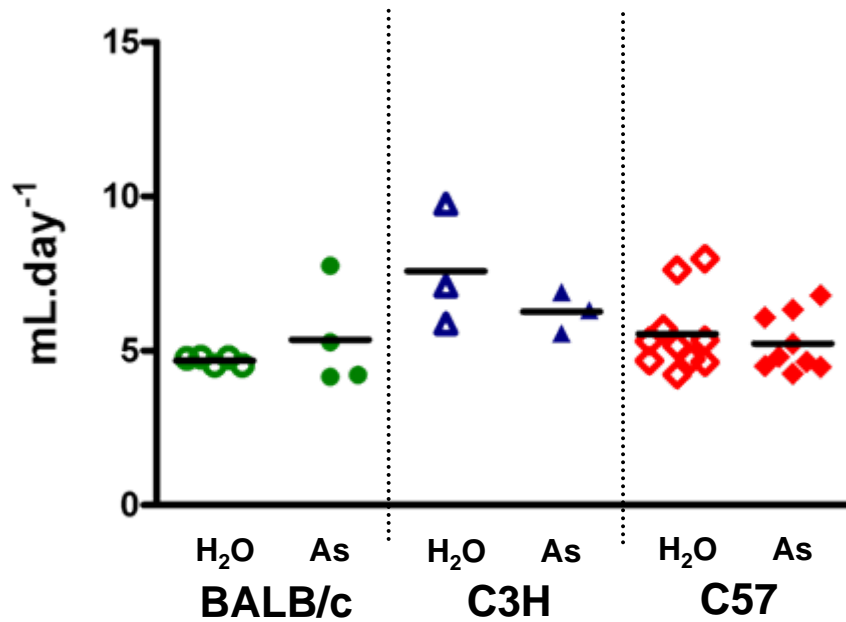
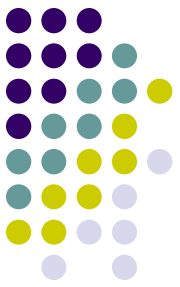
Constant Phase Model

- 1) R_{aw} – Airway resistance
- 2) G – Tissue damping
- 3) H – Tissue elastance

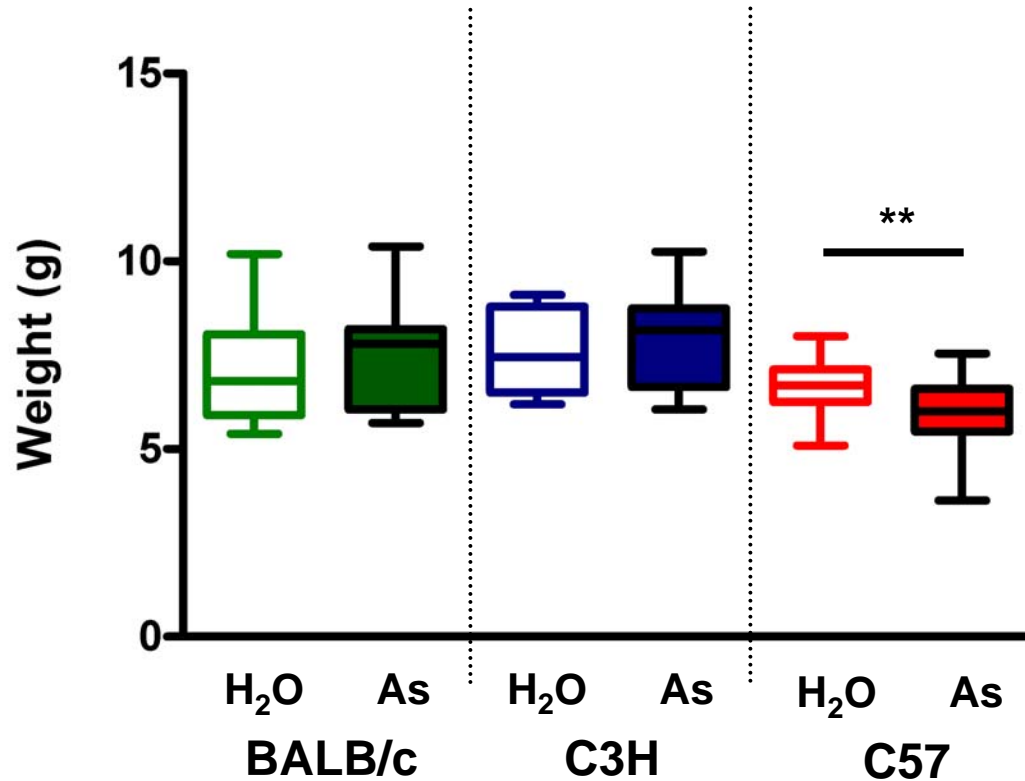
(Lung mechanics)



