Discrepancies and Discovery in Dosimetry Research

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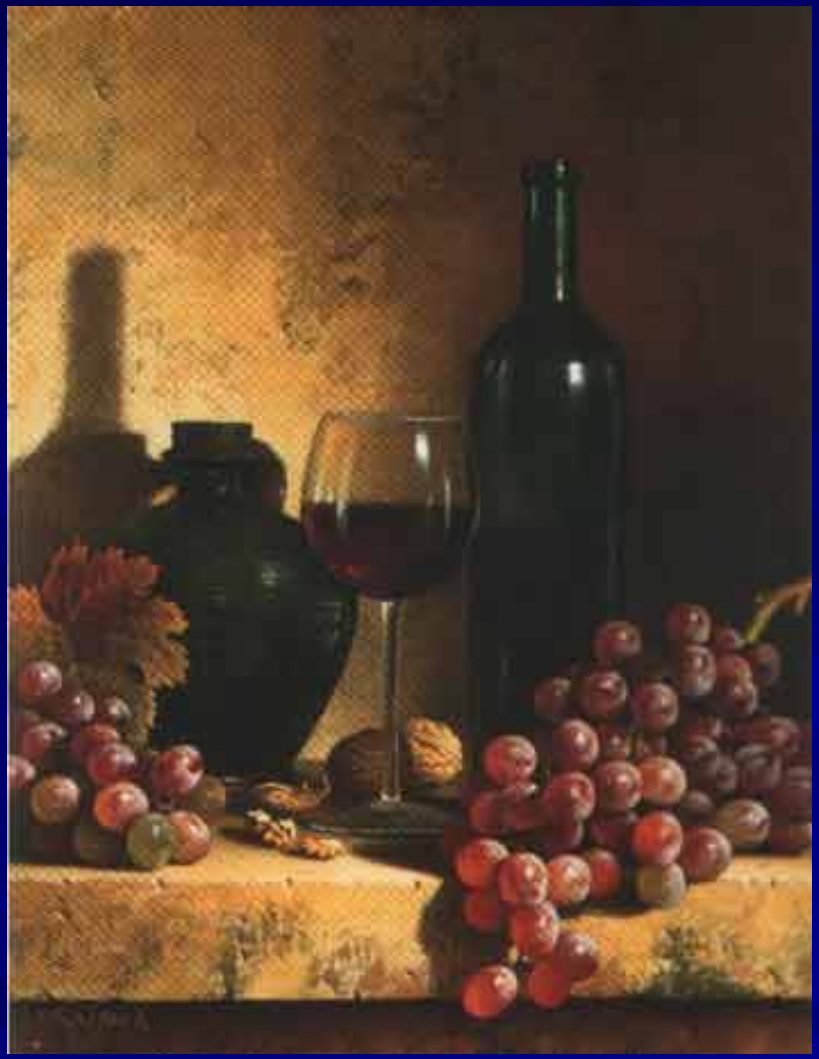
OUTLINE

- Finding out that what we know isn't so
- Using discrepancies to develop new ideas about biological processes
- Designing appropriate experiments to evaluate and test these ideas and reduce uncertainty
- Looking at future directions for PBPK and risk assessment

