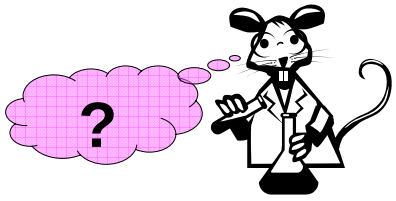



# How Can Animal Studies Help Address Key Questions on Human Biomonitoring?

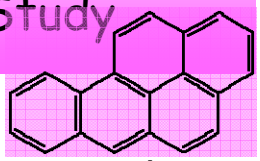
Claude Viau, D.Sc.
Chair in Toxicological Risk Analysis
University of Montreal



## Objective of this presentation

- Through the illustration of several experimental protocols aimed at answering some specific questions about PAH biomarkers, contribute to the identification of elements that could readily be added to "classical" toxicological studies to help develop biomarkers of exposure to chemicals.

## Outline: PAH as Case Study



- Background on PAH
- Controlled dose and exposure scenarios
- Effect of mixtures on toxicokinetics
- Chronic *vs.* acute exposures
- Diet *vs.* metabolite excretion
- BED *vs.* metabolite excretion
- Identification of new potential biomarkers
- Occupational *vs.* animal studies



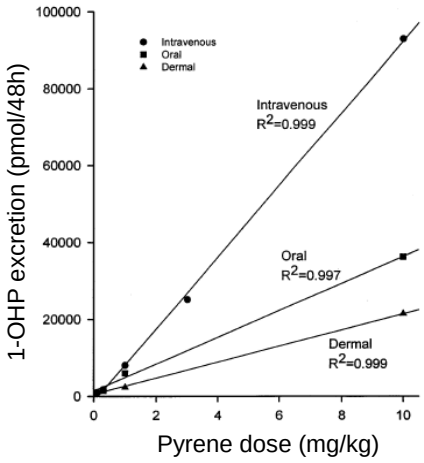
## Background on PAHs

- Ubiquitous in environment
- Some workers exposed to “high” doses
- Hundreds of individual compounds, some carcinogenic, others not
- Always come as mixtures
- Most frequently used biomarker = urine 1-OH-pyrene (1-OHP)
- Other biomarkers: DNA & protein adducts, other urinary OH-metabolites

# Controlled dose and exposure

Starting with the basis…

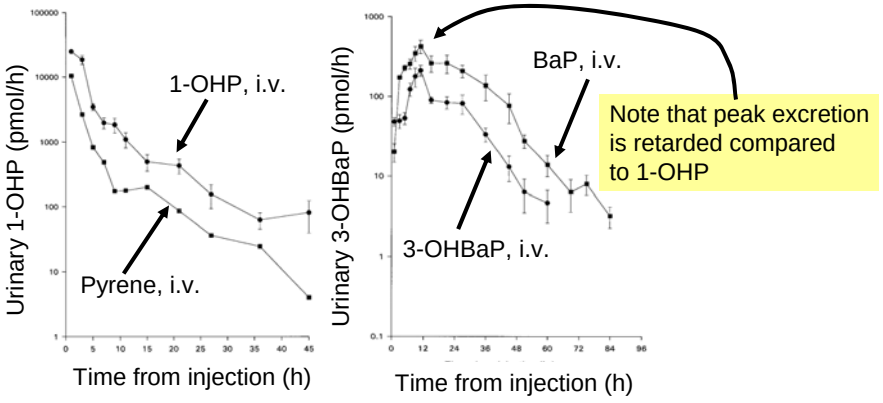
[Biomarker] – dose relationship for:
- I.V
- Oral
- Dermal




