



**Karolinska
Institutet**

Data from controlled human exposure as basis for PBPK modeling of variability

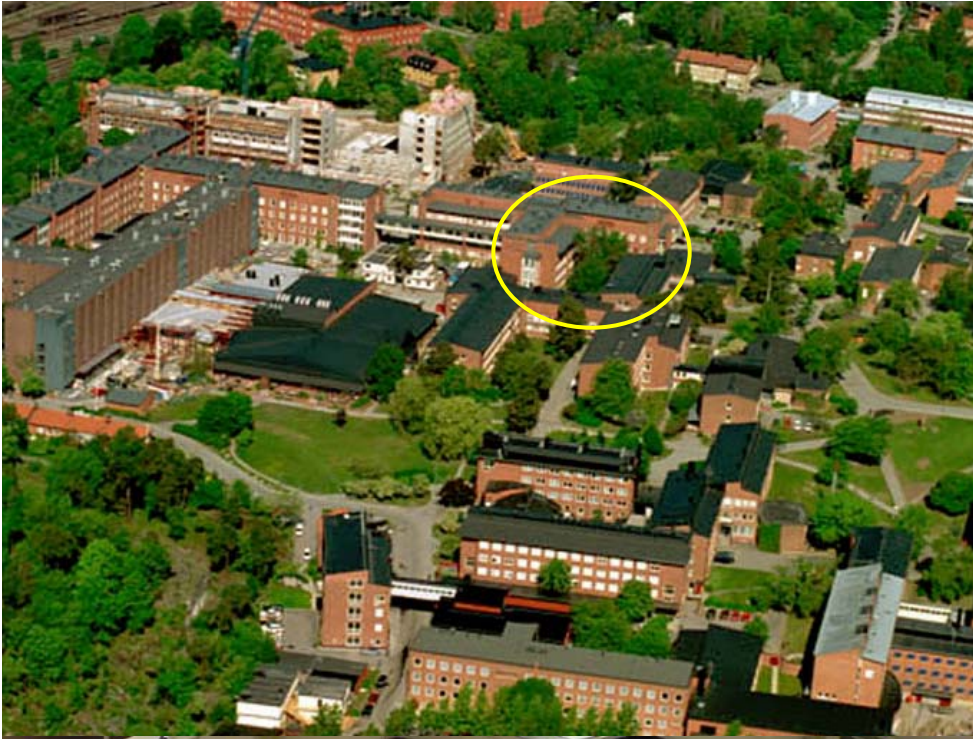
Gunnar Johanson

Work Environment Toxicology
Institute of Environmental Medicine
Karolinska Institutet
Sweden

Gunnar.Johanson@ki.se

Instructions: open packet, eat nuts

(on an American Airlines packet of nuts)



Outline

Data from controlled human exposure as basis for PBPK modeling of variability

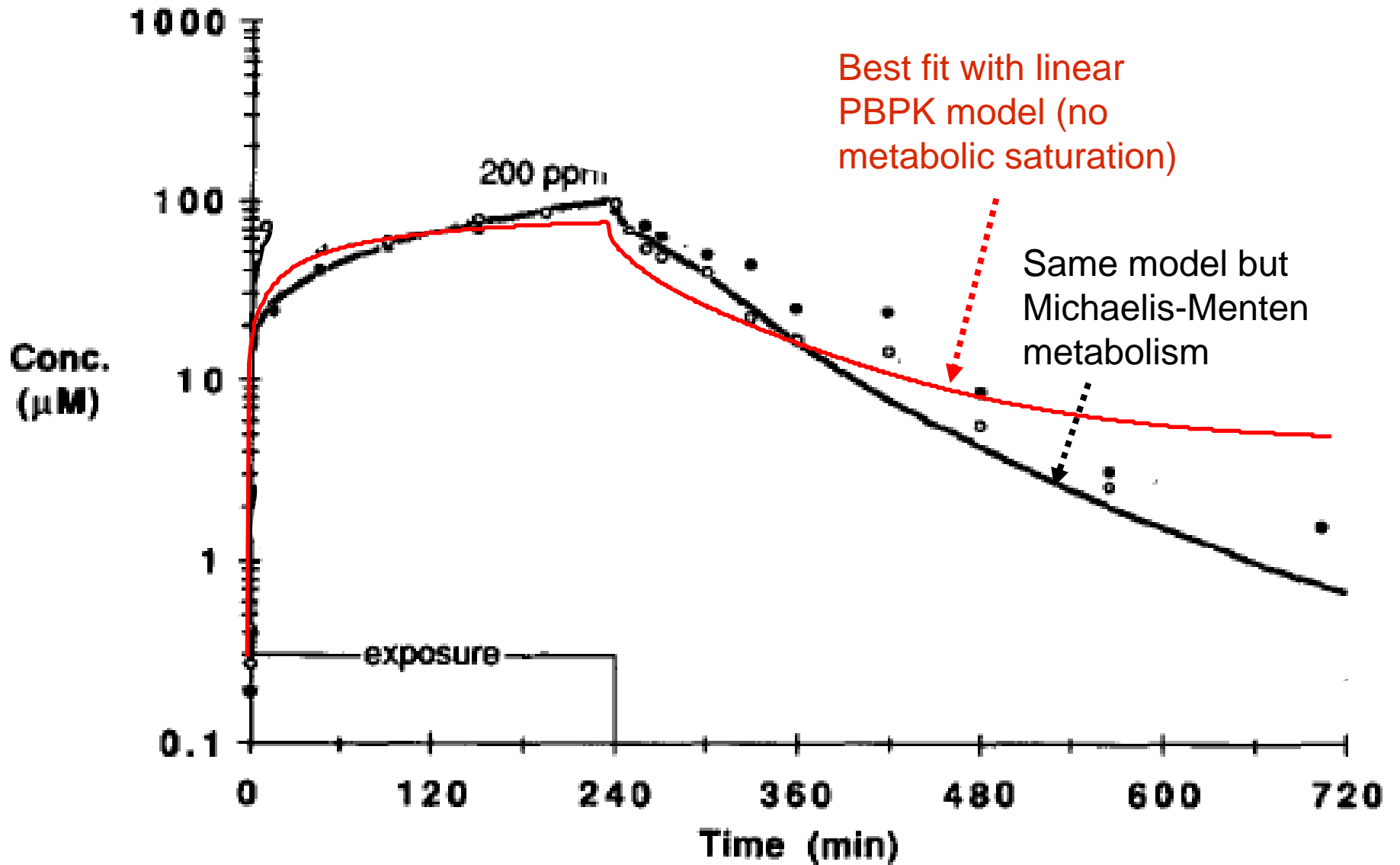
- The exposure chamber
 - Standardized conditions: Exposure, climate, workload
 - Known subjects: health, age, weight, height, genotype, phenotype
 - Control for confounders: smoking, ethanol, etc

- Some of our studies and experiences
 1. Saturation kinetics (**methyl ethyl ketone**)
 2. Workload (**dichloromethane** vs **acetone**)
 3. Washin-washout in the airways (**acetone**)
 4. Variability in adipose tissue blood flow (**toluene**)
 5. CYP2E1 phenotyping (**chlorzoxazone**)

