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What is Keeping Your Toxicologist Up at Night? Exploring the Myth of the Ultra-conservative TRV

Norm Healey

Federal Contaminated Sites National Workshop 2008

Vancouver, BC

April 30, 2008

norm_healey@hc-sc.gc.ca



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Myth of the Ultra-conservative TRV

- What is a Toxicological Reference Value (TRVs)
- How TRVs are described in some Risk Assessments
- Health Canada TRVs for Pb, Cd, and MeHg relative to evidence of health effects
- Challenges to defining a TRV



Define Threshold TRV

“the total intake by ingestion to which it is believed that a person can be exposed daily over a lifetime without deleterious effect” Health Canada (1996)



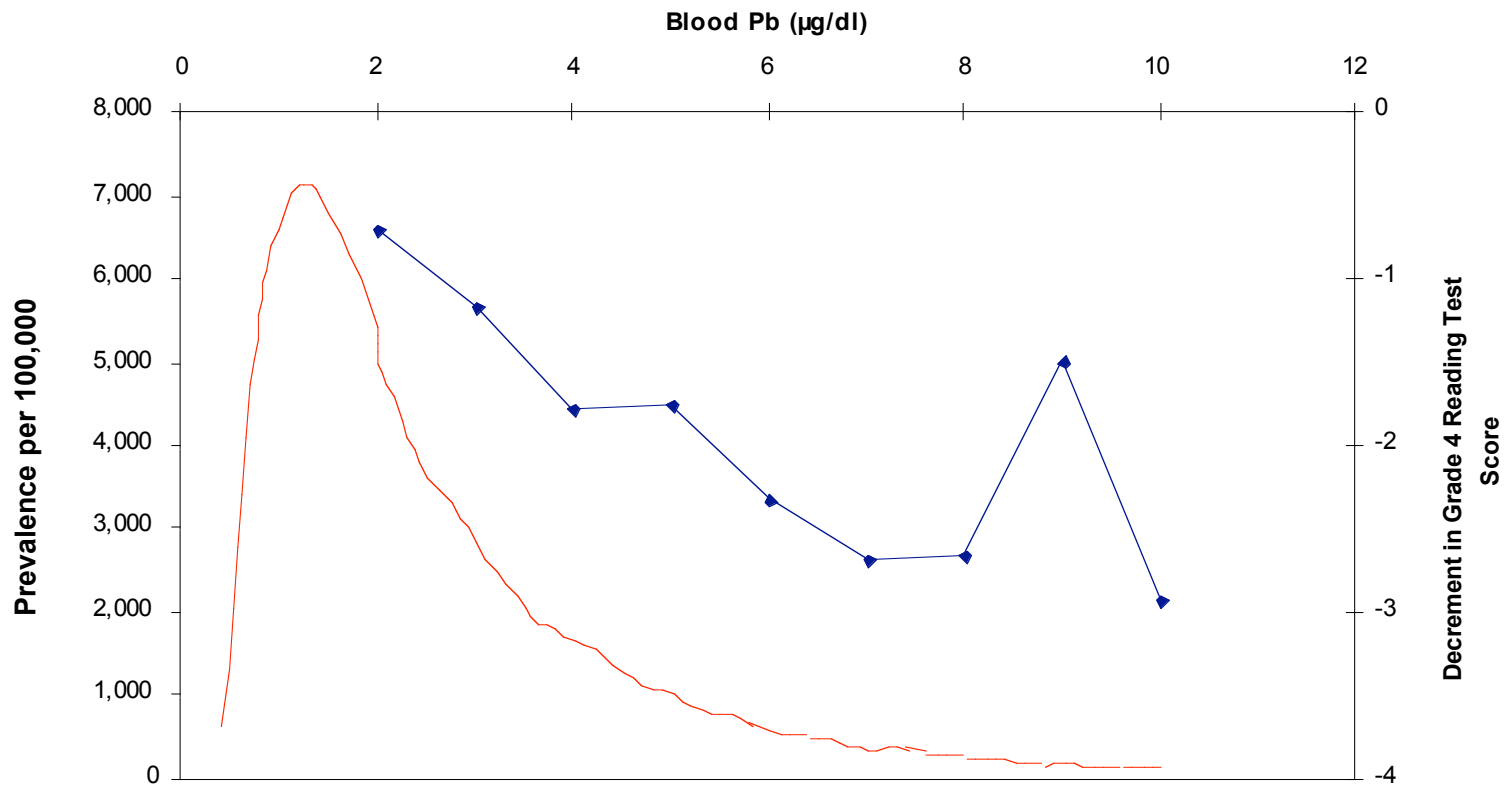
Examples of TRV Characterizations

“risk assessments have been ‘conservative’ relying on multiple safety factors and often overestimating risks.” Lester et al. 2007 Risk Anal. 27(3): 635-658. “physically generally denoted as 10⁻⁶ or 10⁻⁷” extremely conservative”



Health Canada TRVs for Pb, Cd, and MeHg relative to evidence of health effects





- Modeled Population Prevalence of Blood Pb at Exposure Equivalent to pTDI ($3.6 \mu\text{g/kg/d}$)
- ◆— Covariate Adjusted Estimate of Pb Effect on Average Grade 4 Reading Test Score

Effects data from Miranda et al. *Env Health Persp* 115(8) 1242-47.



Chronic dietary Cd intake ($\mu\text{g}/\text{kg}/\text{d}$)^{a,b}	Associated urinary Cd ($\mu\text{g Cd}/\text{g creatinine}$)^c	Associated excess prevalence of renal tubule dysfunction (%)
0.5-2.0	2.5	0
0.8-3.3	4.2	4
1.7-6.7	8.2	20

Table 1. Predicted relationships between chronic oral cadmium intake and excess prevalence of renal tubule dysfunction. From WHO (2001).

