**In utero** exposure to arsenic via drinking water impaired lung growth and mucociliary clearance during infancy

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**Rationale:** Exposure to arsenic via drinking water is a global environmental health problem. Recent studies suggest that *in utero* exposure to arsenic via drinking water increases the risk of lower respiratory tract infections during infancy, and increases the risk of mortality from bronchiectasis (a chronic, progressive disease of the airways caused by repeated bouts of infection and inflammation) in adulthood. Increased susceptibility to infection may occur if there is a decreased capacity to clear pathogens from the respiratory tract. The clearance of pathogens is dependent on the process of mucociliary clearance, whereby mucous in the lumen of the airways traps inhaled particles and the cilia on the surface of epithelial cells transport the mucous into the oral cavity. We hypothesised that exposure to arsenic *in utero* alters the development of mucociliary clearance in the lung.

**Methods:** Pregnant BALB/c, C57BL/6 and C3H/HeARC mice were exposed to 0 (control) or 100μg/L arsenic via drinking water from day 8 gestation (prior to development of the lung buds) until the birth of their pups. At 2 weeks postnatal age (infancy) mice had somatic growth and lung function (lung volume and mechanics) measured. Lung tissue was collected for gene expression analysis by microarray. Subsets of biologically plausible genes that were identified as being differentially expressed by microarray were confirmed by real-time PCR. Fixed lungs were utilised for stereological analysis of lung structure, and histology and immunohistochemistry of the airways.

**Results:** *In utero* exposure to arsenic up-regulated the expression of genes in the lung which play a role in mucous production (mClca3, Muc5b, Sgb3a1), cilia function
(Ttc21a, Dynlrb2), lung morphogenesis (Sox2) and innate mucosal immunity (Reg3γ). Arsenic exposure induced mucous cell metaplasia in the airways of arsenic exposed C57BL/6 mice. Arsenic exposed C57BL/6 mice were also smaller in size, had smaller lungs and impaired tissue mechanics during infancy compared to controls.

**Conclusions:** Exposure to arsenic *in utero* impaired lung growth and mucociliary clearance pathways in the lung which may reduce the ability of the airways to clear pathogens during infancy. Our results provide a mechanism whereby arsenic may increase the susceptibility of the lung to infections in early life and increase the risk of developing chronic lung diseases, such as bronchiectasis, in adulthood.