- Conclusions

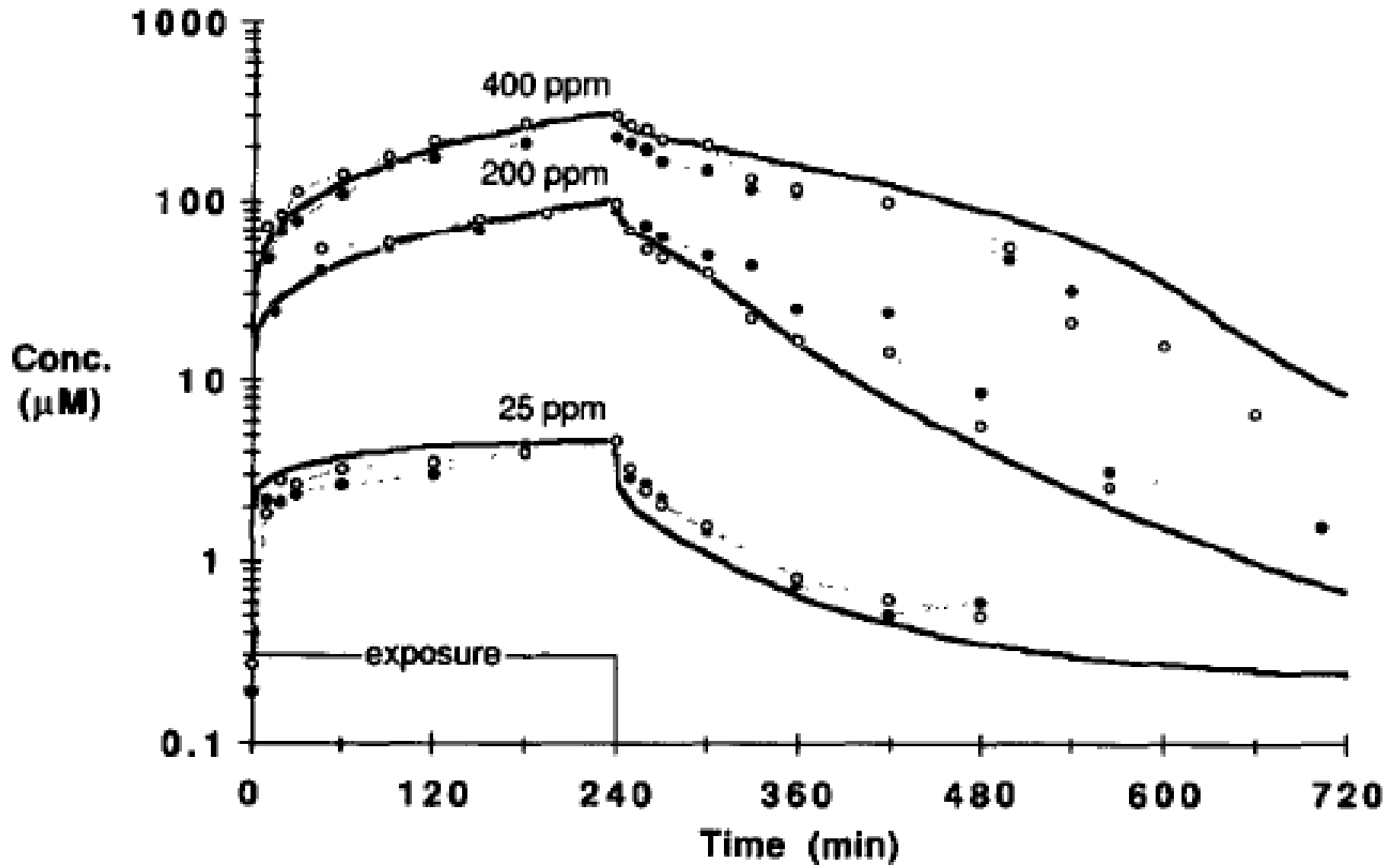
1. Saturation kinetics (MEK)

- Experimental:
 - Two males exposed to 200 ppm methyl ethyl ketone for 4 hours
 - "Strange" time course in blood (compared to previous experience with other solvents)

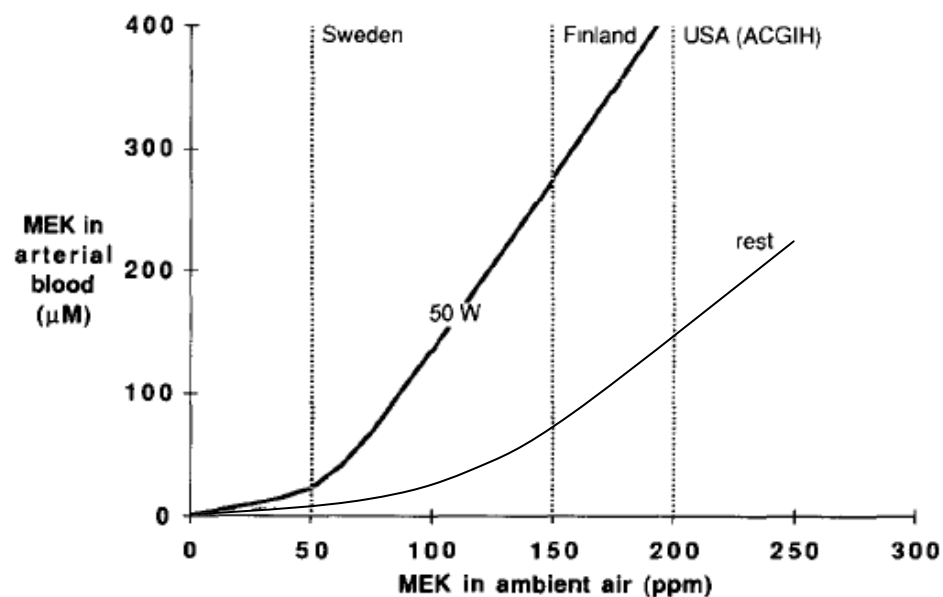


1. Saturation kinetics (MEK)

- Experimental:
 - Two males exposed to 200 ppm methyl ethyl ketone for 4 hours
 - "Strange" time course in blood (compared to previous experience with other solvents)
- PBPK modeling:
 - Linear model cannot explain observed data regardless of clearance value
 - Michealis-menten model explains data well when fitting V_{max} and K_m
 - Results suggest metabolic saturation at realistic workplace exposure levels (200 ppm = TLV)
- Confirm by additional experiments !



1. Saturation kinetics (MEK)



- Failure to detect saturation kinetics may lead to
 - Serious under- (or over-) estimates in dose-response extrapolation
 - Serious errors in parameter estimates

Potentially for all fitted parameters

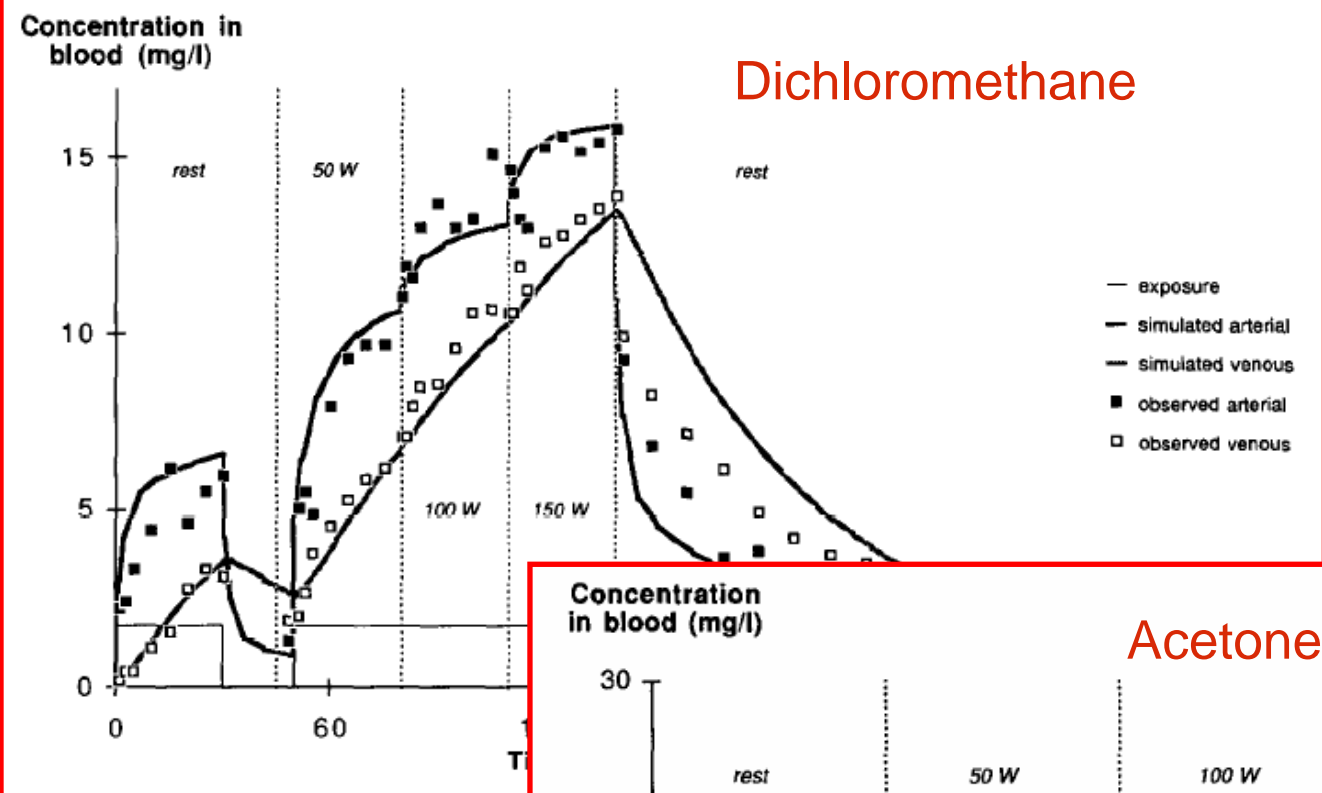
This goes for any kind of model mis-specification !