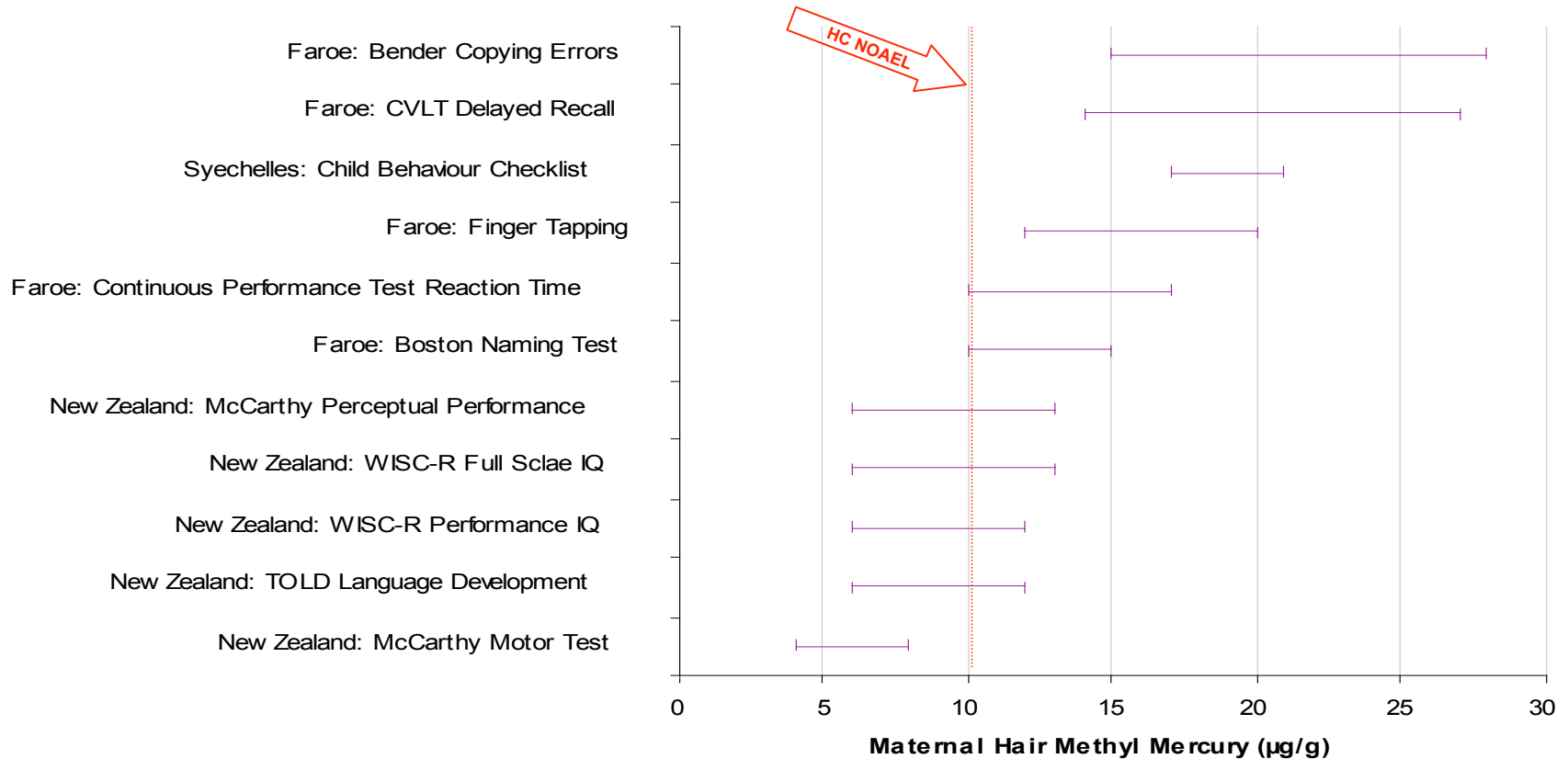
a) Assumed body weight of 60 kg

b) Assumed ratio of dietary intake to urinary excretion ranged from 12-48; oral bioavailability ranged from 5-10%.