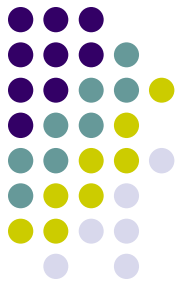
No effect of arsenic on water consumption or litter size



Strain dependent effect on size

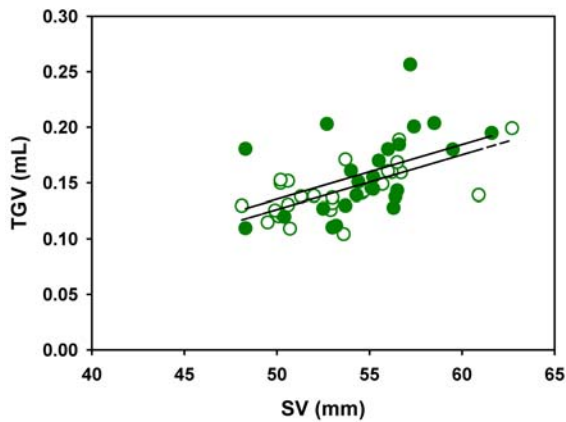


** p < 0.01

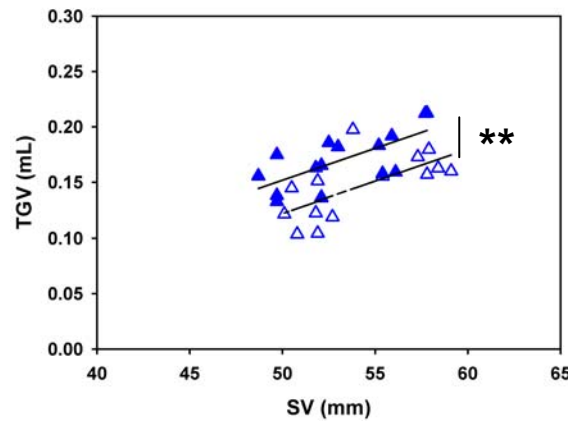


Strain dependent effect on lung volume (corrected for body size)

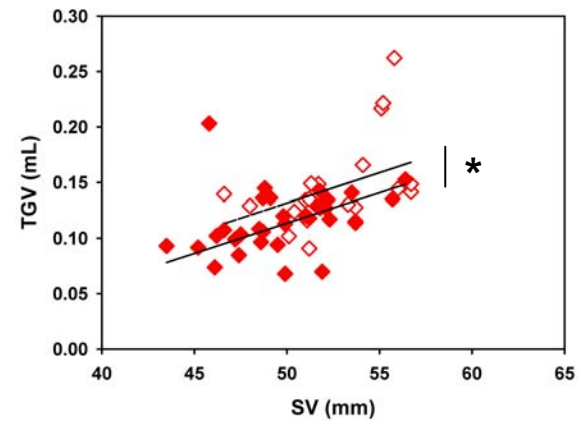
BALB/c



C3H/HeARC



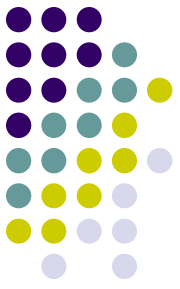
C57BL/6



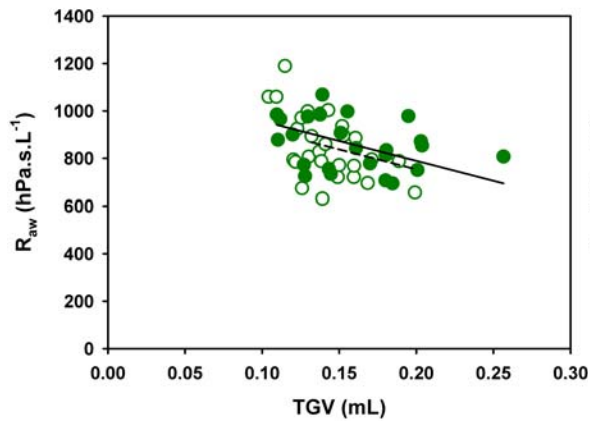
** $p < 0.01$

* $p < 0.05$

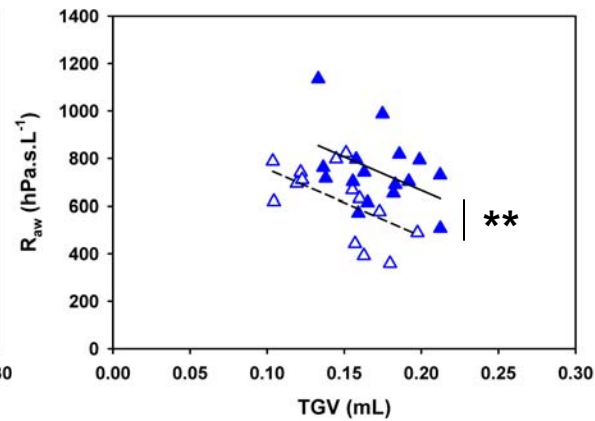
Strain dependent effect on R_{aw} (corrected for TGV)