2. Respiratory uptake in relation to workload

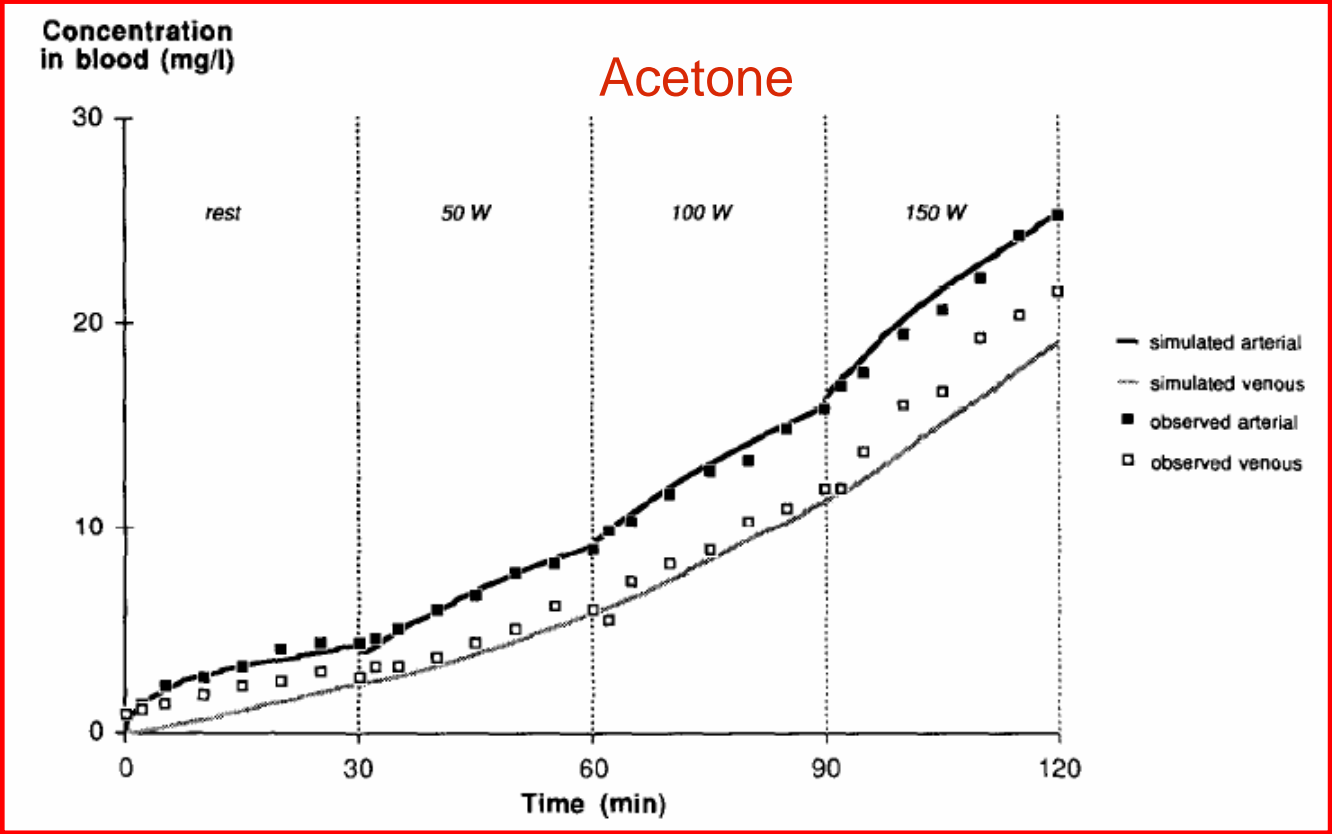
- Pulmonary ventilation varies 10-fold between rest and hard work (5 – 50 L/min in adult)
- Important source of variation
- Is work load properly modeled?

Johanson, Näslund. Toxicol Lett 41 (1988) 115-127

Dichloromethane



Acetone



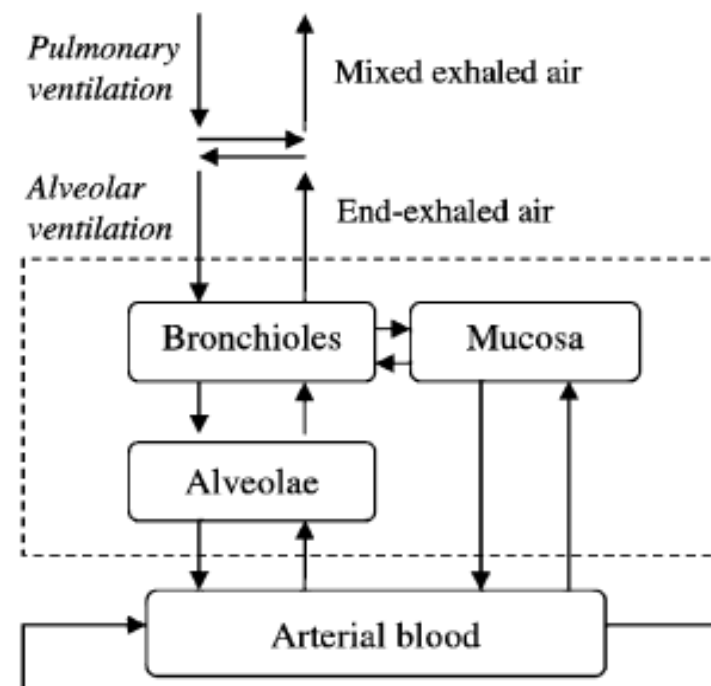
2. Respiratory uptake in relation to workload

- Pulmonary ventilation varies 10-fold between rest and hard work (5 – 50 L/min in adult)
- Important source of variation
- Is work load properly modeled?

- Yes, at least when looking at time course in blood and fitting metabolic parameters

3. Washin-washout in the airways (acetone)

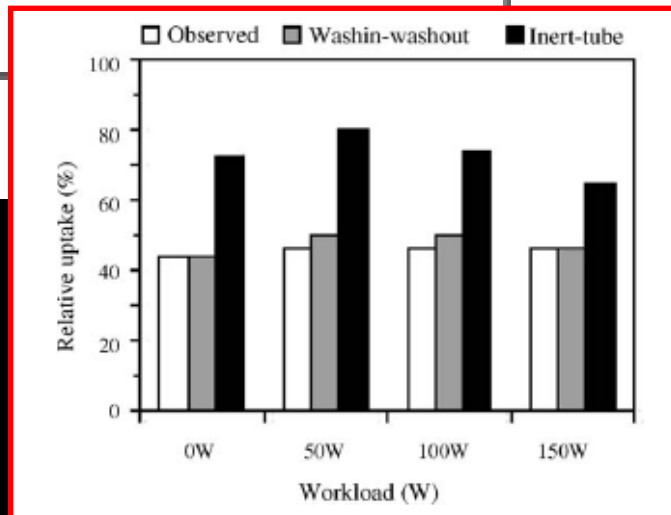
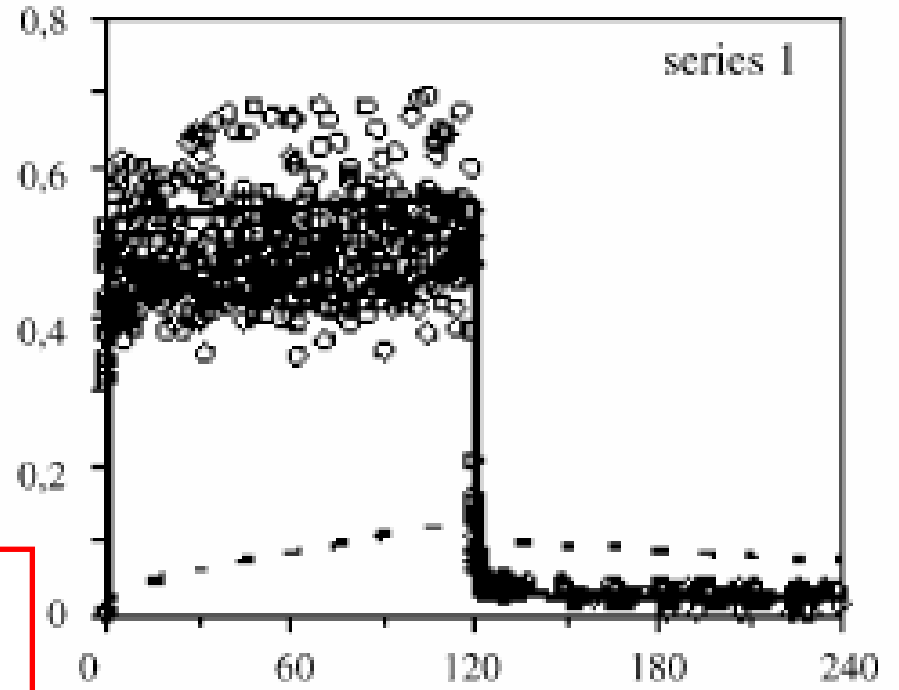
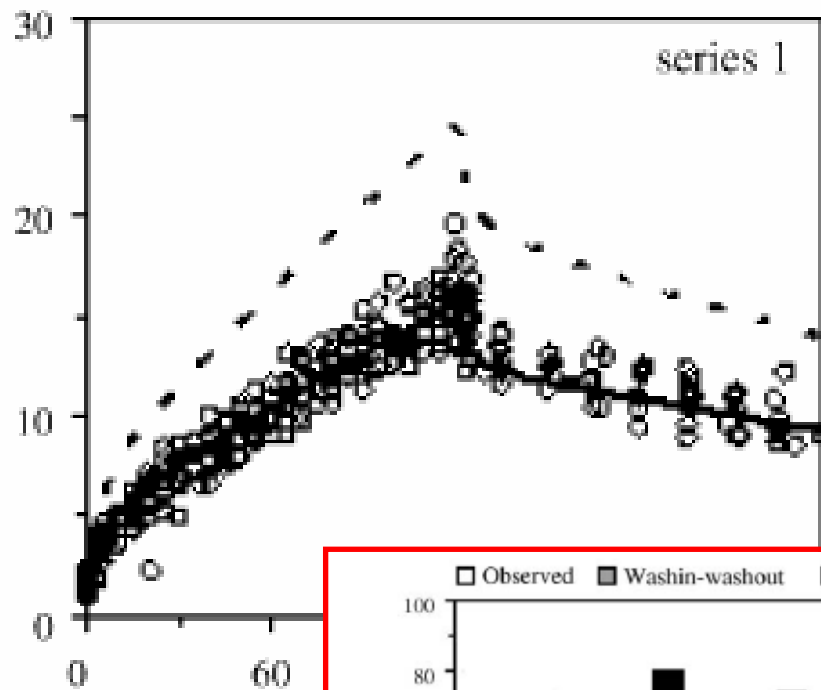
- **Experimental**
 - 26 exposures, 18 subjects
 - 0 - 150 W workload
 - 500 - 1300 mg/m³ acetone for 2 h
 - Acetone in blood, mix-exhaled and end-exhaled air
- **Model**
 - Regular inhalation pbpk (= "inert tube")
 - Same with washin-washout compartments added