c) Assumed creatinine excretion rate of 1.2 g/day



BMD and BMDLs for maternal hair CH₃Hg for neurodevelopmental endpoints



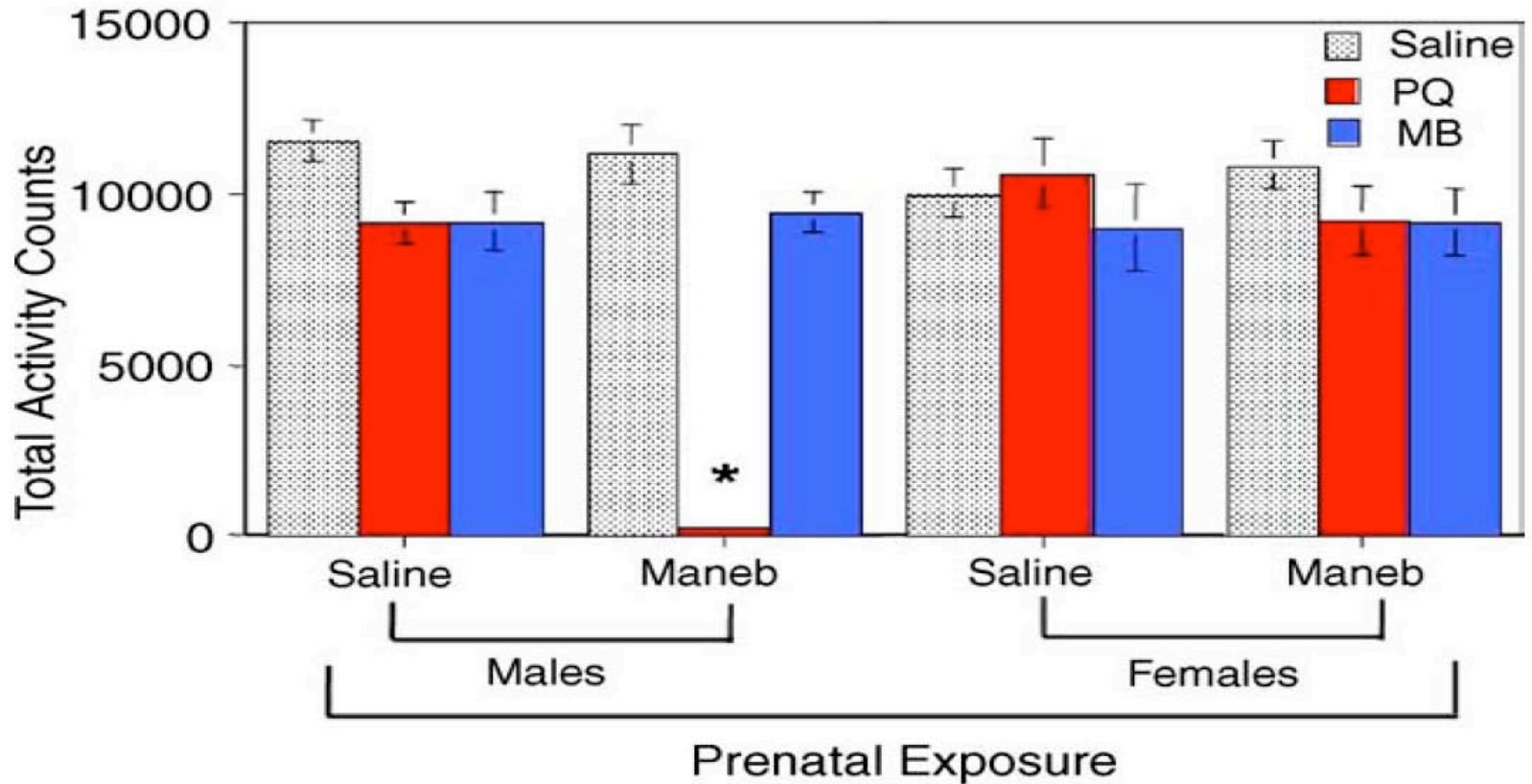
Challenges to defining a TRV

Effect modifiers