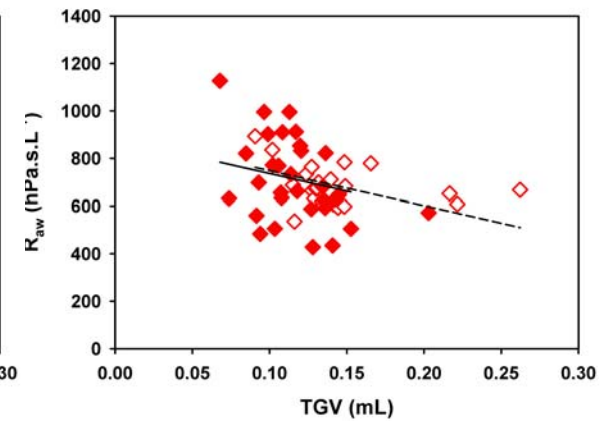
BALB/c



C3H/HeARC



C57BL/6

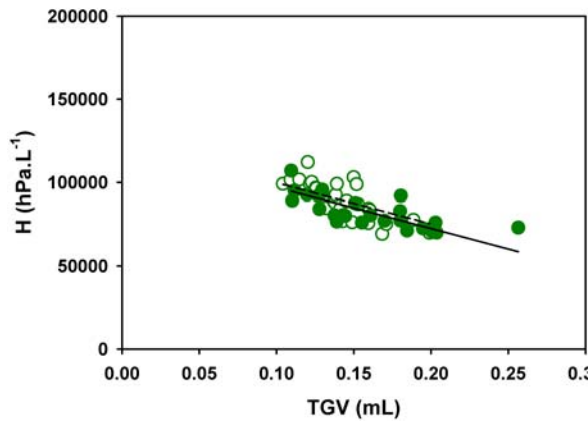


** $p < 0.01$

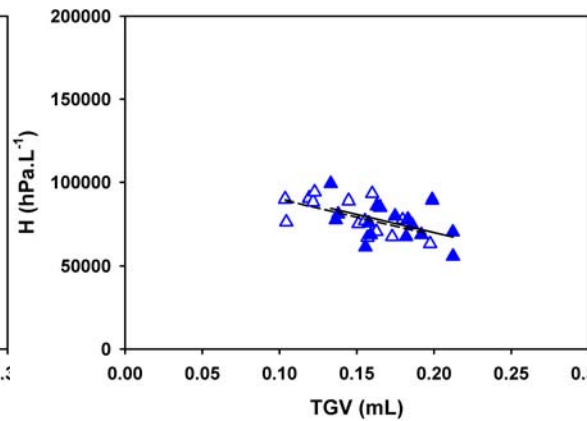
Strain dependent effect on H (corrected for TGV)



