n-Hexane, Why is a Separate Guideline Being Developed and Why is it Being Considered for Oil and Gas Impacted Sites?

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Presentation Overview

- ***What is the F1 Fraction?***
  - ***amount of n-Hexane (HX) in the F1 fraction***
- ***F1 Fraction Toxicity***
  - ***include an evaluation of HX***
- ***What drives the risk?***
- ***Why is one of these compounds being considered for removal from the mixture (like BTEX)?***
- ***This talk focuses on the inhalation route of exposure!!***

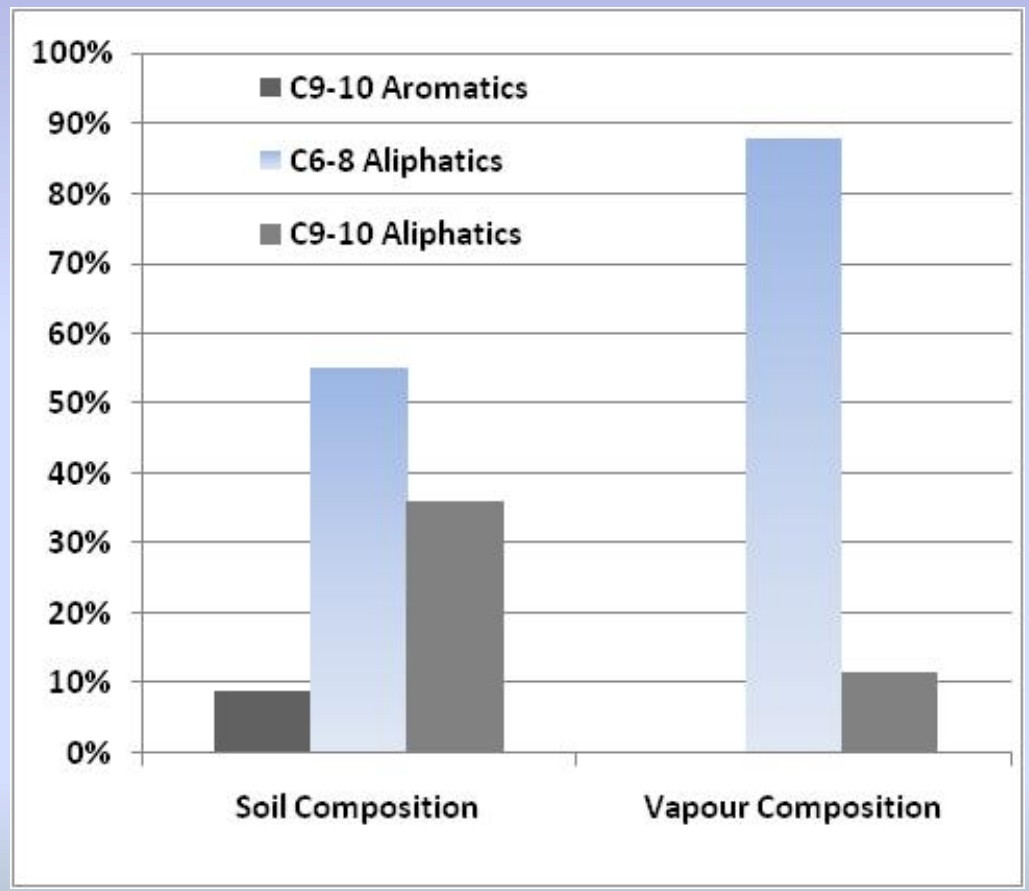
What is the F1 Fraction?

- Default F1 ($C_{>6}$ to C_{10}) Soil Composition (CCME, AENV)
  - aromatic PHCs
    - 0% C_7 to C_8 aromatics (B – C_6; T – C_7; EX – C_8)
    - 9% C_9 to C_{10} aromatics
  - aliphatic PHCs
    - 55% C_7 to C_8 aliphatics
    - 36% C_9 to C_{10} aliphatics

- Estimate default vapour composition:

- 0.3% C_9 to C_{10} aromatics
- 88% $C_{>6}$ to C_8 aliphatics
- 11.6% $C_{>8}$ to C_{10} aliphatics

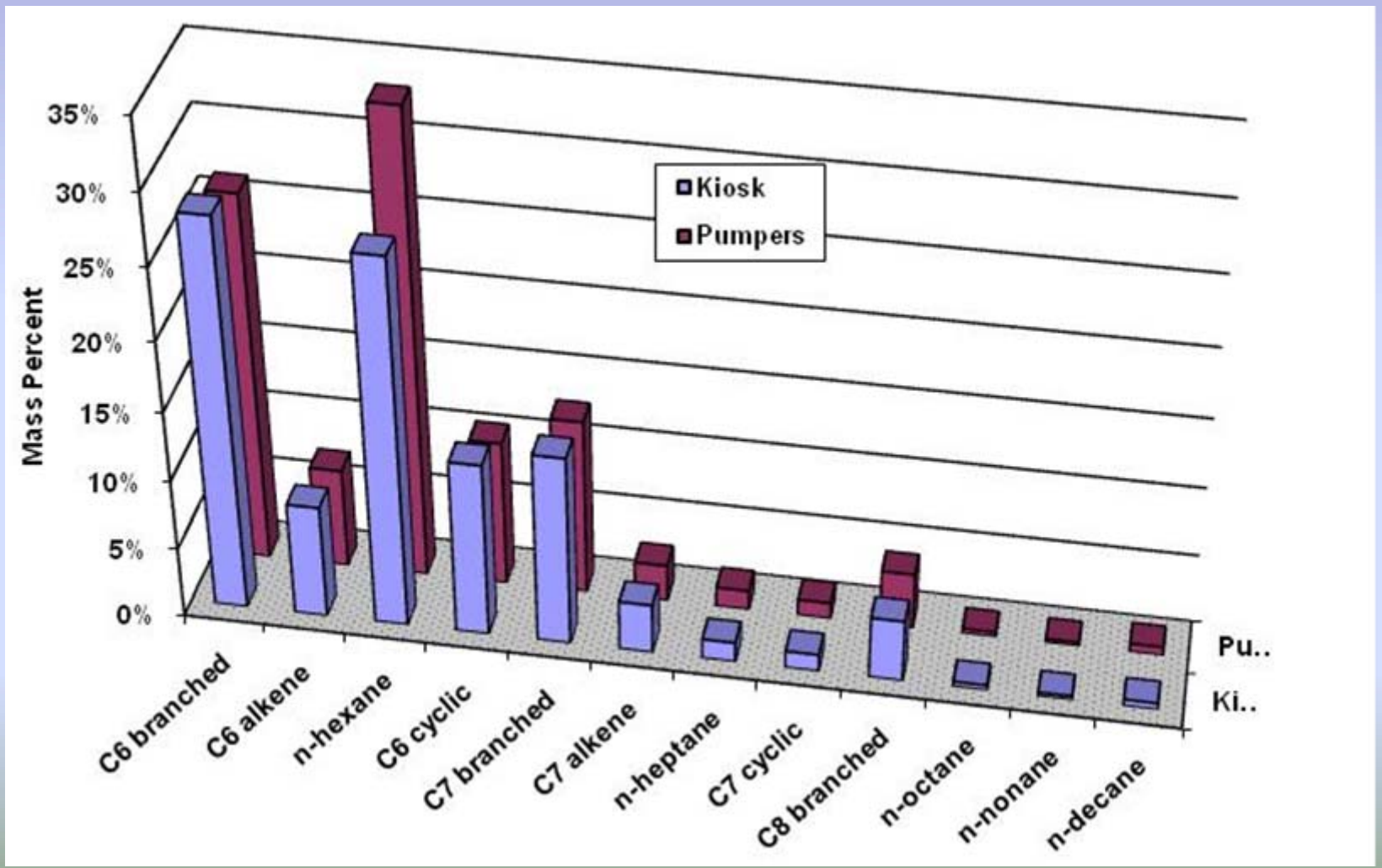
- no default info for HX



** vapour composition estimated using physical/chemical properties for each subfraction*

Environmental Data for F1

- **Unweathered Product: Gas Stations (PACE, 1987)**
- **Mass % of F1 Aliphatic Vapours in Breathing Zone of Gasoline Station Workers – more than 85% due to $C_{>6}$ to C_8 aliphatics**