- Other chemicals
- Psychological & physiological state
- Genetics



Locomotor Activity 7 Days After Last Adult Re-Challenge



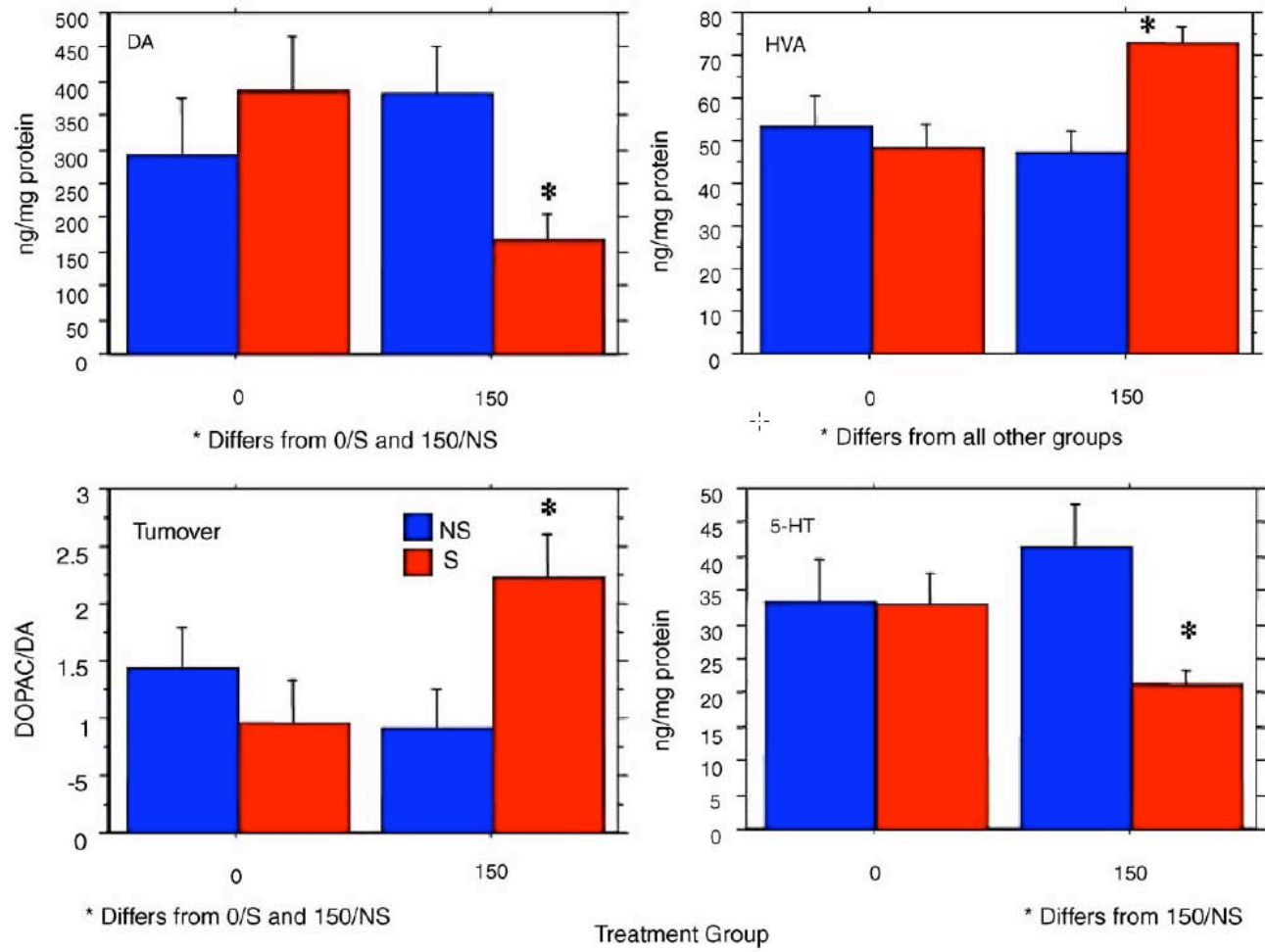
*Differs from all other groups