New Wine from an Old Vine

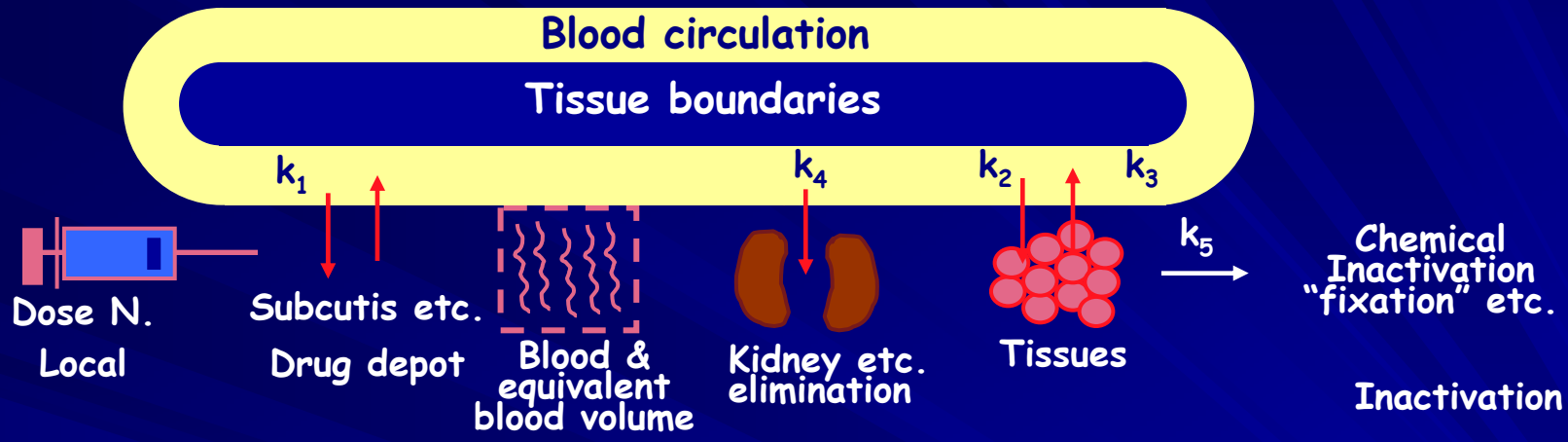


Surgeon General's Warning:
Paying attention to this talk may adversely affect your otherwise rosy outlook.

Andersen Red – 2006

A usually light-hearted grape, the 2006 vintage was too rapidly aged, producing overtones of bitterness, skepticism and disillusionment.