Environmental Data for F1

- **Weathered Product - Gas Stations (Sevigny *et al*. 2003)**

- **soil vapour concentrations**

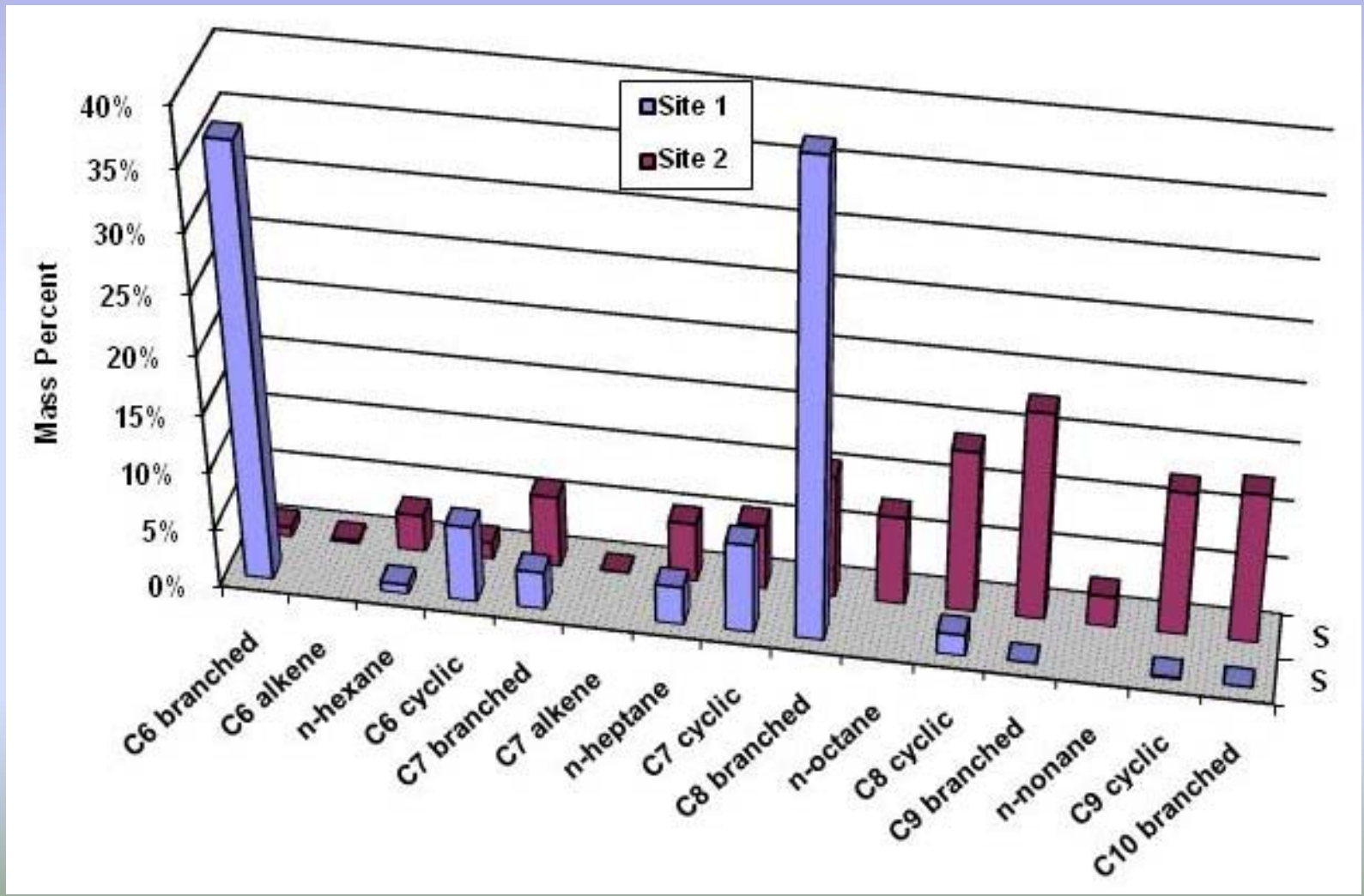
- **90 to 95% of the vapour mass was C_5 to C_8 aliphatics**
- **aromatics typically < 1% of the volatile hydrocarbon mass**

- **Concentrations of HX ranged from 0.006 to 6.7 ppm (0.021 to 24 mg/m3) and represented 0.1 to 3.4% of the total vapour mass**

- **Significantly lower concentrations of HX compared to PACE (1987) – likely due to weathering**

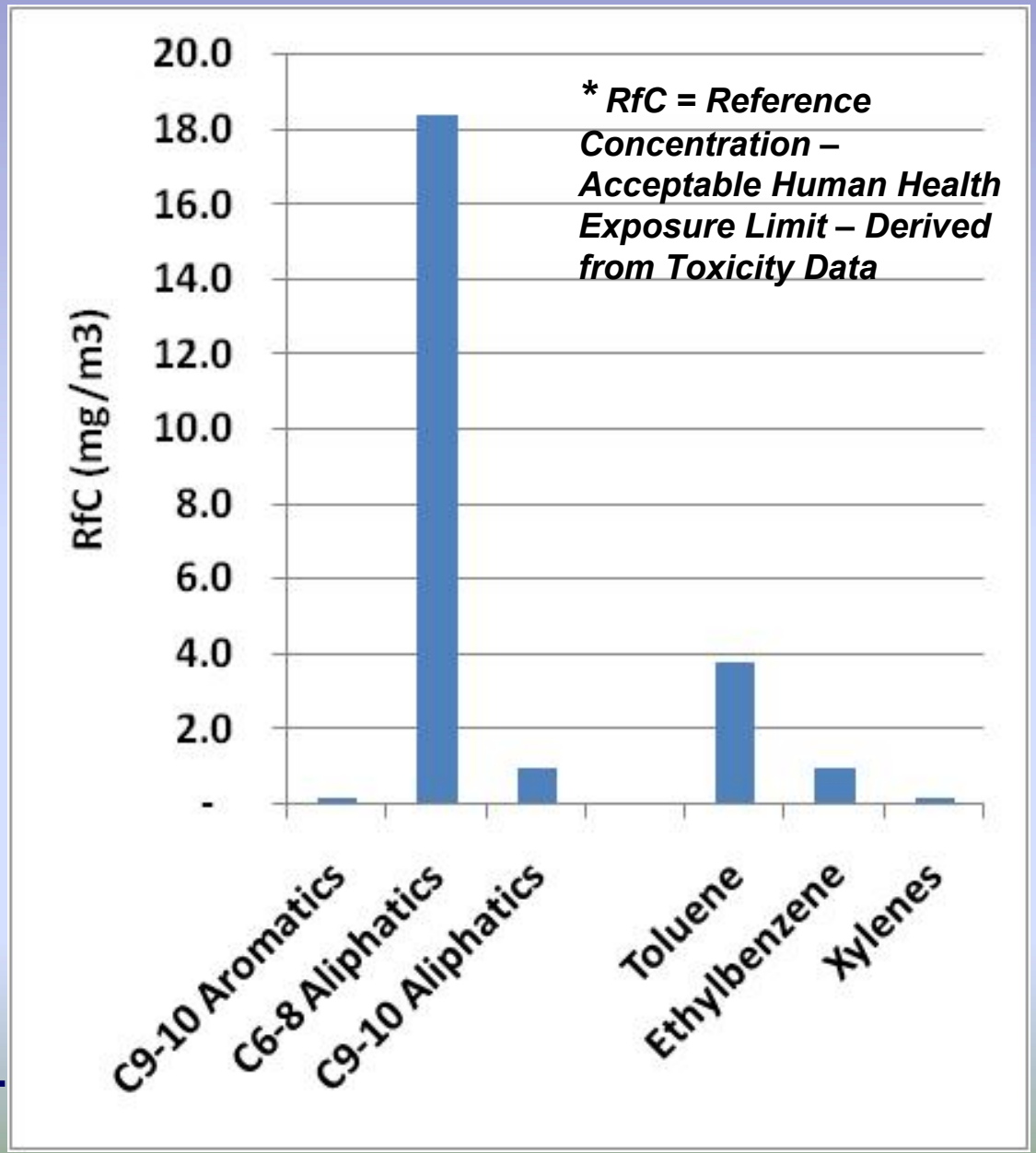
Environmental Data for F1

- Upstream O&G Condensate Sites; Soil vapour probes (EEI)
- Mass % of F1 Aliphatic Soil Vapours (Knafla et al., 1999)
- HX up to ~ 3% of mass – <u>COULD DRIVE RISK!</u>