Barlow et al. 2004. Dev Neurosci. 26(1):11-23.





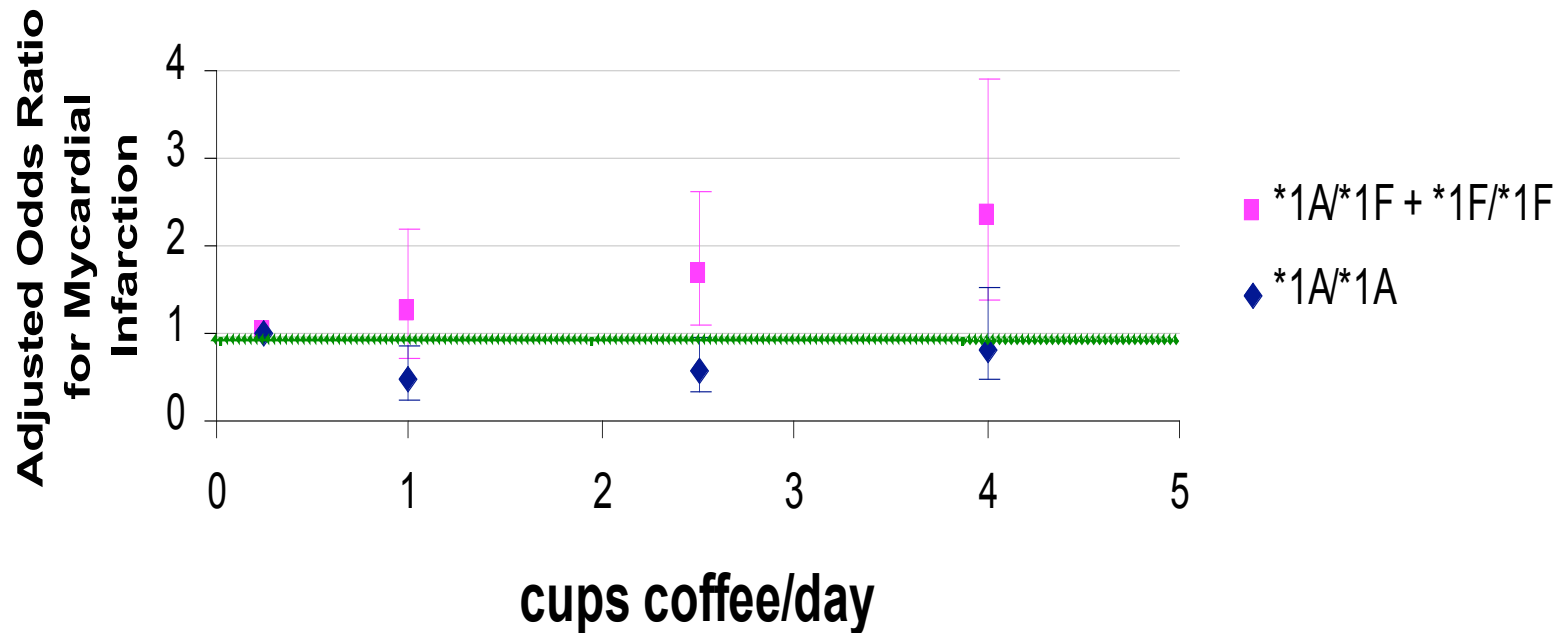
Dams Day 1 Nucleus Accumbens Neurotransmitter Levels: Pb x Stress Interactions



Cory-Slechta et al. 2004. Environ Health Perspect. 112(6):717-30.