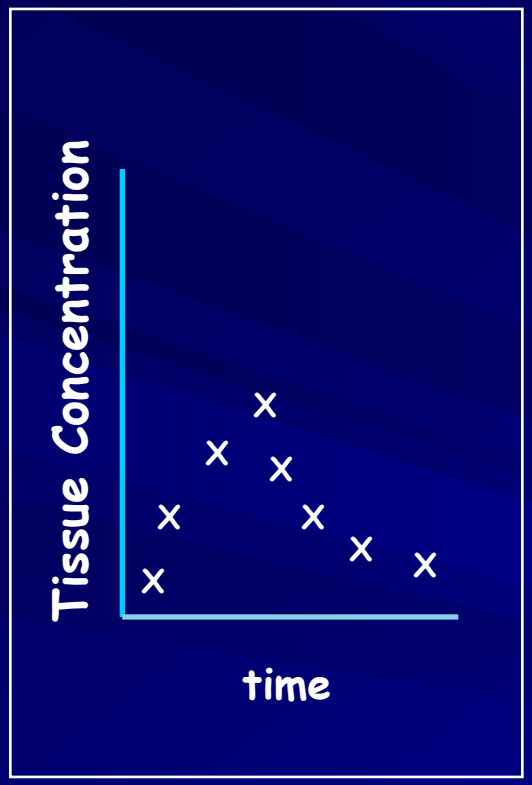
Some History

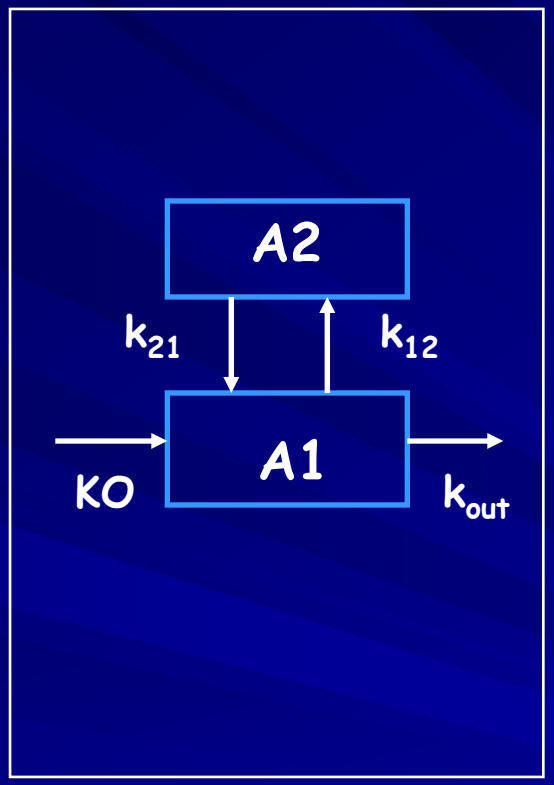


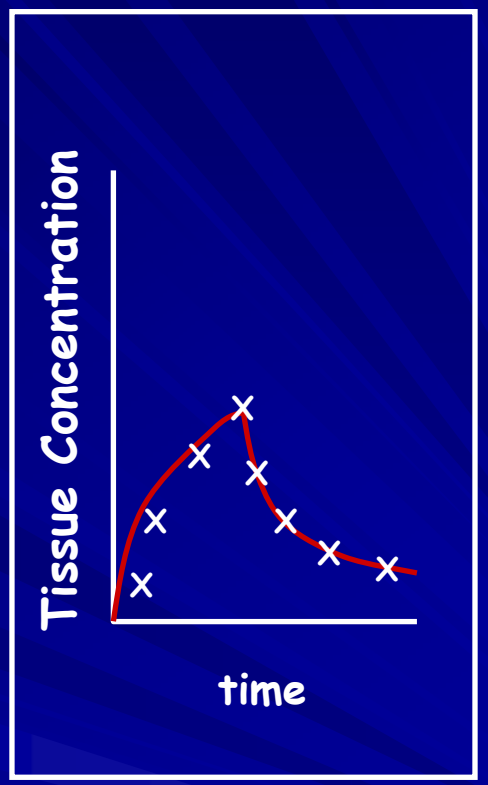
- Teorell (1937) 70 BPE*
- Bischoff and Dedrick (1971) 35 BPE
- Fiserova-Bergerova (1974) 32 BPE
- Gehring et al (1974-1980) 32 BPE
- Ramsey and Andersen (1984) 22 BPE
- Andersen et al.- Methylene Chloride Risk Assessment (1987) 19 BPE
- IRIS Vinyl Chloride (2000) 6 BPE

* BPE – before the present era

Compartmental Representations







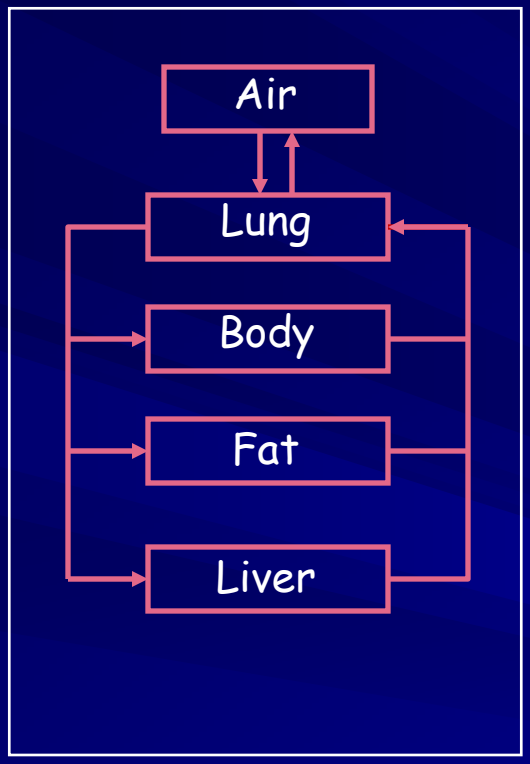
Collect Data → Select Model → Fit Model to Data

$$C_t = A\, e^{-ka \cdot time} + B\, e^{-kb \cdot time}$$

Even they needed to be Extended

- Dose dependent elimination of aspirin and ethanol
- Metabolic clearance paradoxically appeared to be unrelated to the amount of enzyme available for clearance leading to ideas about flow limited metabolism.