Arterial blood

End-exhaled air

○ Observed — Washin-washout model - - - Inert tube model



3. Washin-washout in the airways (acetone)

- **Experimental**

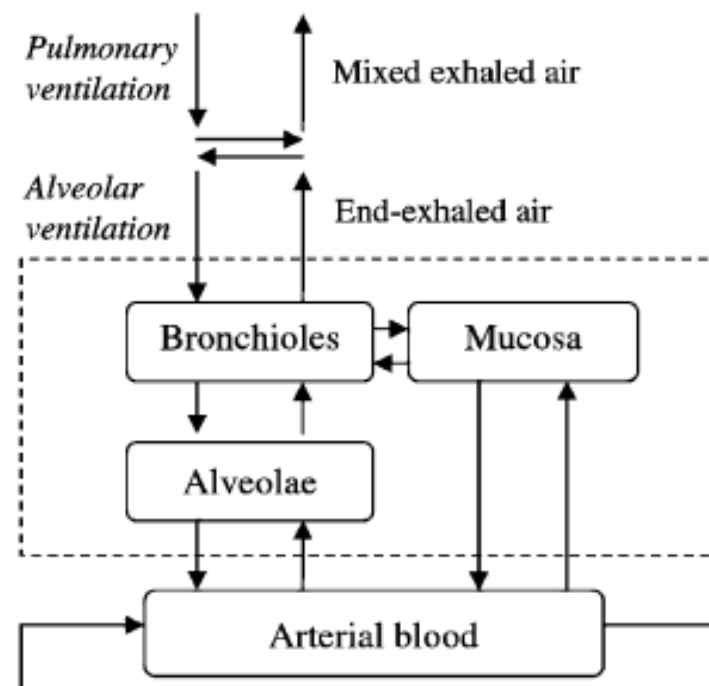
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- **Model**

- Regular inhalation pbpk (= "inert tube")
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- **Results**

- Inert tube model incompatible with breath data, washin-washout model works well
- Washin-washout models need further development and validation



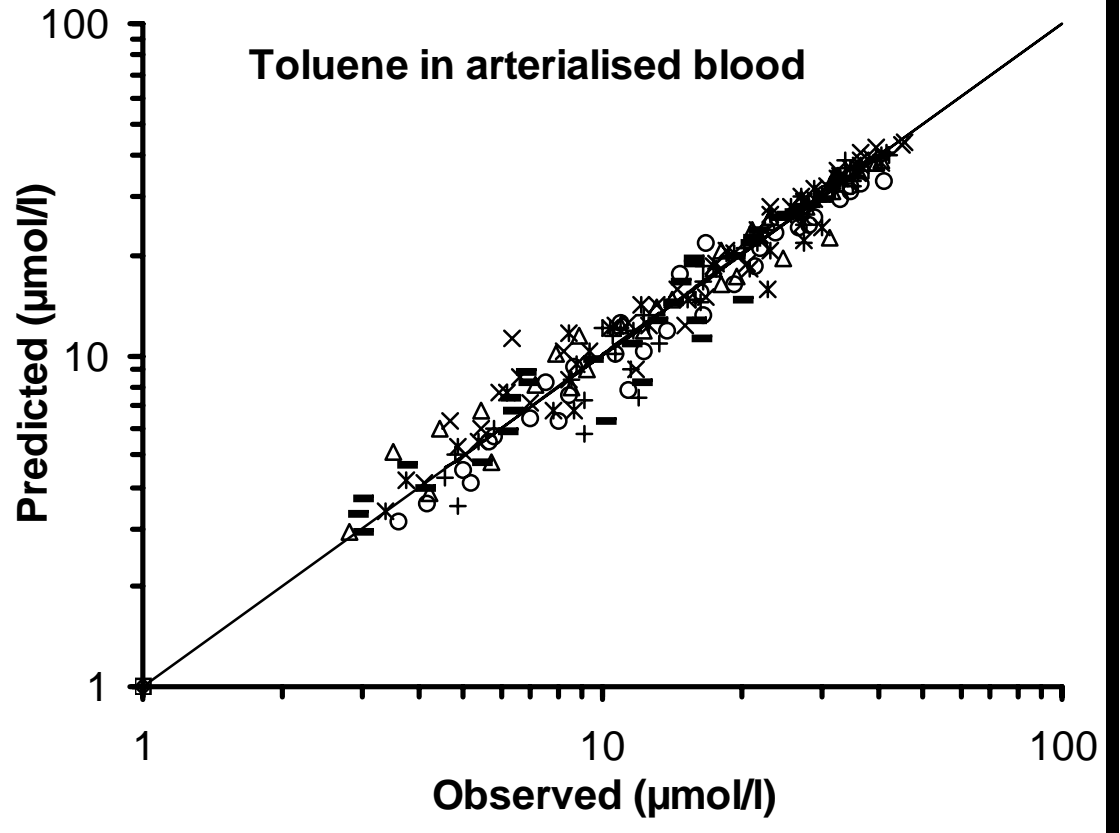
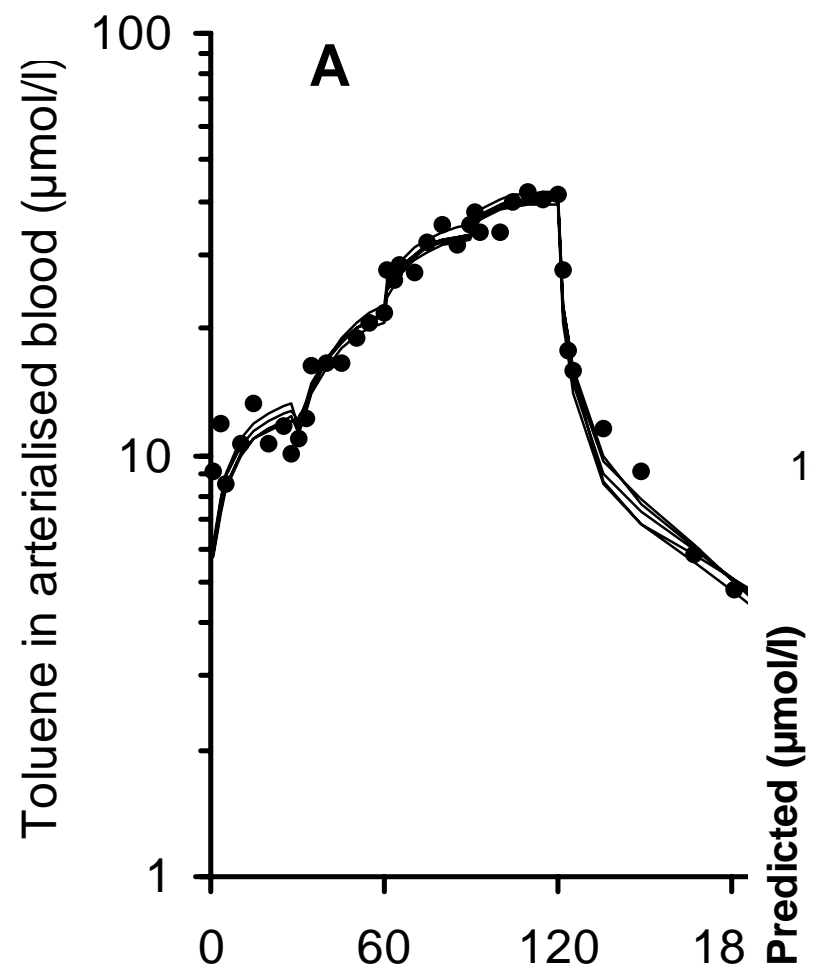
3. Washin-washout in the airways (acetone)