1,3,7-trimethylxanthine, *CYP1A2* polymorphism, and Risk of AMI



Cornelis et al. 2006. JAMA 295(10): 1135-1141



Challenges to defining a TRV

Epigenetic effects

F0



F1



F2

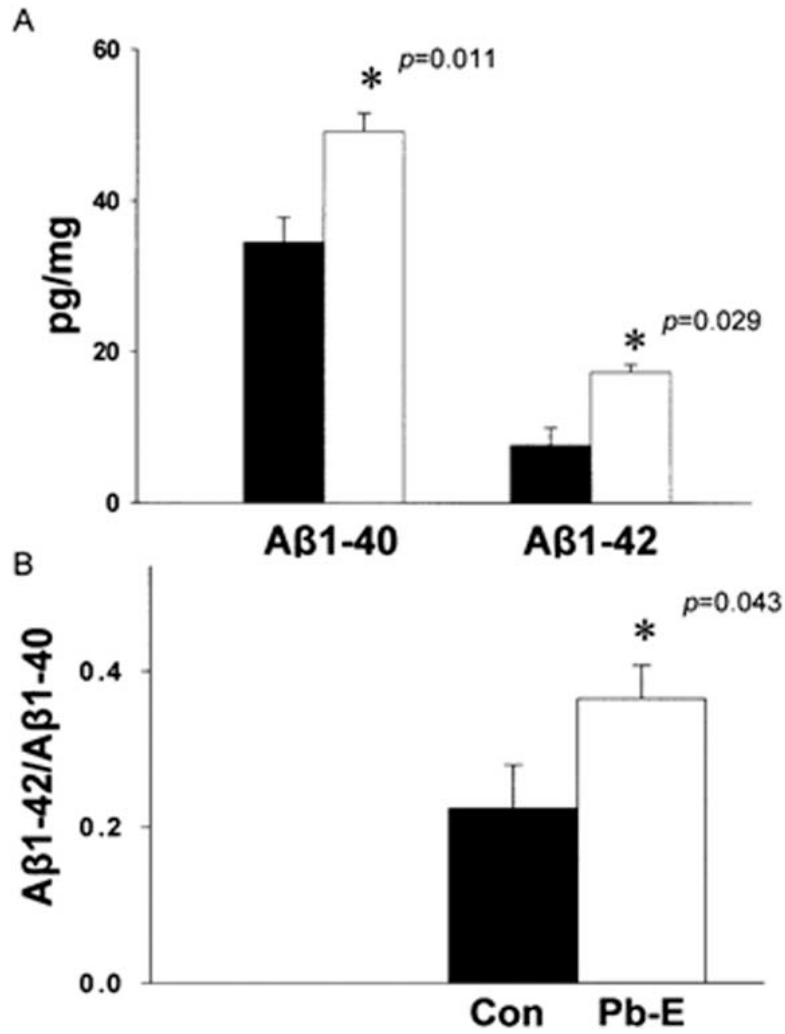