Physiological Representations of those Biological Processes Controlling Dose to Tissues



Metabolic Constants

Tissue Solubility

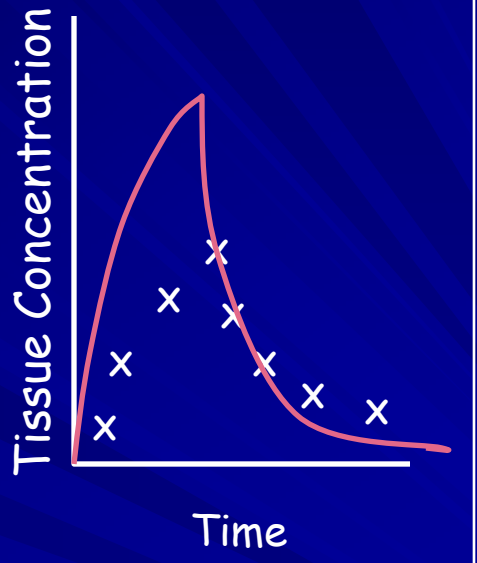
Tissue Volumes

Blood and Air Flows

Experimental System

State Equations

You can be wrong!



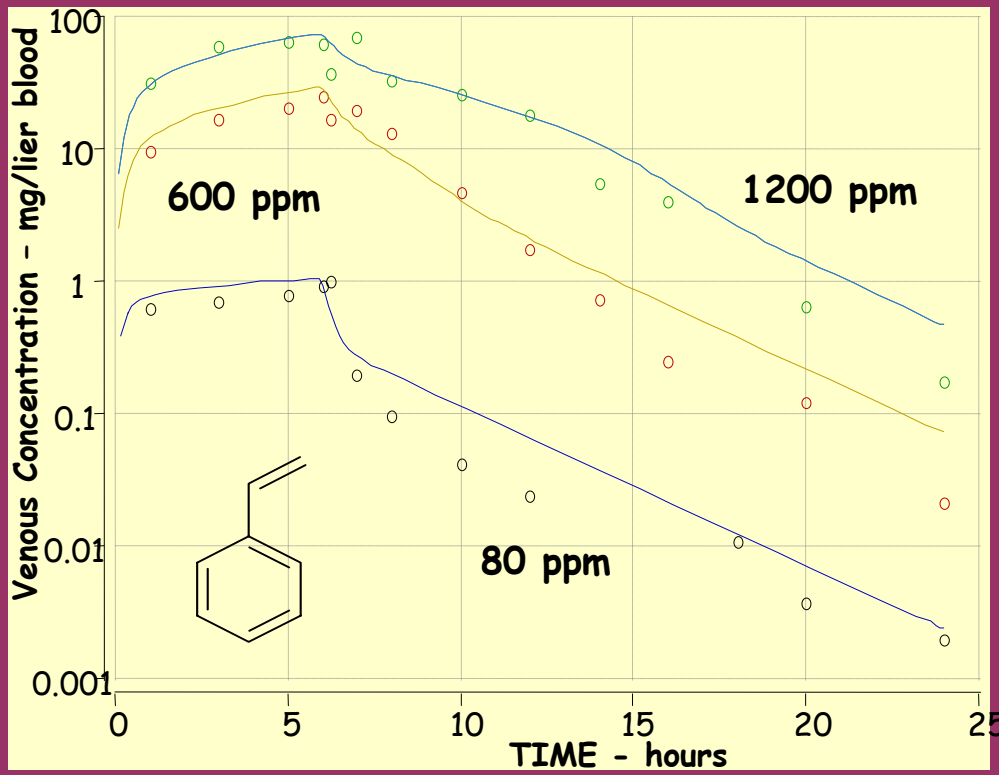
Define Realistic Structure → Collect Needed Data → Make Predictions