Toxicity Data for F1 Aromatics

- C_7 to C_8 aromatics
  - TEX;
- $C_{>8}$ to C_{10} aromatics
  - isopropyl benzene
  - high flash aromatic naphtha
  - trimethylbenezenes
- $C_{>6}$ to C_8 aliphatics
  - commercial hexane:
  - HX – 53%
  - 3-methylpentane – 16%
  - methylcyclopentane – 14%
  - 2-methylpentane – 12%
  - cyclohexane – 3%
  - 2,3-dimethylbutane – 1%
- $C_{>8}$ to C_{10} aliphatics
  - dearomatized petroleum frac.
  - dearomatized white spirit

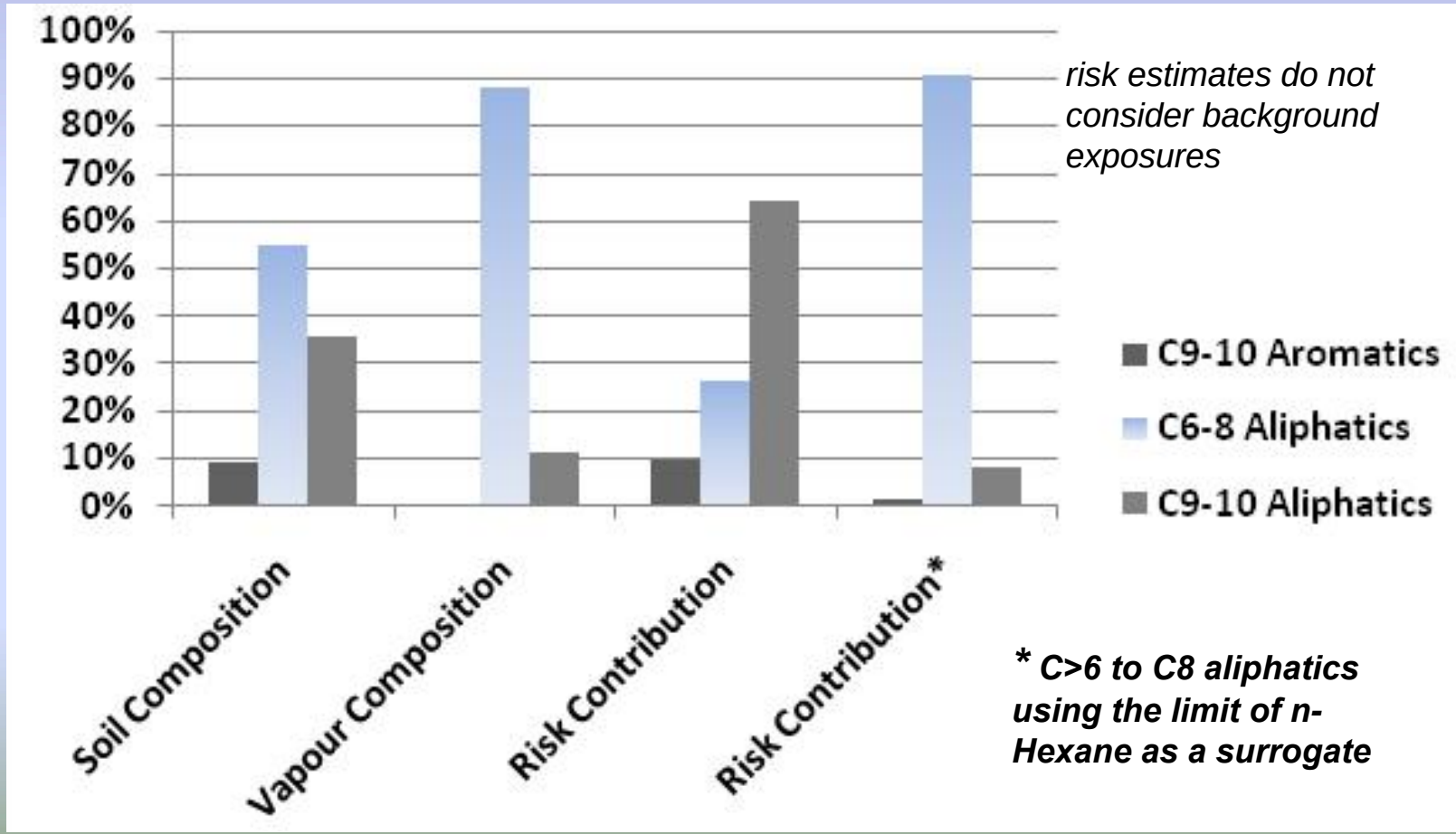


Wait a second…

- RfC for $C_{>6}$ to C_8 aliphatics is 18.4 mg/m^3
  - based on a commercial hexane mixture containing HX
- the RfC (US EPA) for HX is 0.7 mg/m^3
- A BIG DIFFERENCE (26x)!
- Why aren't we seeing the toxicity of n-Hexane?
- Some people have suggested the presence of other C_6 isomers causes antagonism on the neurotoxicity of HX
- MDEP (and other agencies) did not feel that this was appropriate - suggested instead the limit for HX be used for the $C_{>6}$ to C_8 aliphatics
  - such an assumption has significant implications (26x!) – crux of today's discussion

Relative Risk

- 3 sub-fractions to assess: C>8 to C10 aromatics; C>6 to C8 aliphatics; C>8 to C10 aliphatics
- look at source proportions, physical properties, toxic potency and determine inhalation risk contribution
- need to explore the toxicity data of commercial hexane