F3



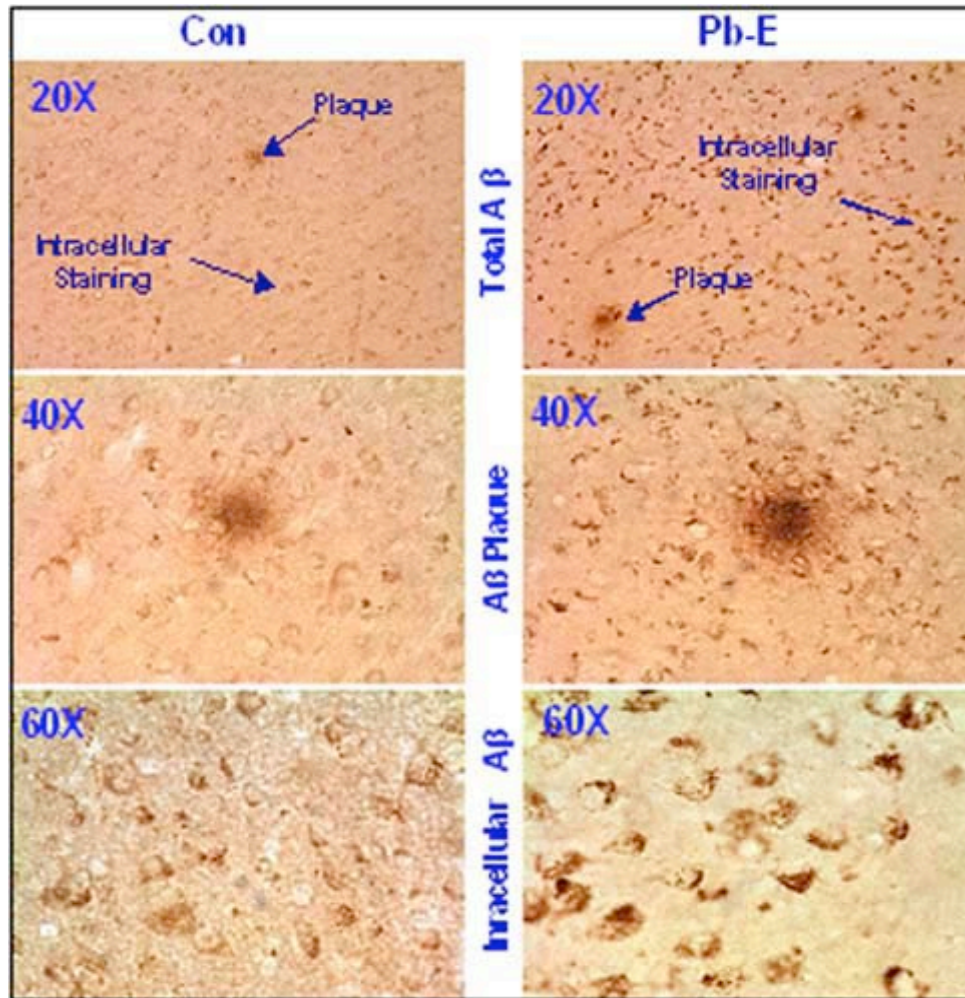
F4





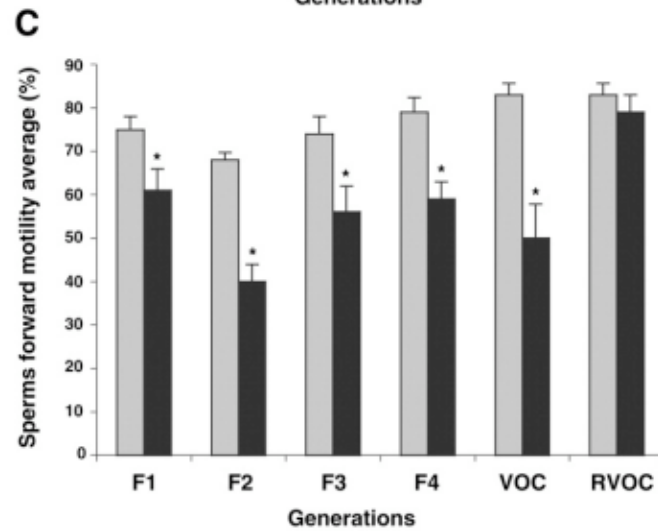
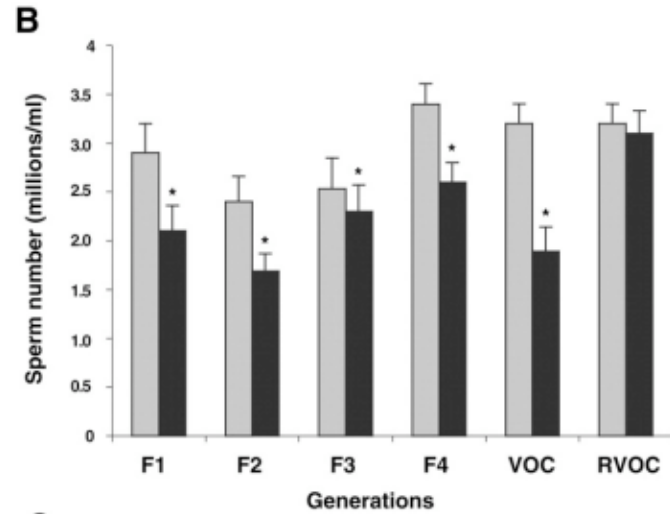
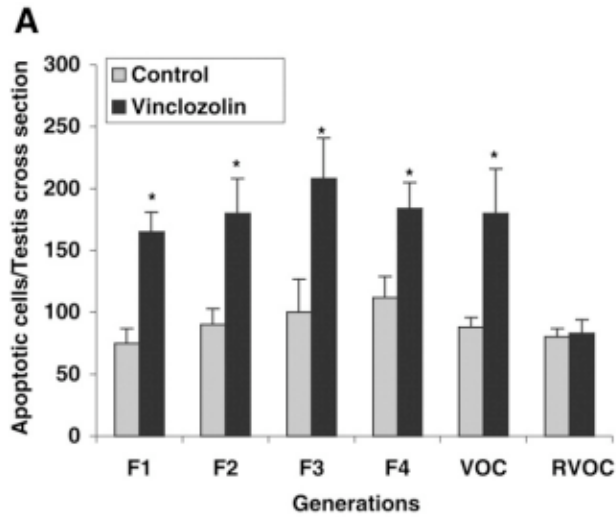
Wu et al. 2008. J. Neurosci. 28(1): 3-9