Refine Structure

Styrene

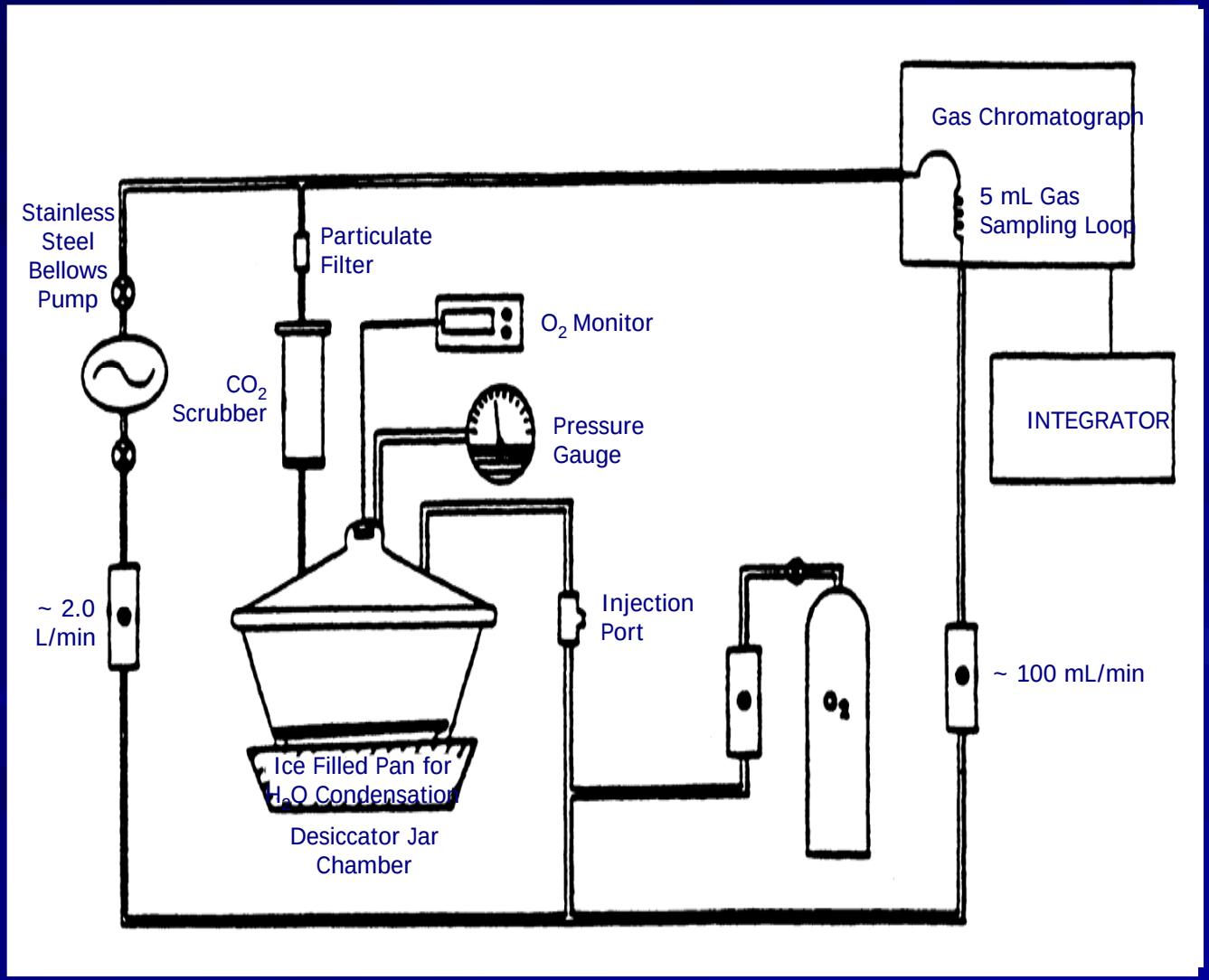
Part of large body of work conducted at Dow Chemical in the 1970's by Dr. Perry Gehring and colleagues.