- **Experimental**
 - 26 exposures w. 18 subjects
 - X-y ppm acetone, x-y hours
 - 0, 50, 100, 150 W workload
- **Model**
 - Regular inhalation pbpk (= "inert tube" model)
 - Same model with washin-washout compartment added
- Inert tube model incompatible with breath data for acetone (and other polar solvent vapors) **Model mis-specification**
- "Washin-washout" models need to be developed and validated

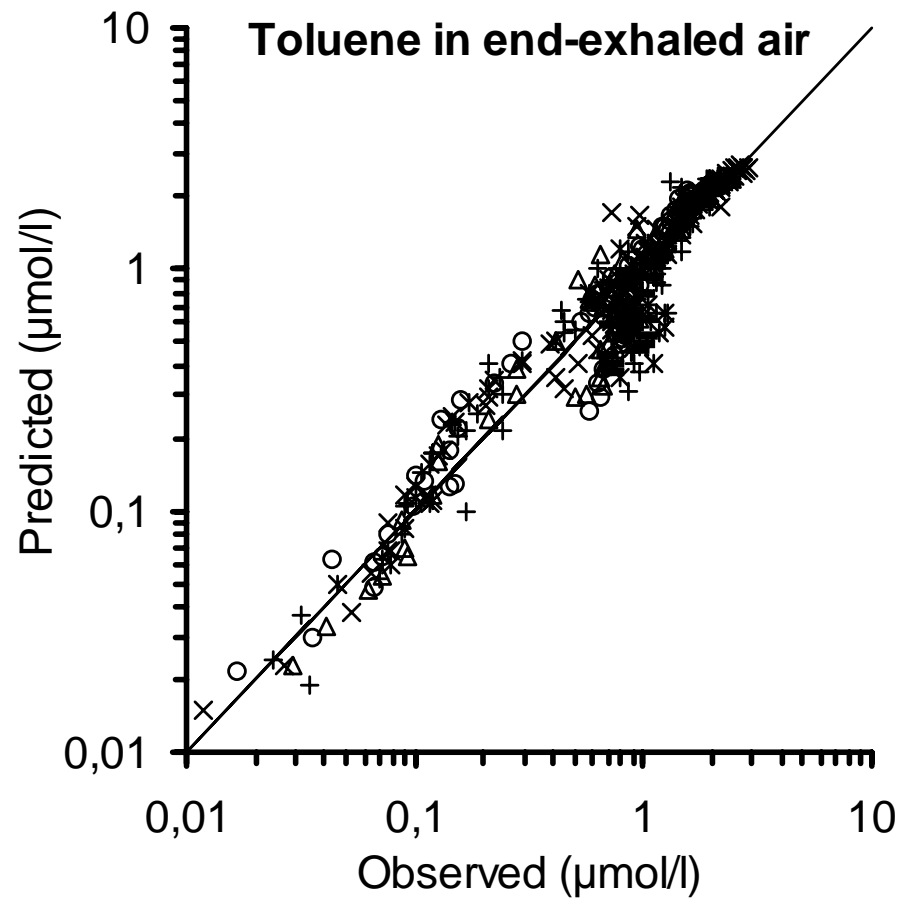
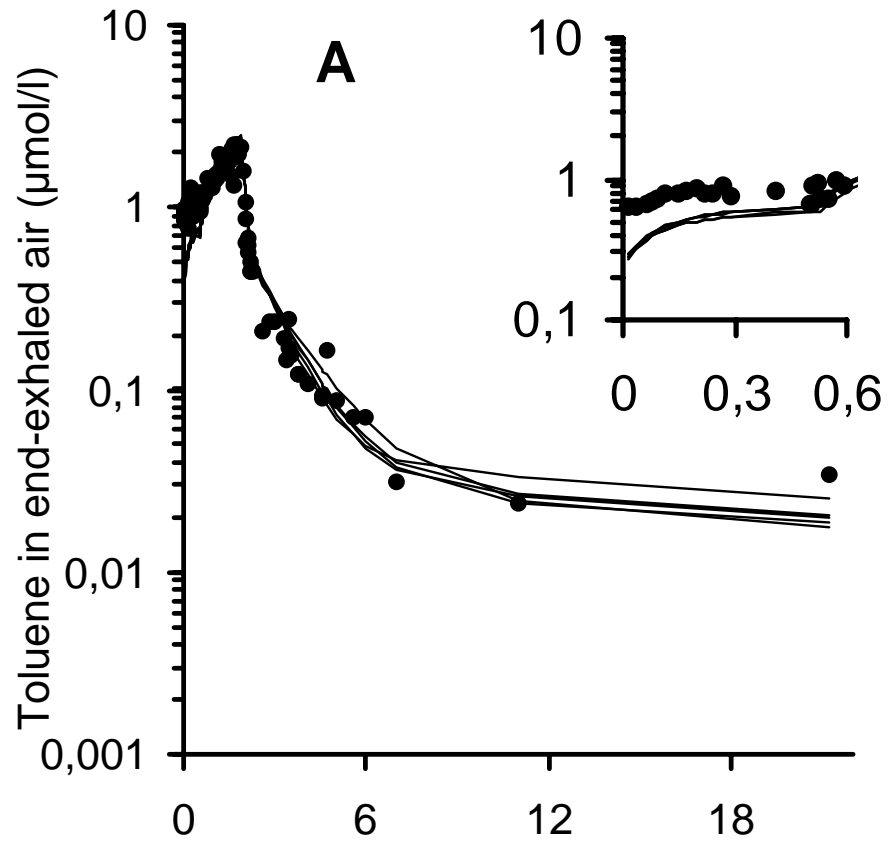
4. Variability in adipose tissue blood flow (toluene)

- **Experimental:**
 - Six male volunteers exposed to 80 ppm toluene for 2 hours during rest and moderate to heavy exercise (50–150 W)
 - Toluene measured in arterial blood, exhaled breath and subcutaneous fat tissue
- **Model:**
 - population PBPK model, scaling to bw, ht, workload
 - Split fat compartment in two
 - Bayesian approach, hierarchical statistical model
 - MCMC simulation