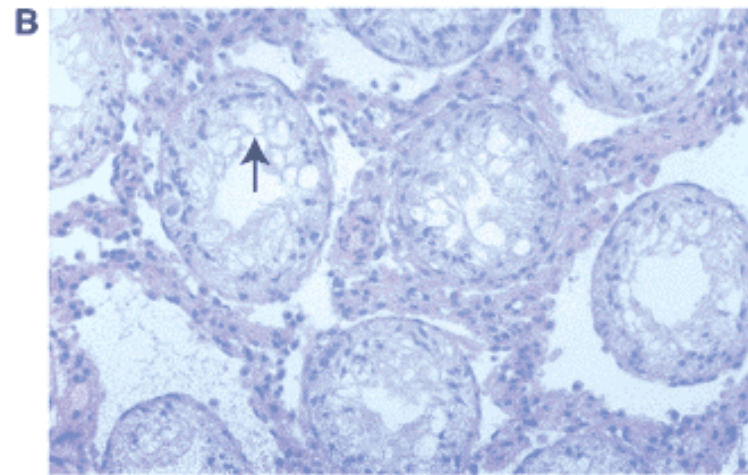
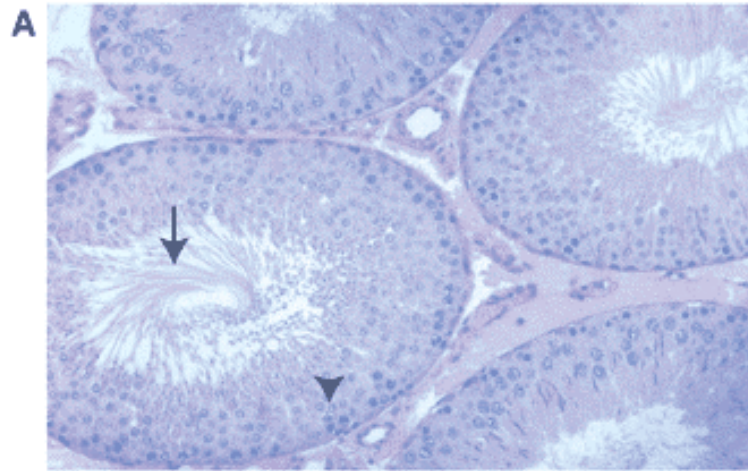




Wu et al. 2008. J. Neurosci. 28(1): 3-9







Summary

Identification of toxic thresholds is challenging

- Effect modification
 - Co-exposure

Uncertainty Factors account for expected variability, uncertainties and methodological limitations

- Epigenetic effects

Some TRVs for important contaminants, Pb, Cd, MeHg, have small or no Uncertainty Factors