*Viau et al. (1999)*
*Toxicol. Lett. 108: 201-208*



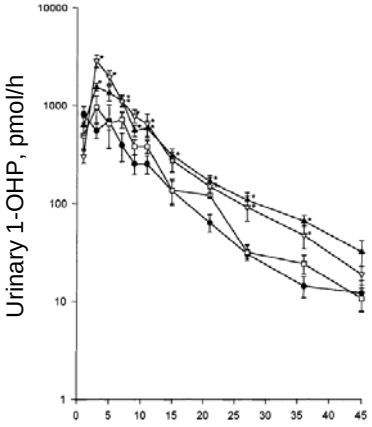
# Controlled dose and exposure




Note that peak excretion is retarded compared to 1-OHP

*Bouchard and Viau (1996) TAP 139: 301-309*

# Mixtures and toxicokinetics




Constant dose of pyrene
Varying doses of BaP

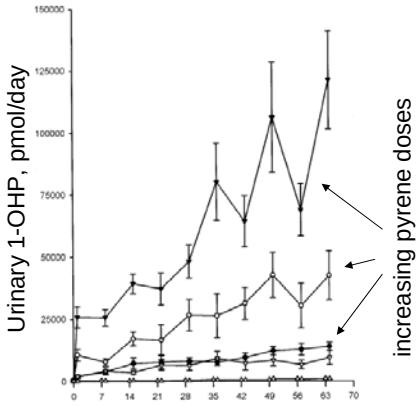
*********

1-OHP time course unchanged
Total 1-OHP excretion
increases at high BaP doses
but not at "realistic doses"

*Bouchard et al. (1998) Arch. Toxicol. 72: 475-482*



# Sub-chronic *vs.* acute exposures



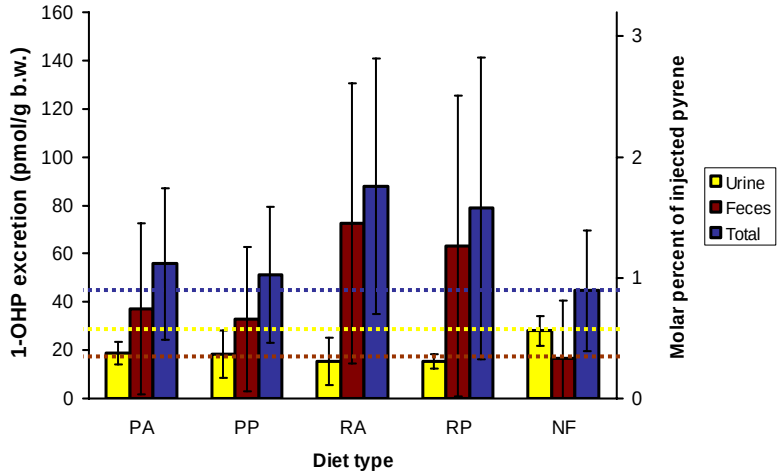

Acute studies:
→ t½ = 5 h
→ no accumulation in fat
(pyrene or 1-OHP)

********

Parallels observations
in workers (e.g. creosote)
Origin of accumulation
yet to be identified