Initial PK approach treated each curve independently. The PBPK approach used a common Vmax and Km.

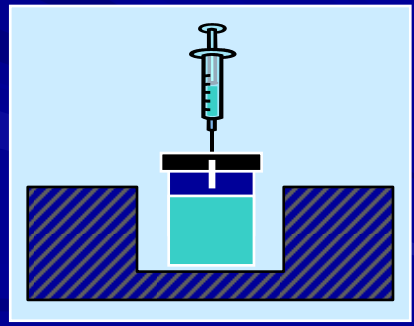


Ramsey and Andersen, Toxicol. Appl. Pharmacol., 73, 159, 1984.

Experiments to Get Needed Parameters



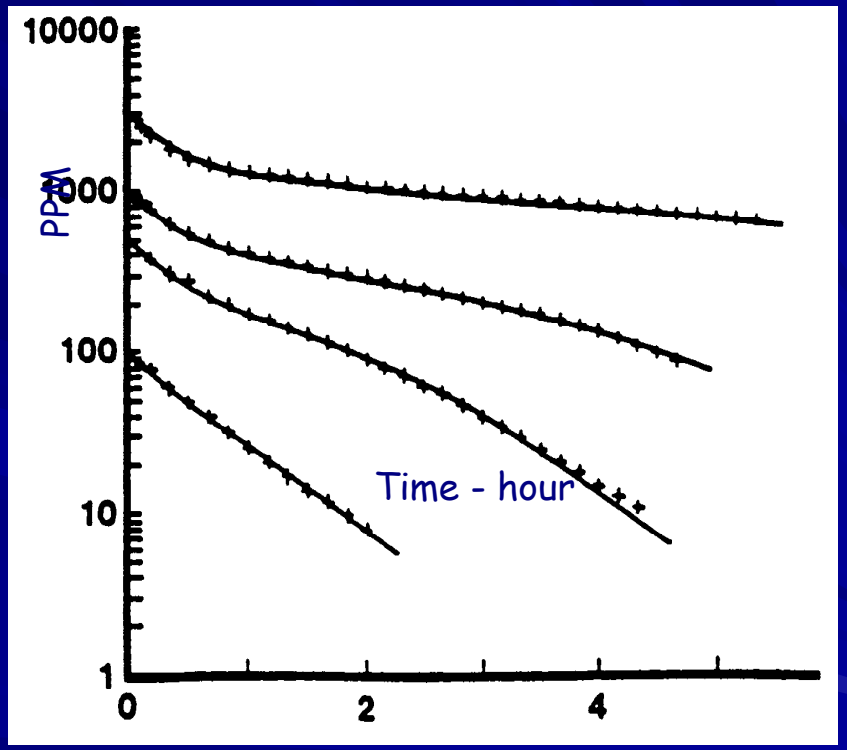
Gas Uptake for Metabolic Parameters; vial equilibration and Partitioning