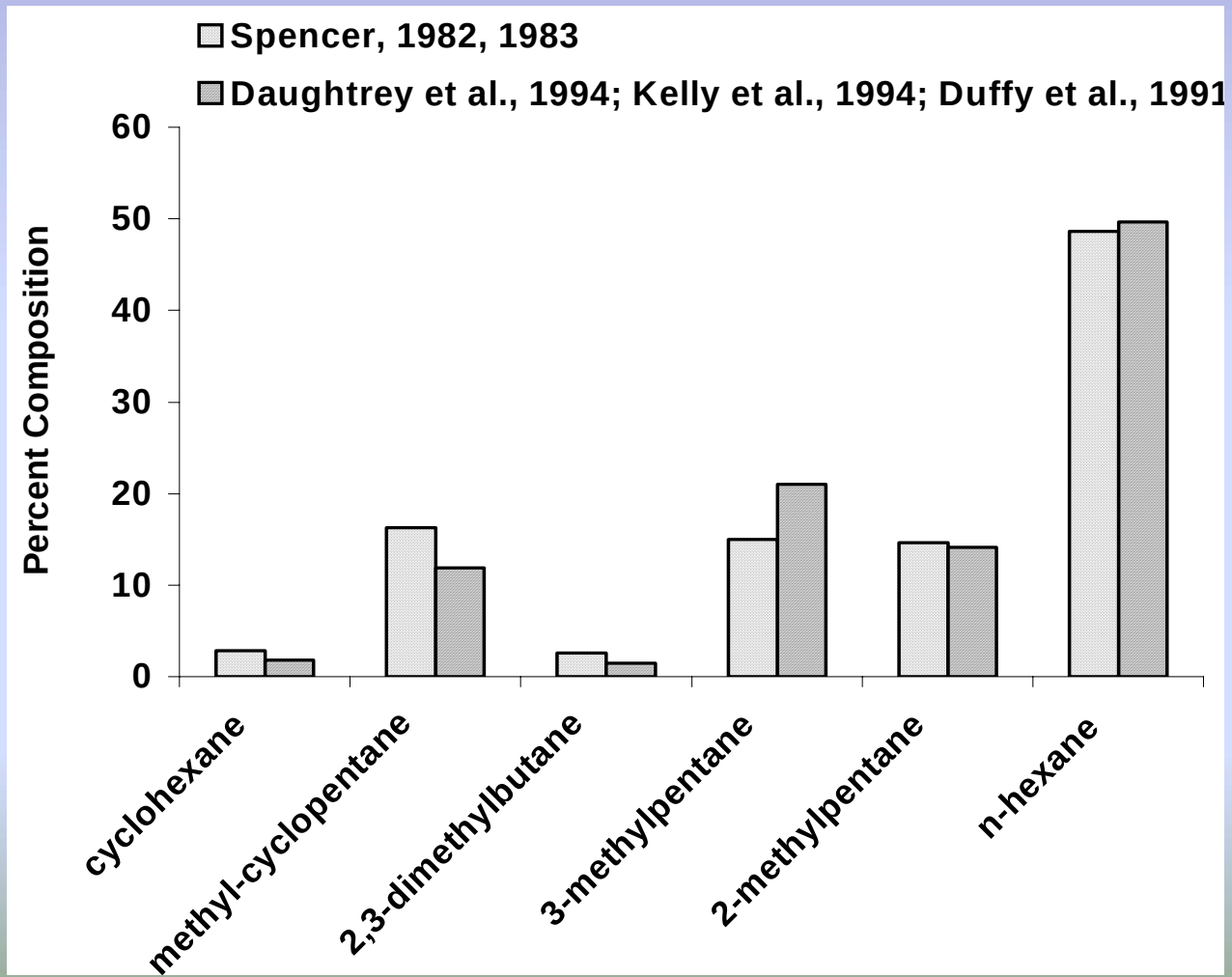
To Make Matters Worse…

- **Spencer study (1983) gives contrasting results & supports MDEP**
- **SD rats - vapour concentrations of 500 ppm HX alone or in combination with 500 ppm of other C_6 hexane isomers**
  - ***i.e.,* HX - 50%; cyclohexane - 5.4%; methylcyclopentane - 30.2%; 3-methylpentane - 29.4%; 2,3-dimethylbutane - 5%; 2-methylpentane - 29.3%; other isomers - < 1%**
- **Exposed continuously (22 h/d; 7 d/w) up to 17 weeks**
  - **versus intermittently in studies used to develop the RfC**
- **At weeks 16 and 17, mice had abnormal gaits (characteristic clinical effect of HX), and histopathological signs of nerve damage**
  - **Generally, similar symptoms onset time for neurotoxicity observed for 500 ppm HX alone or 500 ppm HX plus 500 ppm of other C_6 isomers**
  - **No neurotoxic symptoms for 500 ppm of the C_6 isomers without HX**

Exploring Commercial HX Toxicity

- Daughtrey et al. (1994); Kelly et al. (1994); and Duffy et al. (1991); Dunnick et al (1989) Studies
- SD rats and B6C3F1 mice exposed 6 h/d, 5 d/w, up to 2 yr, to 900 to 9000 ppm (450 to 4500 ppm HX)

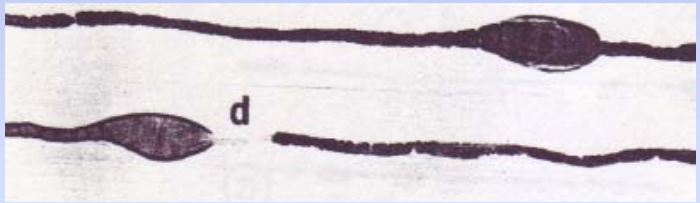
- minimal clinical evidence of neurotoxicity –in mice histo-pathological evidence – axon swelling tibia nerve; Dunnick et al., 1989)
- studies used to determined a RfC of 18 mg/m^3



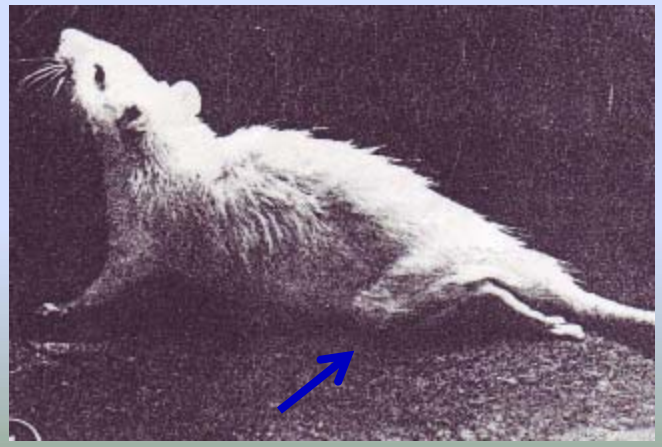
The Toxicity of HX is Significant

- **Primary Effects:**
- **neurotoxicity - paralysis of arms and legs, impaired touch and pain senses**
- **Visual system toxicity, Reproductive toxicity (testicular atrophy)**

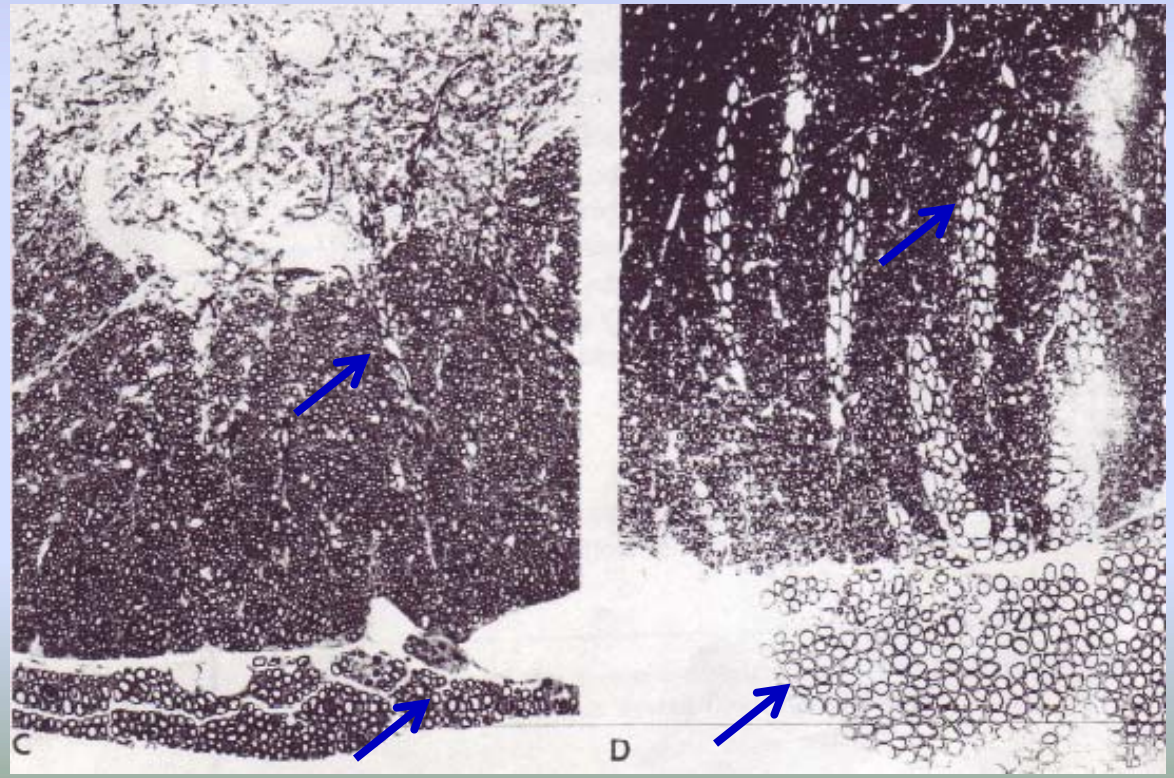
Teased nerve fibers – HX exposed, gluteraldehyde fixed; Spencer, 1980



Sprague Dawley Rat, hindlimb Paralysis; Schaumberg, 1976



Cross-section – lumbar spinal cord; DMHD exposed rats– example of γ-diketone neurotoxicity; Rosenberg, 1987; C=control; D=exposed