*Bouchard et al. (2002) JTEH 65: 1195-1209*

# Diet *vs.* metabolite excretion

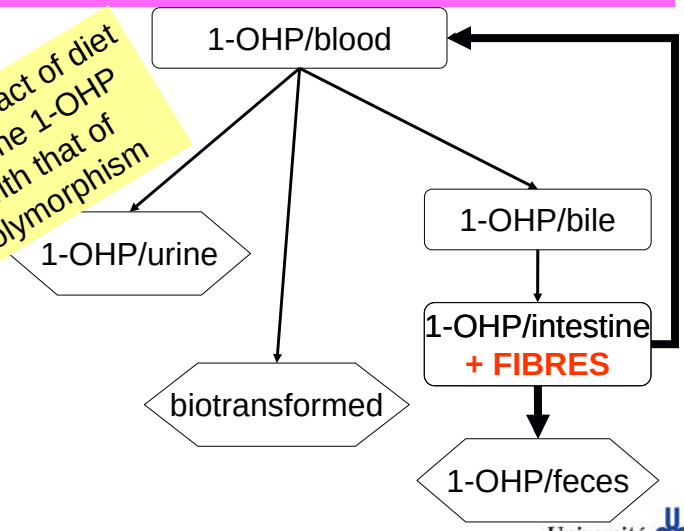



*Viau et al. (2004) Toxicol. Sci. 78: 15-19*

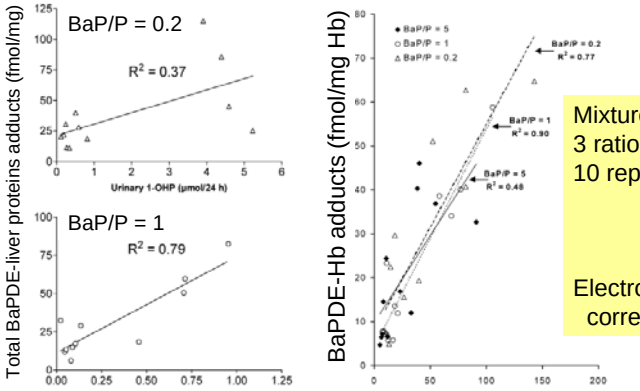


# Diet *vs.* metabolite excretion

Quantitative impact of diet on yield of urine 1-OHP compares with that of enzyme polymorphism



# BED *vs.* metabolite excretion




Mixture P + BaP
3 ratios: 0.2, 1, 5
10 repeated doses

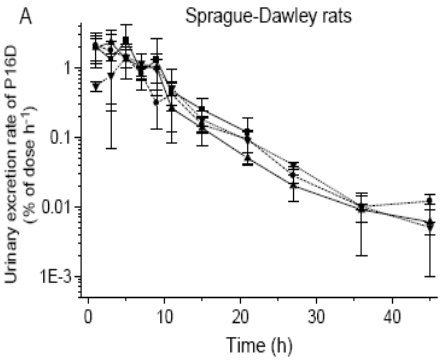
****

Electrophilic tissue burden correlates with urine BM

*Tzekova et al. (2004) Arch. Toxicol. 78: 351-361*



# Identification of new biomarkers



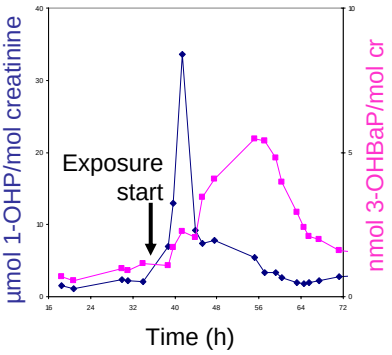

Doses: 0.05, 0.5, 5, and 50 µmol P/kg

********

Urine P16D = 14-24% of dose
Urine 1-OHP = 0.4-0.7% of dose
Comparable results for Wistar rats

*Ruzgyte et al. (2006) Biomarkers, in press*

# Occupational *vs.* animal studies




Worker with dermal, but no respiratory protection

Note time lag in peak excretion for 3-OHBaP *vs.* 1-OHP as previously observed in rats

*M. Lafontaine, Personal Communication*



# Discussion: Useful animal data for BM

- Identification of potential BM from ADME
- Quantitative dose-[BM] relationship
- Time course, especially for short-lived BM
- Dose-[BM] relationship in acute vs. chronic
- Effect-[BM] relationships
- Effect of "environmental factors" e.g.:
  - Mixtures
  - Diet

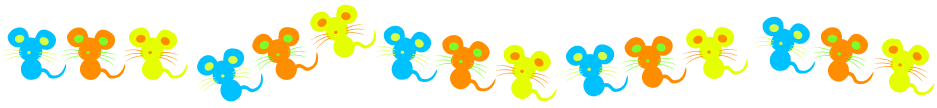
## Conclusion

- Animal studies are key in the development of BM for chemical exposure
- A first step in the identification of potential BMs and of the conditions under which they can be used
- A necessary step for the biomonitoring of substances for which volunteer studies are unethical



## In closing…

- Thanks to the many colleagues, students and technical staff who participated in these numerous studies



- Thank you for your kind attention