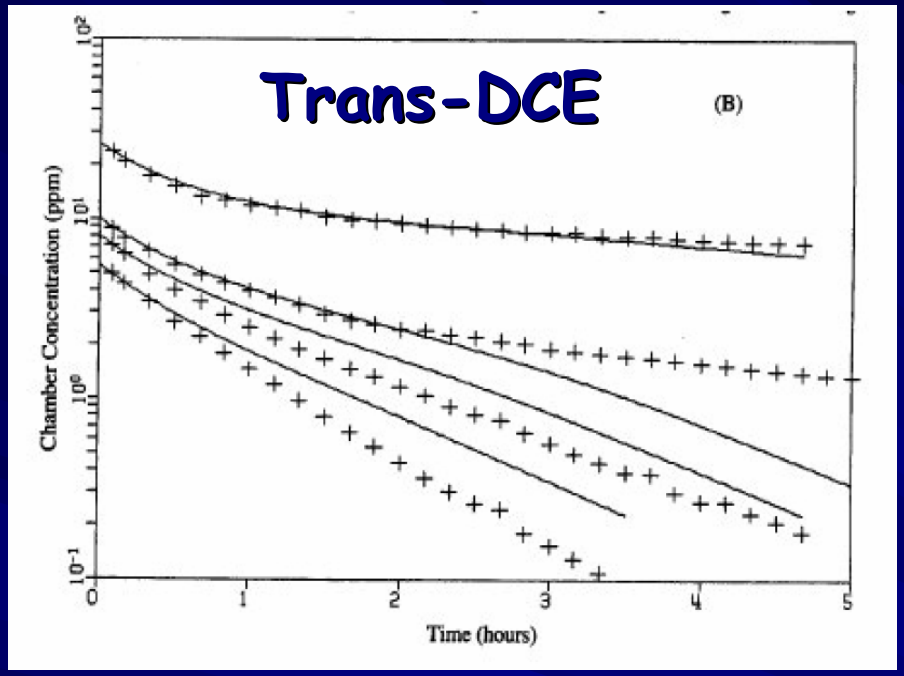
1985 saw development of a methylene chloride risk assessment relying heavily on a physiological representation of dosimetry and PK.

Nearly got me fired from Civil Service.

CH_2Cl_2



Andersen et al. ,Toxicol. Appl. Pharmacol. 87, 185-205, 1987.



Looked at 30-40 Chemicals

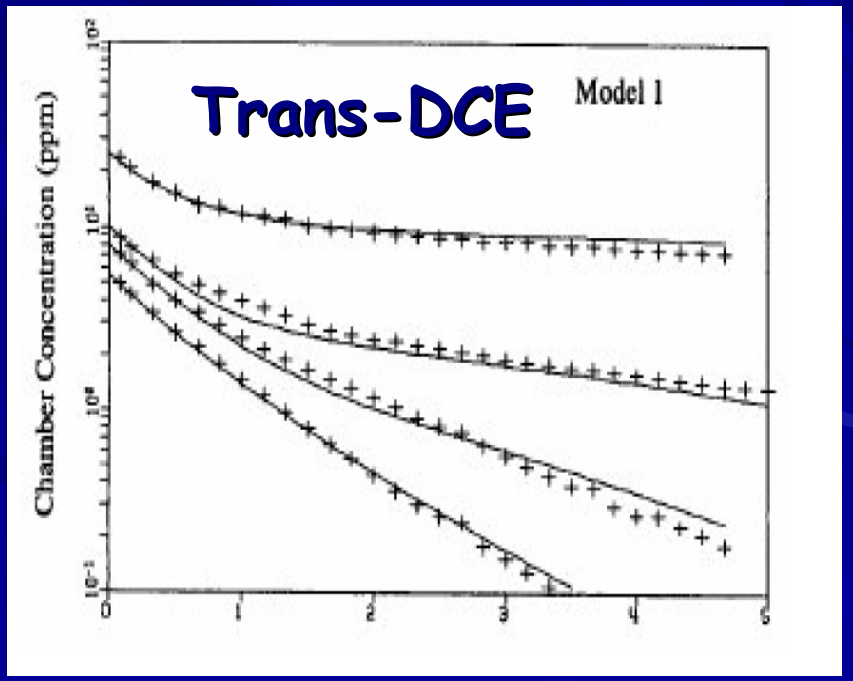
Didn't work when applied to all compounds. Trans-1,2-DCE and cis-1,2-DCE could not be fit with a consistent set of metabolic parameters across exposure concentrations). See left.

Added terms for suicide inhibition.

Conducted *in vitro* studies.