Supported by Human Data

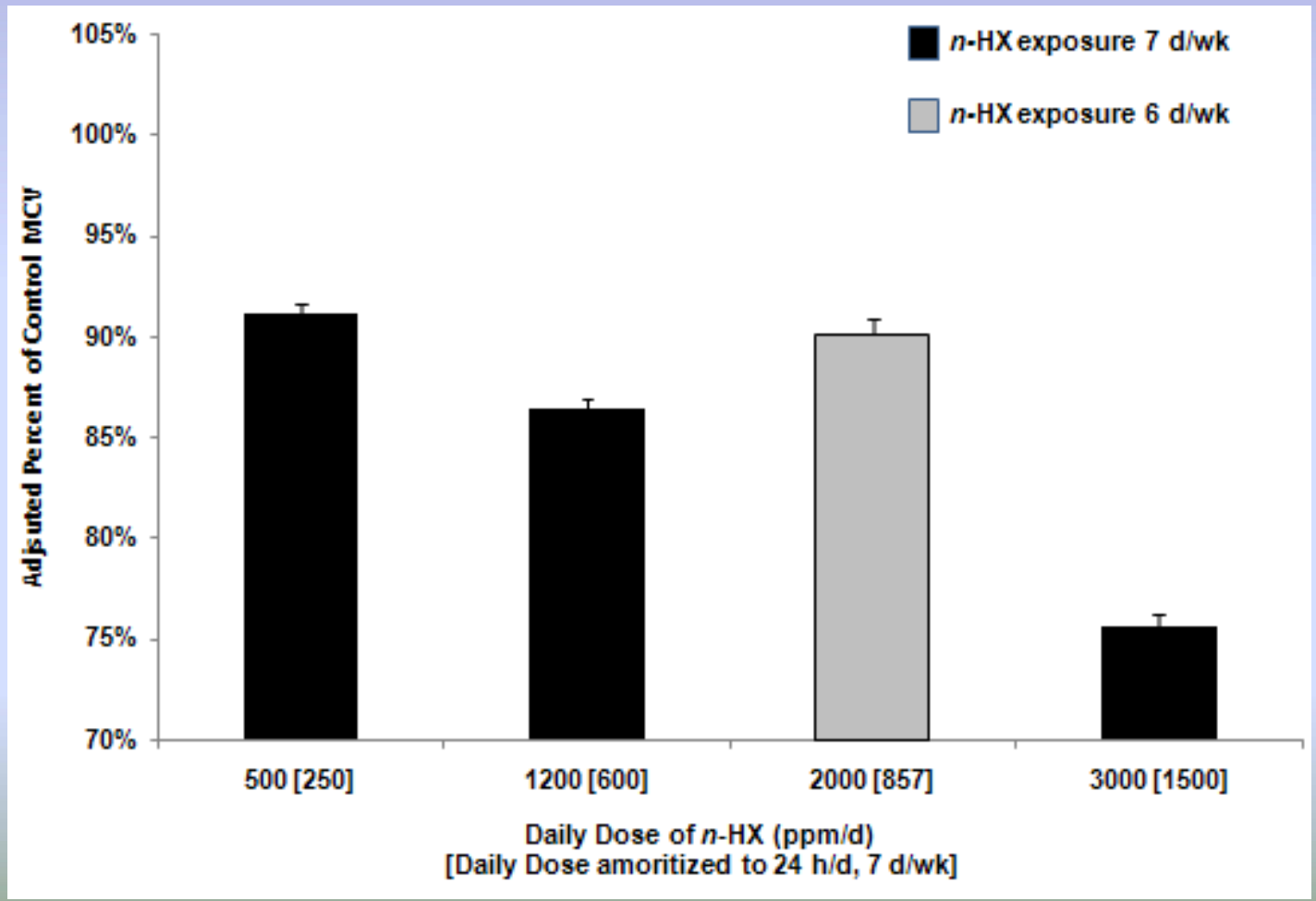
- **Mixtures of F1 aliphatic as well as other hydrocarbons**
- **HX proportion as low as 5% and neurotoxicity observed**
  - **Sandal makers, Leather coats, Shoe makers, Proofing workers, Tungsten carbide mill, Automotive repair workers (2001)**

Study Group	*Hydrocarbon*	*Solvent Composition*	*Concentration (ppm)*	*n*	*Duration (years)*	*Clinical?*	*Electro-Phsy?*	*Source*
Sporting Goods Manufacturer	HX	14.1%	110		0.25 to 9.1	Yes		Huang et al., 1989
	Benzene	0.8%						
	Toluene	3.1%						
	Xylene	0.1%						
	others?	81.9%						
Leather Coat or Shoe Production Factories	HX	47 to 99%	60 to 830	27	4.4 (0.3 to 20)	Yes	Yes	Oge et al., 1994
	others?							
Belt Making Shop	HX	5%				Yes		Gaultier, 1973
	pentanes	14%						
	heptanes	80%						
	total		< 5625 (mg/cu.m)					
Brocade Sash Cleaning Shop	HX	12.3%			0.5	Yes		Takeuchi et al., 1975
	pentanes (P)	13.0%						
	heptanes (H)	10.0%						
	octanes (O)	7.5%						
	benzene	3						
	toluene	3.0%						
	unspecified	57.0%						
	total		1250 (mg/cu.m)					
Shoe Factory	HX	15 to 71.6%		122	34.8 (15 to 59)	Yes		Abritti, 1976
	other C6 (CX)	12.7 to 50.4%						
	pentanes	typically low						
	heptanes	18 to 50%						
	toluene	3%						

Continuous vs Intermittent Exposure

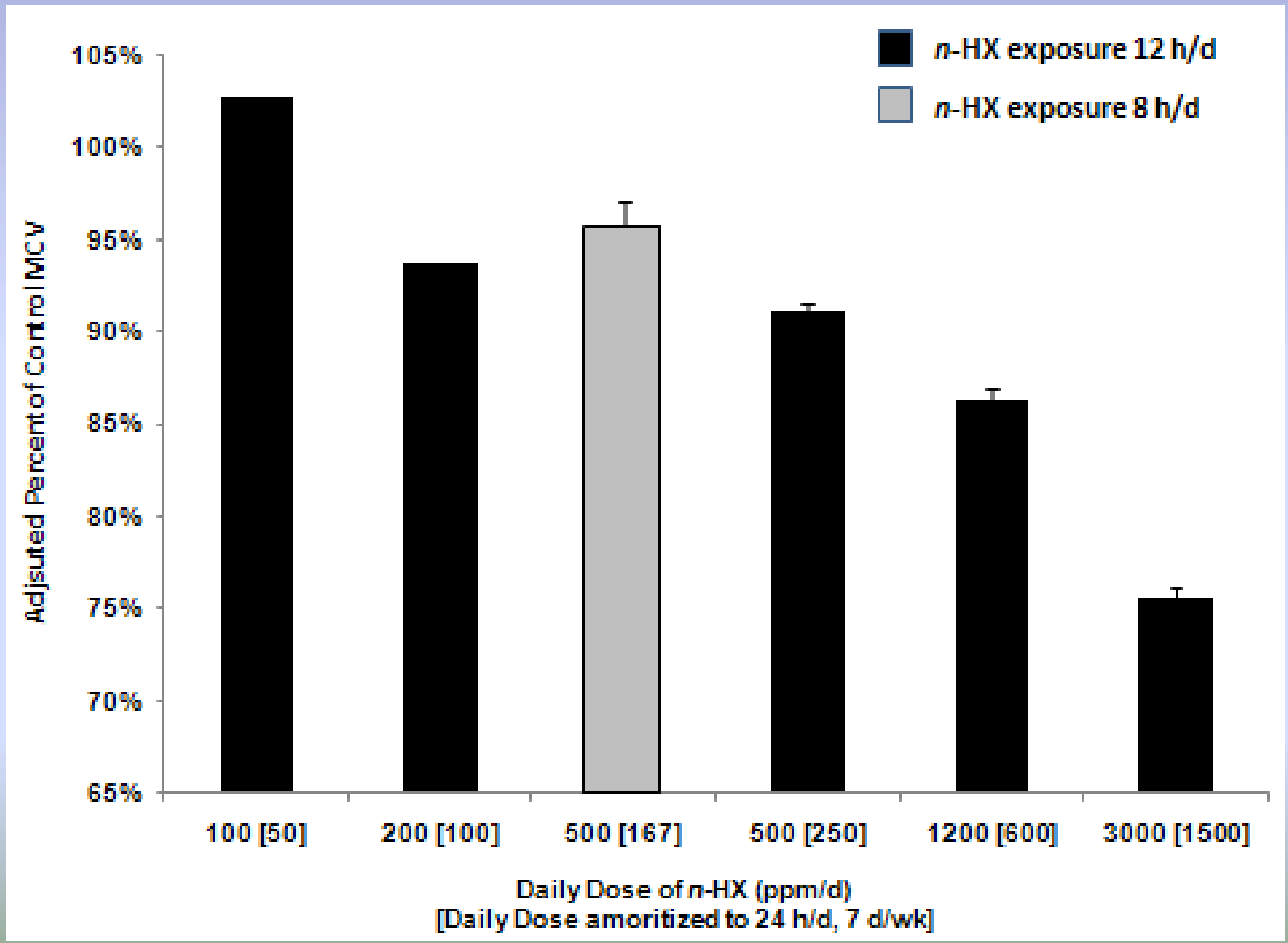
- Evaluate mean percent of control MCV (± SE)
- HX inhalation exposures 12 h/d, 7 d/w, 12 weeks (500ppm/d; 1200 ppm/d; 3000 ppm/d) (Huang et al. 1989)
- contrast against 6 d/wk 2000 ppm/d (Ichihara et al. 1998)