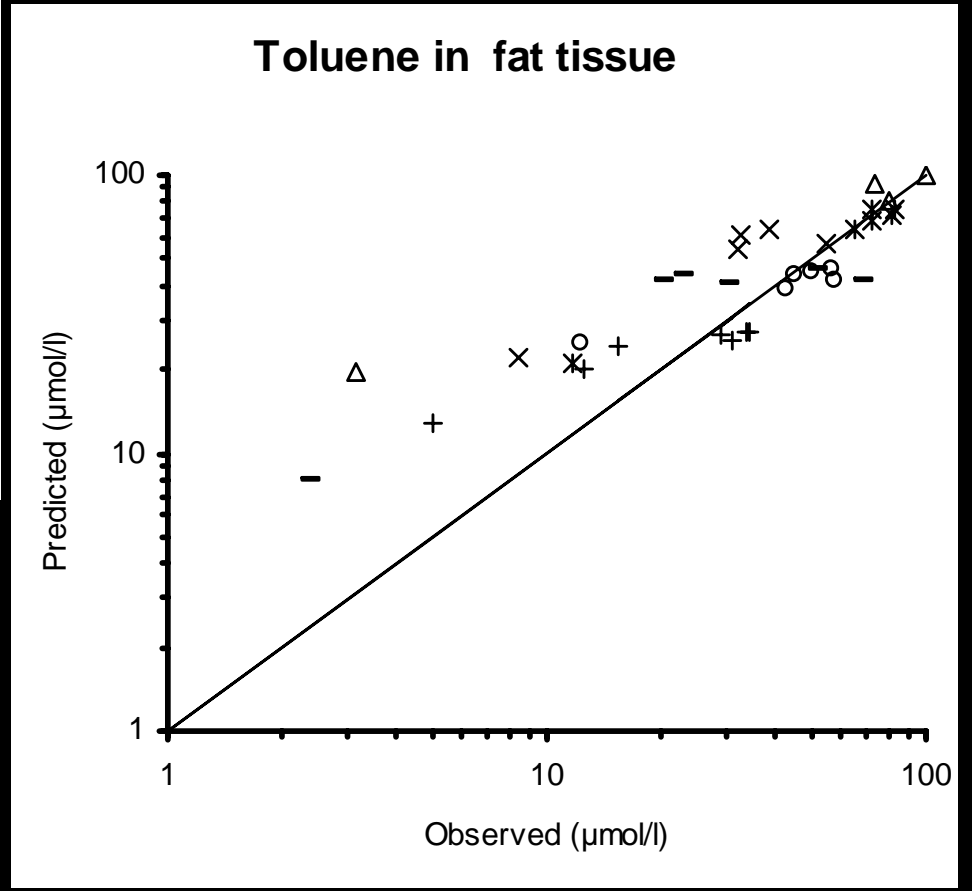
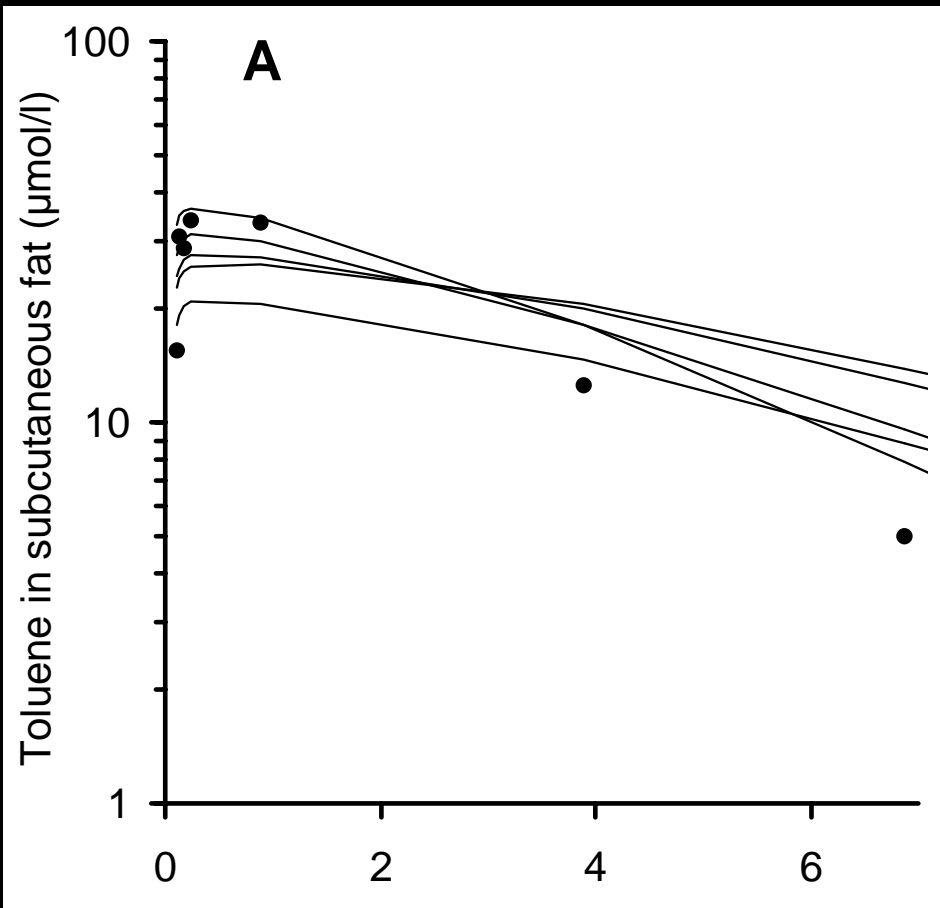
Jonsson, Johanson. Toxicology
157 (2001) 177-193



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4. Variability in adipose tissue blood flow (toluene)

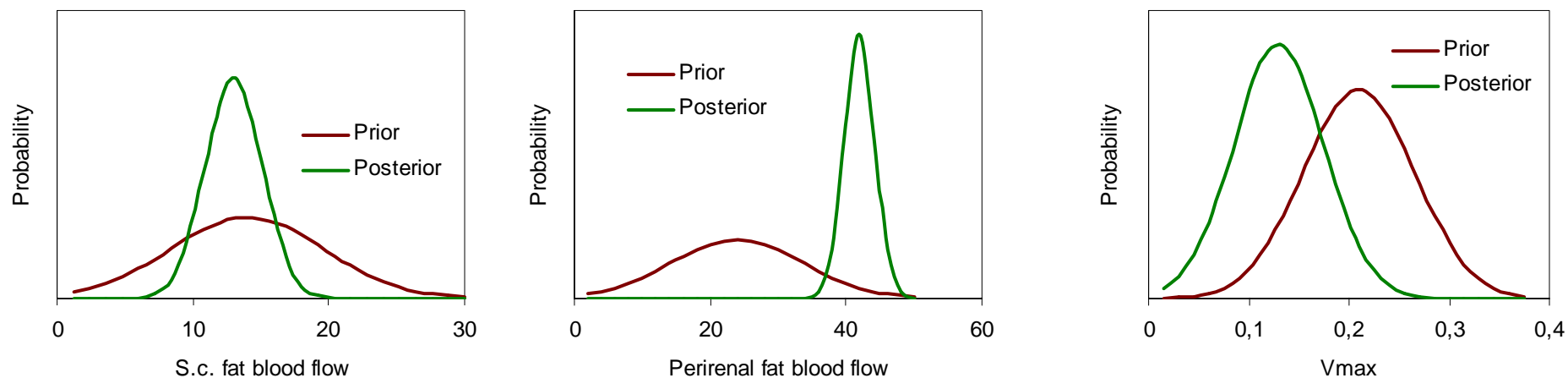
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 - Toluene measured in arterial blood, exhaled breath and subcutaneous fat tissue
- **Model:**
 - population PBPK model, scaling to bw, ht, workload
 - Split fat compartment in two
 - Bayesian approach, hierarchical statistical model
 - MCMC simulation
- **Results:**
 - Increased perfusion of perirenal fat with physical workload best described when set to the same, elevated, level at all exercise levels, rather than scaled directly to increase in oxygen uptake
 - No increase in subcutaneous fat perfusion detected
 - Improved posteriors

Improved posteriors (toluene)

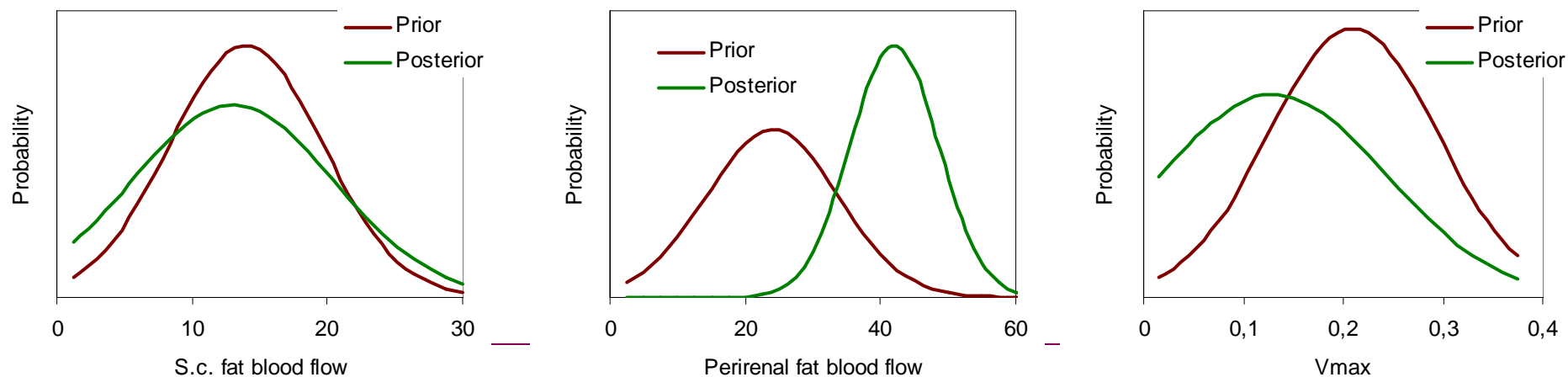
	Prior distribution		Posterior distribution	
	Mean	SD of mean	Mean	SD of mean
<i>Blood flows at rest (ml/min/l tissue)</i>				
Subcutaneous fat	14	41%	13	15%
Perirenal fat	24	41%	42	9%
<i>Increase in blood flow with exercise (ml/min/l tissue)</i>				
Subcutaneous fat	-	-	-	-
Perirenal fat	30	10%	71	15%
<i>Tissue:air partition coefficients</i>				
Fat	984	10%	870	10%
Liver	84	10%	81	9%
Well-perfused	84	10%	59	8%
Muscle	28	10%	21	6%
Blood	18	18%	16	10%
<i>Metabolism (nmol/min/kg)</i>				
Vmax	0.21	26%	0.13	22%