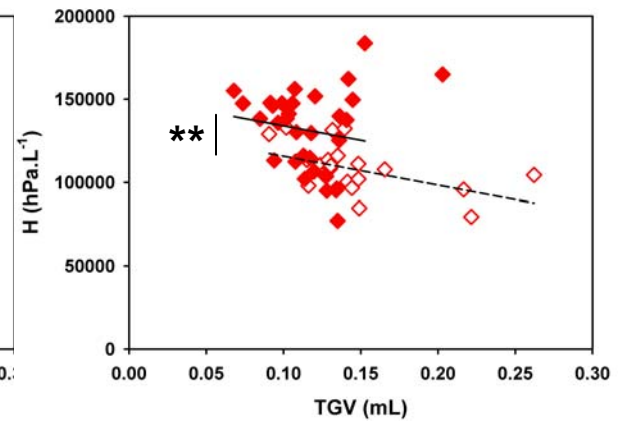
BALB/c



C3H/HeARC

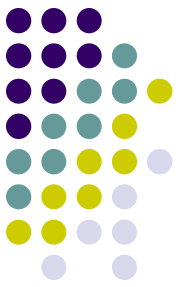


C57BL/6

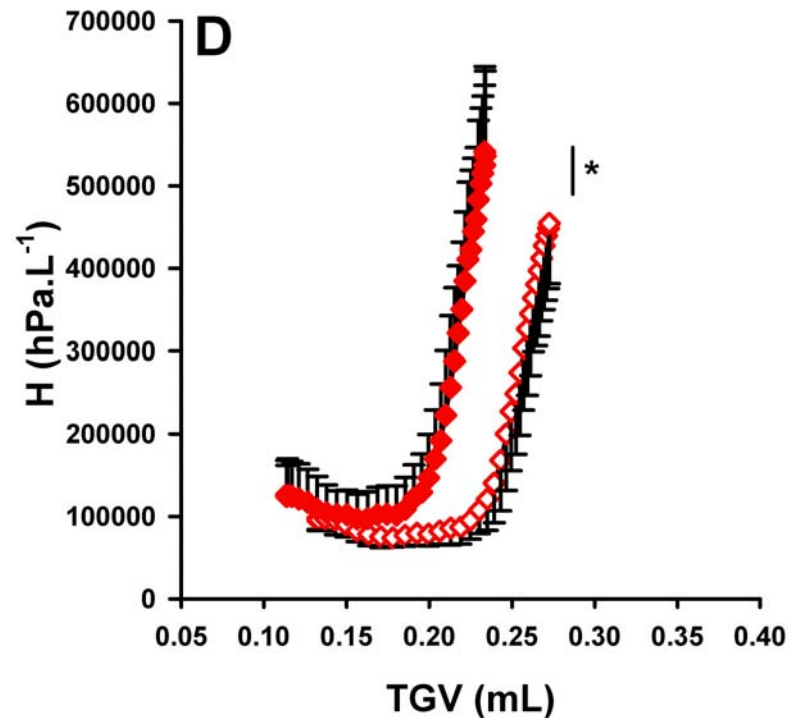
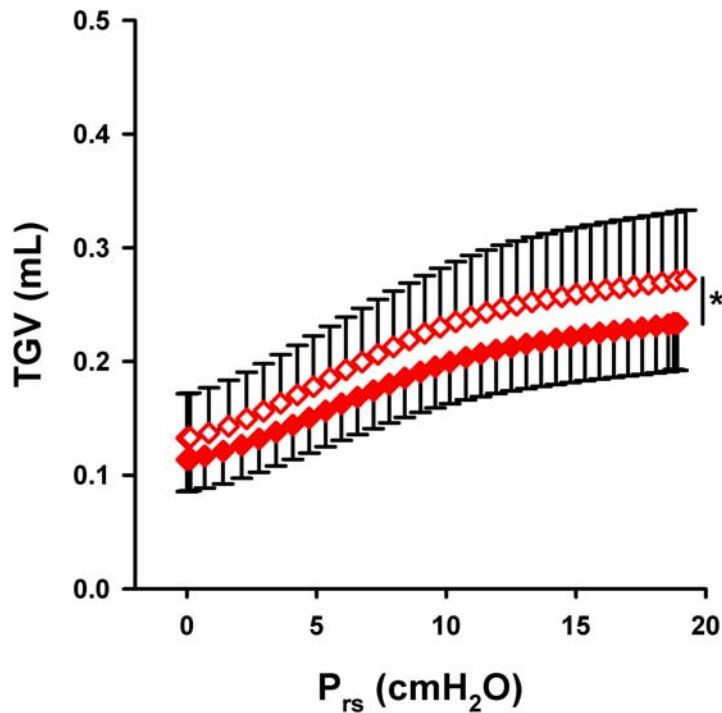


** p < 0.01

Impaired tissue mechanics are maintained over the functional range of the lung

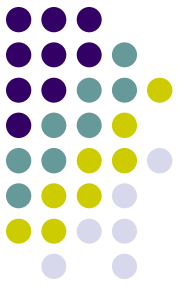


C57BL/6



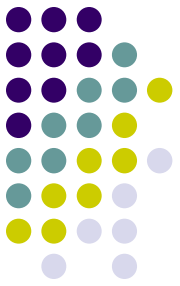
* $p < 0.05$

Summary



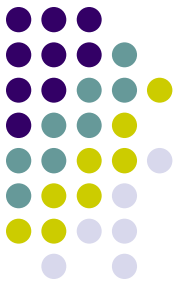
- BALB/c
 - No evidence for altered growth or lung development/function in response to As
- C3H/HeARC
 - Larger than predicted lung volume for body size in As exposed mice
 - Airway resistance was higher than predicted for lung volume
 - Emphysema phenotype?
- C57BL/6
 - As exposed mice smaller (somatic effect)
 - Lung volume smaller than predicted for body size
 - Parenchymal mechanics higher than predicted for lung volume
 - Fibrotic phenotype?

Conclusions and directions

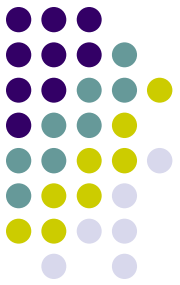


- *In utero* exposure alone to As via drinking water is sufficient to alter post-natal lung development/function
- As has the capacity to alter the development of the conducting airways and the lung parenchyma
- Genetic susceptibility plays a role in lung growth responses to As exposure *in utero*

Conclusions and directions



- What structural changes are driving these functional changes?
 - Lung morphometry
- What are the mechanisms of genetic susceptibility?
 - Gene expression (network analysis to identify pathways involved)
 - Oxidative stress responses?



National Health and Medical Research Council (Australia)