P-value - trend was 0.06 with inclusion of a 6 d/wk exposure, and 0.018 if the exposure of 6 d/wk was excluded



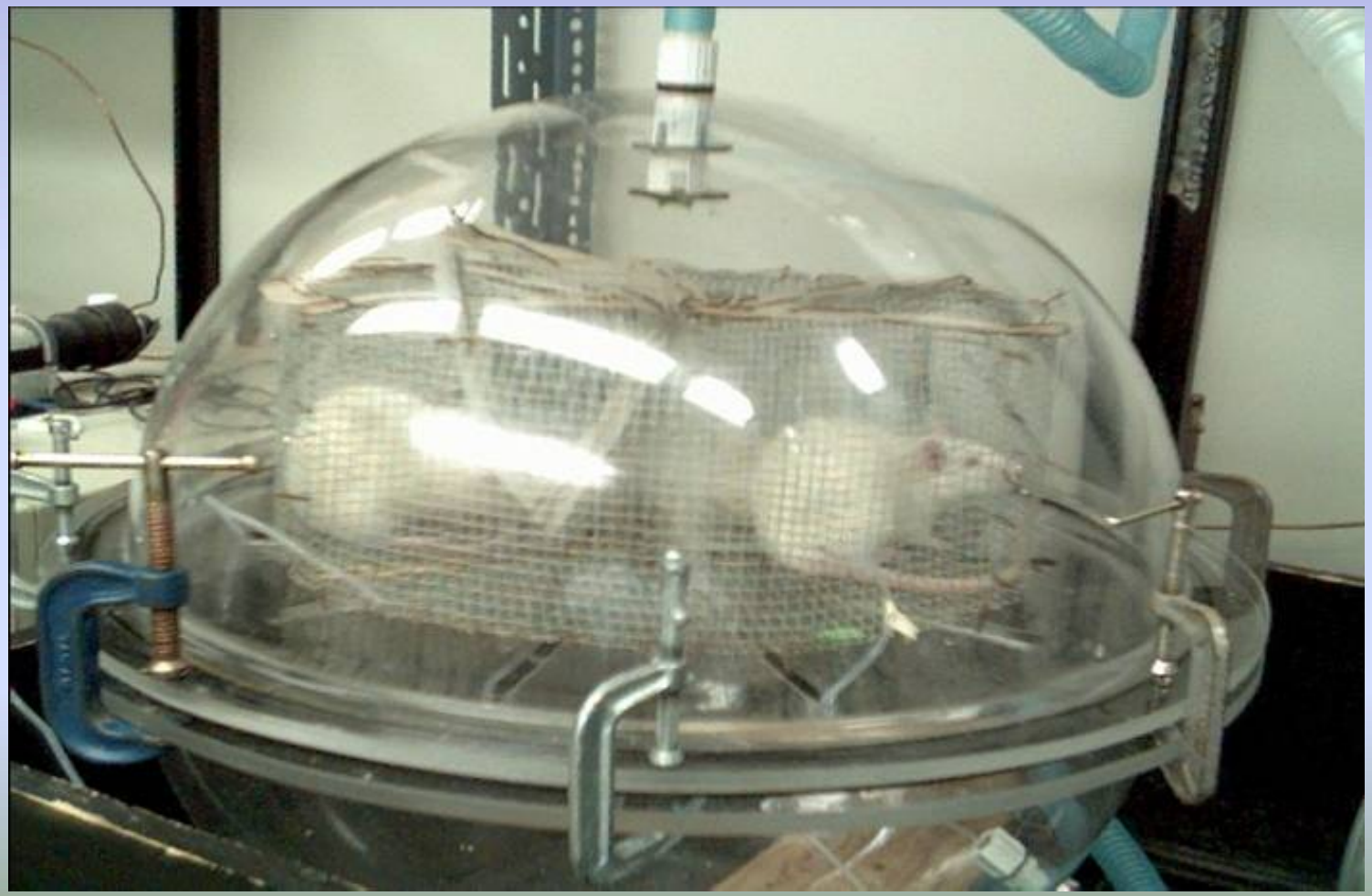
Shorter Daily Exposures

- HX exposures – compare 12 h/d versus 8 hr/d (amortized)
- MCV ± SE (Takeuchi et al. 1983; Ono et al. 1982; Huang et al. 1989; Iwata et al. 1984