Improved posteriors (toluene)

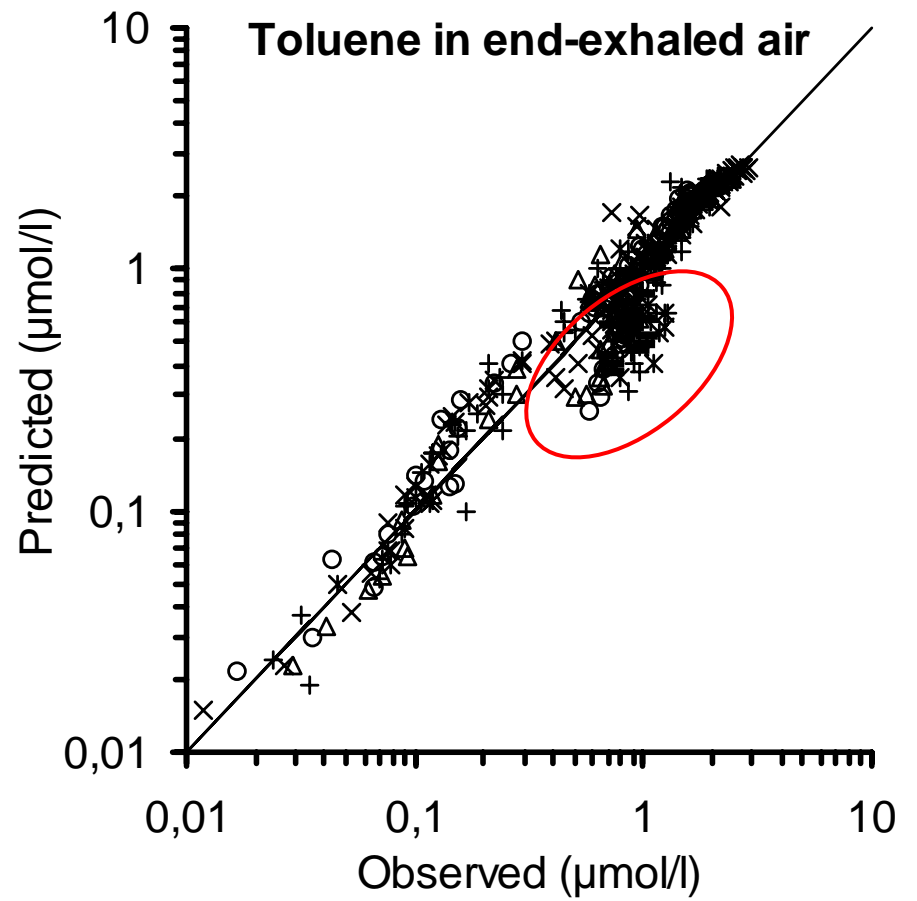
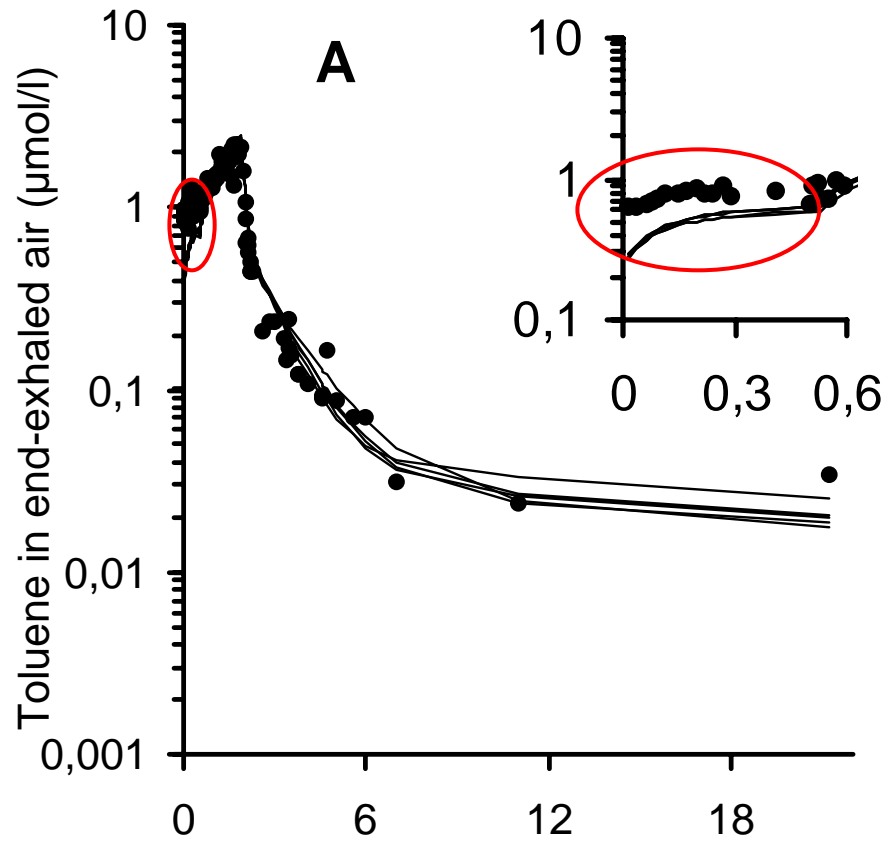
Distribution of population mean (uncertainty)