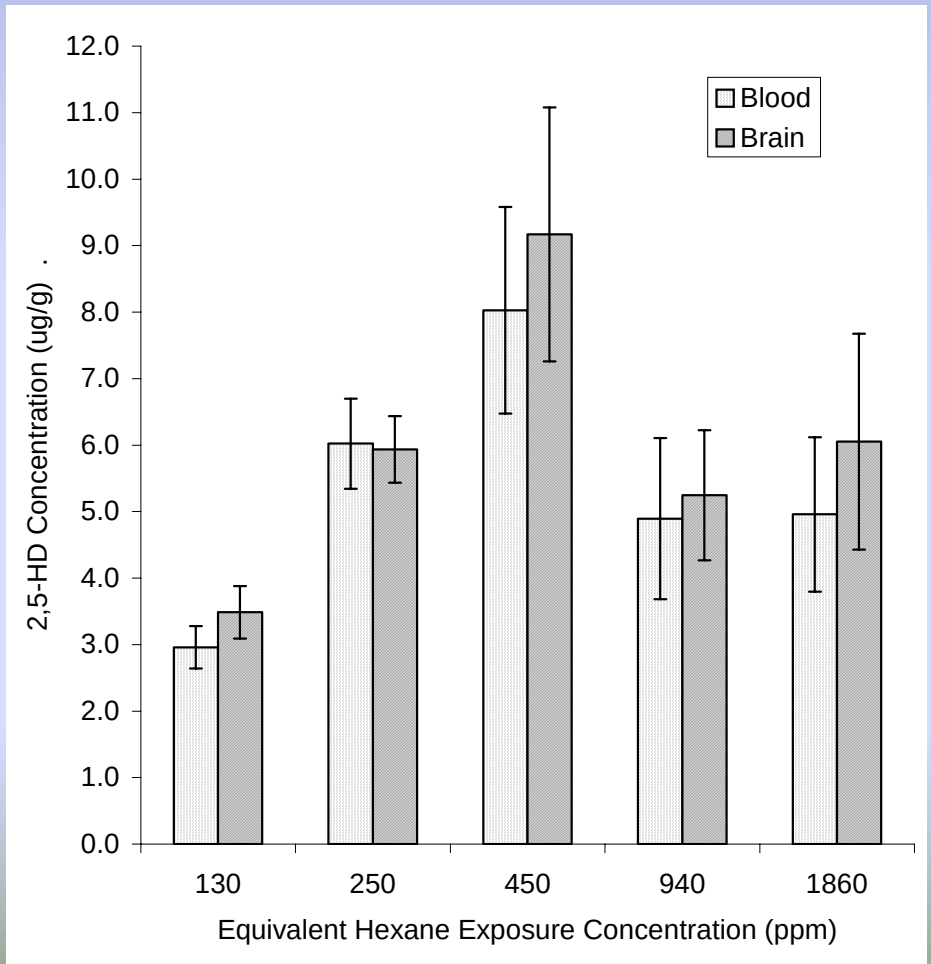
Toxicokinetic Differences

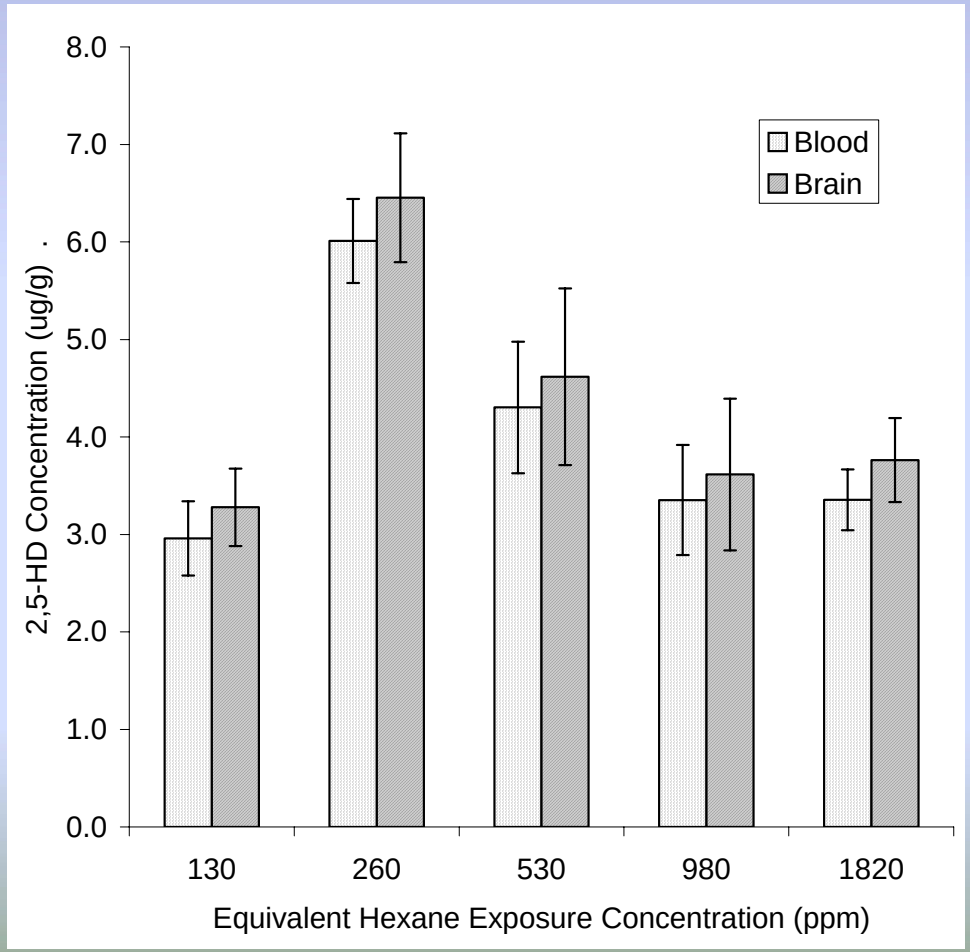
- Knafla and Roth (U of C, Faculty of Medicine)
- SD rats inhalation exposures – HX & commercial hexane
- Analyze blood and brain tissue for 2,5-hexanedione (toxic metabolite), varying doses, 6 h/d



Toxicokinetic Effects

- **Lower Doses are more Toxic!**
- **At higher doses, there is non-competitive and competitive inhibition by other C_6 isomers and HX itself**
- **explains the results of studies used to derive the RfC**



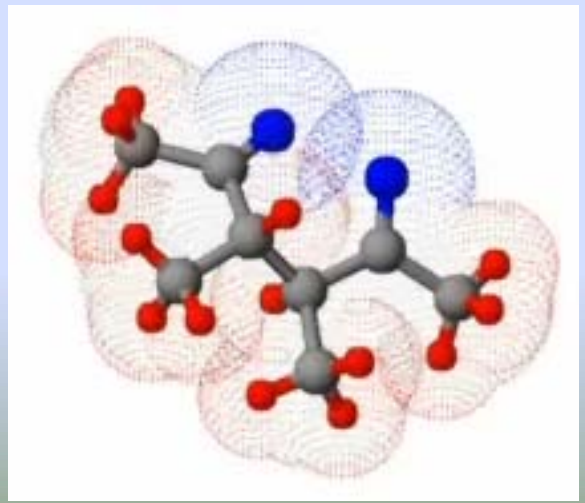


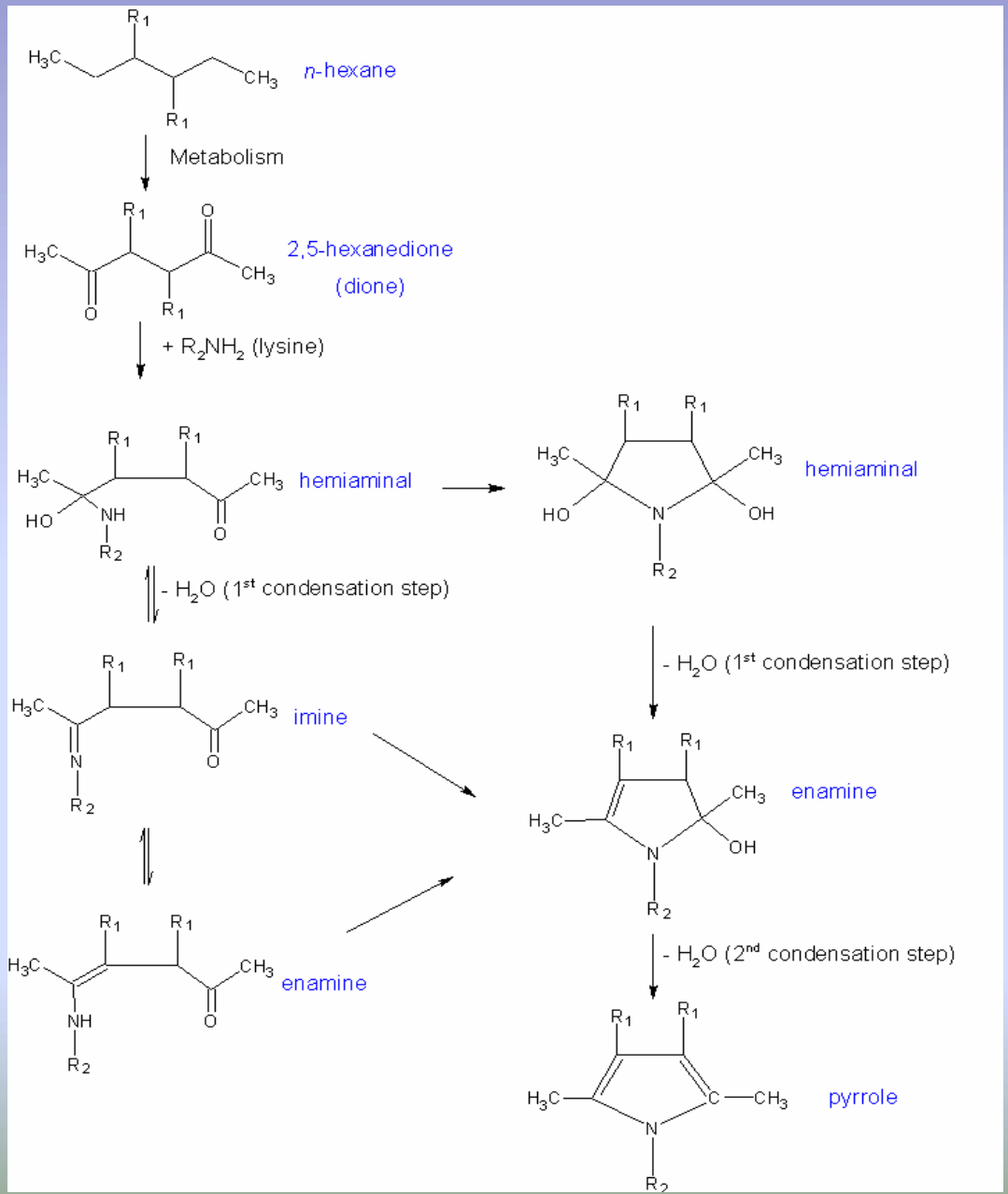
Why is HX so Unique??

- **Mechanism of Action:**

- **formation of 2,5-HD**
- **protein binding**
- **pyrrole formation**
- **protein crosslinking via pyrrole bridges**

- **don't see this with other aliphatics**





So, What are our Choices?

- **Ignore HX in most situations**
  - **Previous approach in US and Canada**
- **MDEP approach**
  - **Use the US EPA limit (0.7 mg/m$^{3)}$ for $C_{>6}$ to C_8 aliphatics**
- **Separate HX from the mixture like BTEX**
  - **use US EPA limit (0.7 mg/m$^{3)}$ for HX**
- **Equilibrium comments**
  - **problem with the US EPA limit**
  - **could use an alternate limit**

Problems with the US EPA Limit

- Equilibrium identified a problem with the US EPA limit
  - Simple error – not due to scientific approach
  - Due to data collection, not interpretation
  - Error with the y-axis scale

– Limit should be ~2x greater!

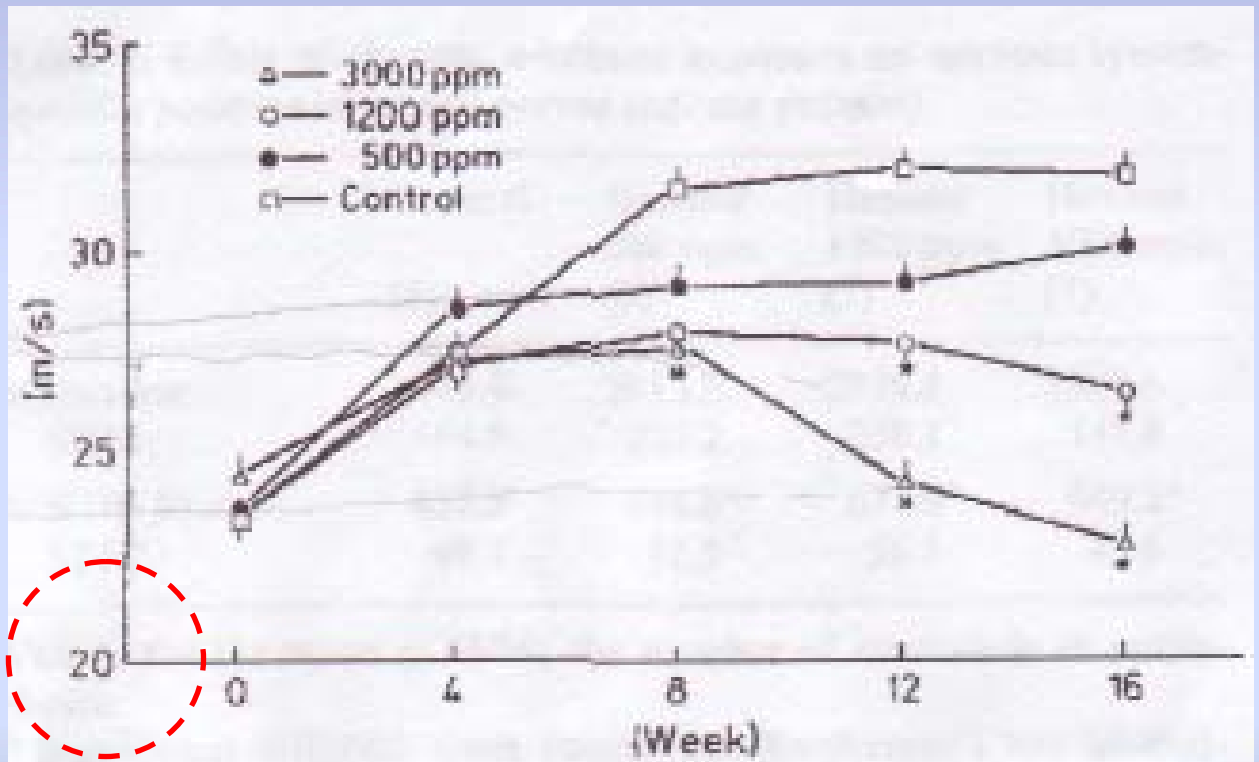
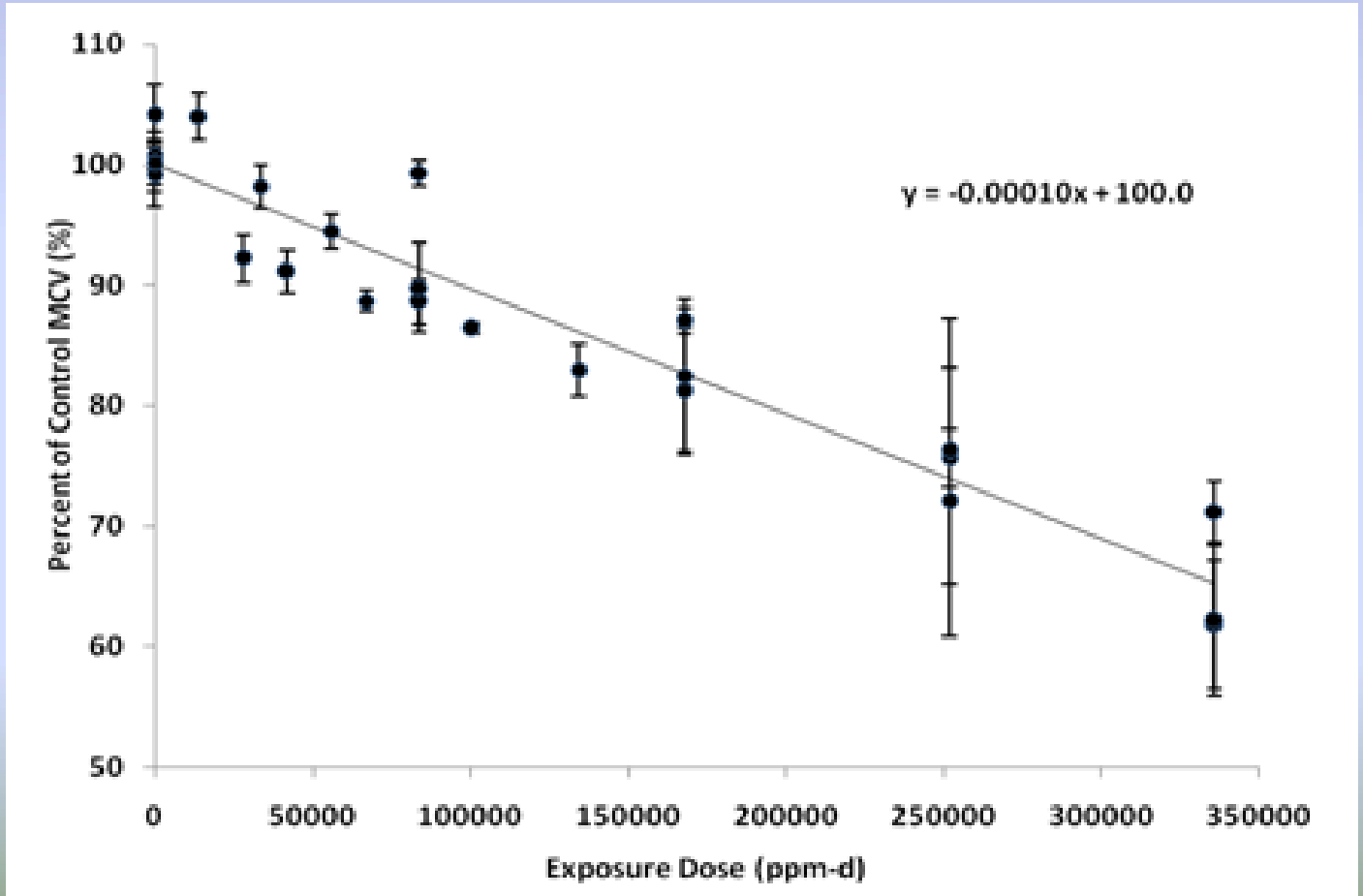


Fig. 2. Changes in motor nerve conduction Velocity (mean ± SEM). * Significant different from control by Bonferroni's test of multiple group means, $p < 0.05$

Equilibrium Approach

- OR, – use larger dataset generated in Japan
  - Huang et al. 1989; Takeuchi et al. 1980, 1981
  - results in a limit of 3.5 mg/m^3 versus 0.7 mg/m^3
    - occupational exposures may have lower risks because of intermittent exposure – a limit of 7 mg/m^3 would be recommended



Analytical Considerations

- **Discussions held with labs and research conducted at the U of C**
  - **HX can be detected as part of a hydrocarbon mixture**
  - **GC/MS could be used – greater certainty**
  - **GC-FID could be used – greater uncertainty**

Conclusions

- HX is a significant component of the F1 fraction
- HX has a unique toxicity due to its mechanism of action
- Toxicity occurs in the presence of other F1 hydrocarbons
- HX should not be used as a surrogate for F1
- It should be separated and included with BTEX (BTEHX!)
- HX can be detected as part of a F1 using GC/MS or GC/FID
  - Thus, F1 = F1 – BTEX – HX
- some toxicity limit should be selected to represent HX