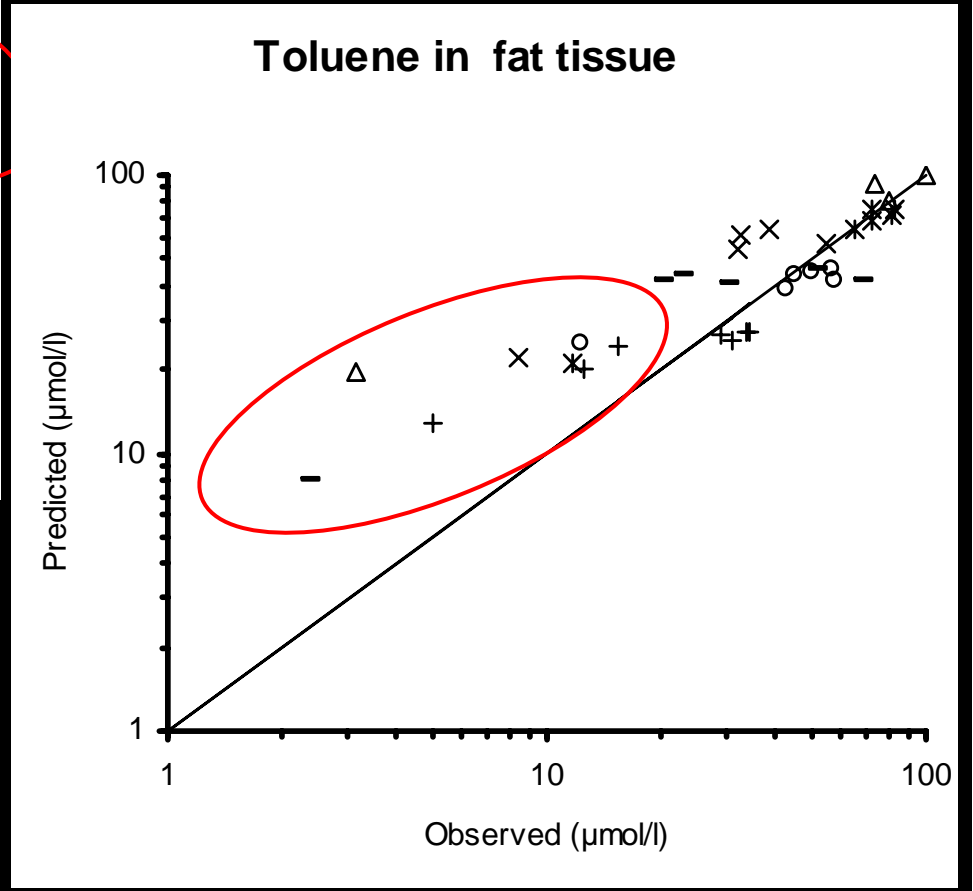
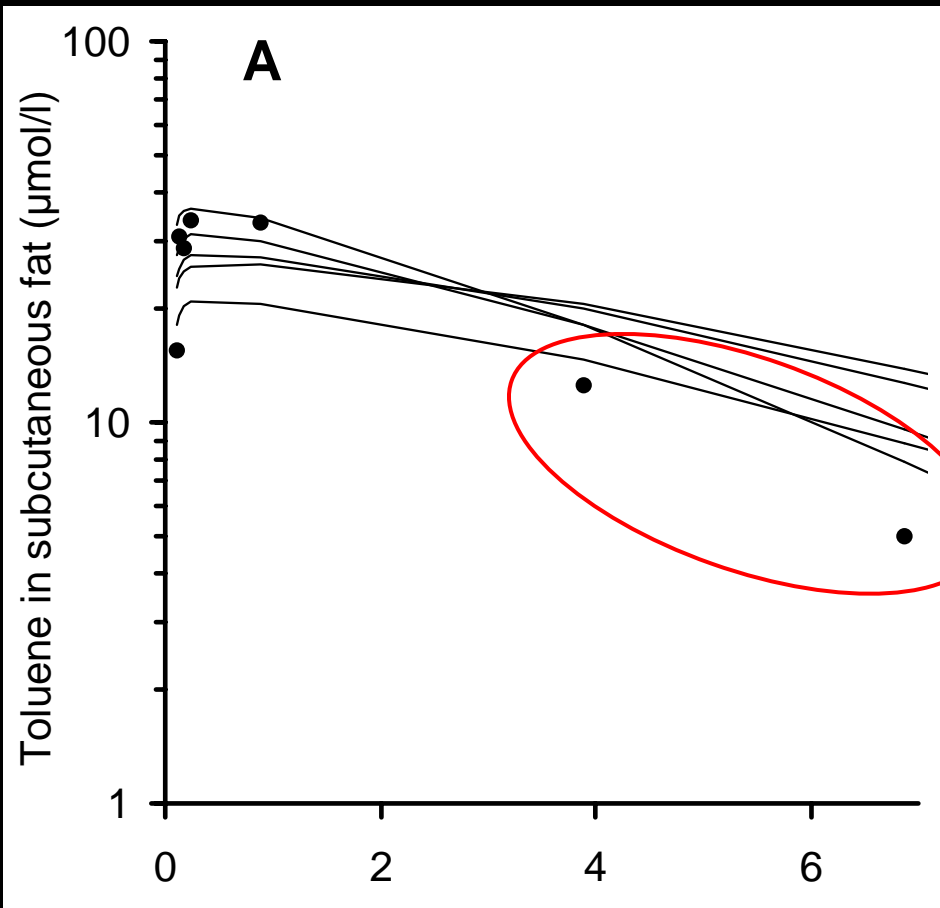
Distribution of population variability



Jonsson, Johanson. Toxicology
157 (2001) 177-193



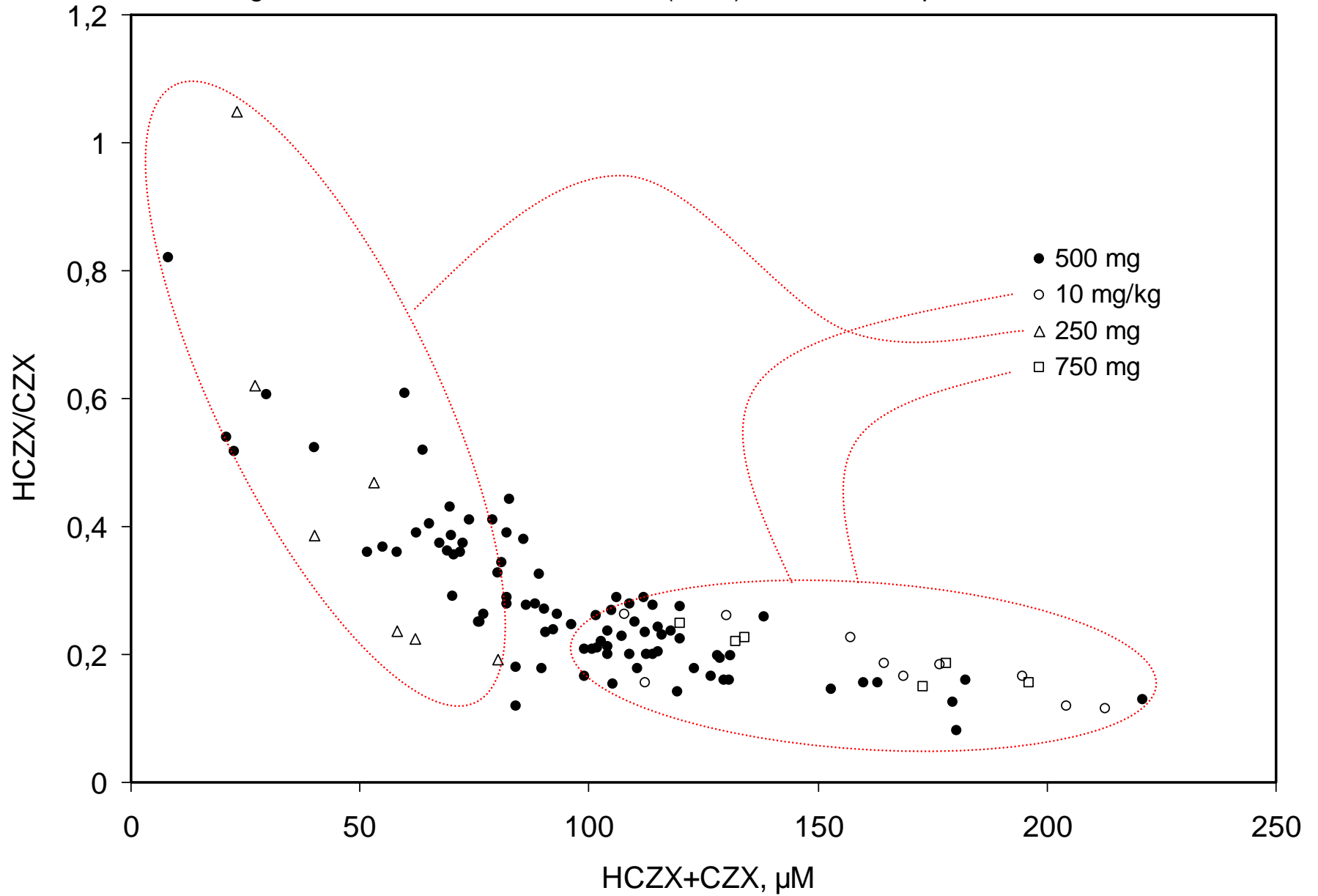
Jonsson, Johanson. Toxicology
157 (2001) 177-193



5. Phenotyping of CYP2E1 activity

- Metabolic capacity major determinant in population variability
- CYP2E1 major enzyme for many industrial chemicals
- Current practice for in vivo phenotyping:
 - Oral dose of 500 mg chlorzoxazone
 - Metabolite/parent ratio in plasma after 2 hours

Ernstgård et al, Br J Clin Pharmacol 58 (2004)190-200 & unpublished data



5. Phenotyping of CYP2E1 activity

- Metabolic capacity major determinant in population variability
- CYP2E1 major enzyme for many industrial chemicals
- Current practice for in vivo phenotyping:
Oral dose of 500 mg chlorzoxazone
 - Metabolite/parent ratio in plasma after 2 hours
- Our studies suggest:
 - Metabolic ratio is dose-dependent
 - Metabolic ratio is absorption-dependent
- Hence, does not only reflect CYP2E1 activity

Conclusions

- **Controlled human exposure studies are very useful**

Frequent sampling \Rightarrow reduced uncertainty and/or better knowledge on intra-individual variability

but...

1. ...cost and ethics limit number of subjects \Rightarrow little knowledge on inter-individual variability
2. ...erroneous model \Rightarrow erroneous parameter estimates

therefore

1. Simple measurements in many subjects, addressing population variability of specific parameters
 - E.g. work load, pulmonary ventilation, CYP2E1 phenotype
2. Specific (small) experiments addressing specific mechanisms or parameters
 - E.g. V_{max} for MEK, washin-washout of acetone