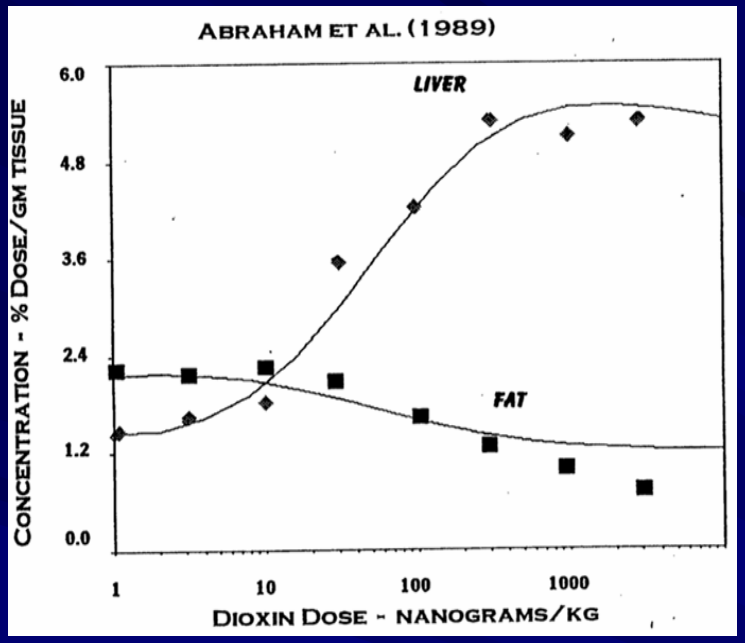
Goodness of fit used for discriminating among several mechanistic hypotheses.

Lilly et al., Arch. Toxicol. 72, 609-621, 1999



Other chemicals where discrepancies were important in refining physiological characteristics.

- Styrene – blood concentrations complexly related to partition coefficient
- Dioxin – very lipophilic compound, more found in liver than fat
- PFOA and PFOS – renal elimination enhanced and half-lives diminished as concentration increases.
- Allyl chloride – gas uptake results complicated by glutathione depletion (Clewell, Drinking Water and Health Volume 8, 1987)
- Chlordecone – similar structure to mirex, but found at highest concentrations in liver rather than fat.



Dioxin

Used a PK description with protein binding to estimate parameters for binding and induction.

Al Poland took the challenge to determine the presence of the binding protein, shown to be CYP 1A2.

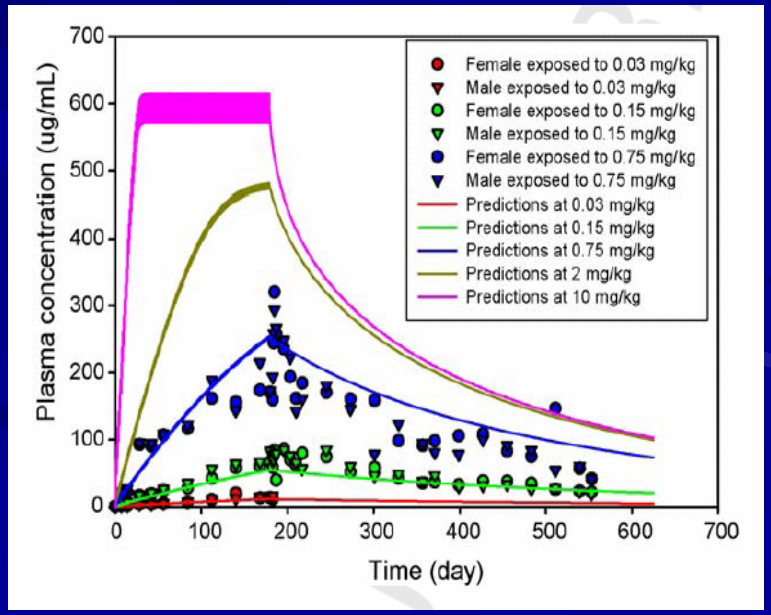
Andersen et al. (1997). Toxicol. Appl. Pharmacol. 144, 145-155

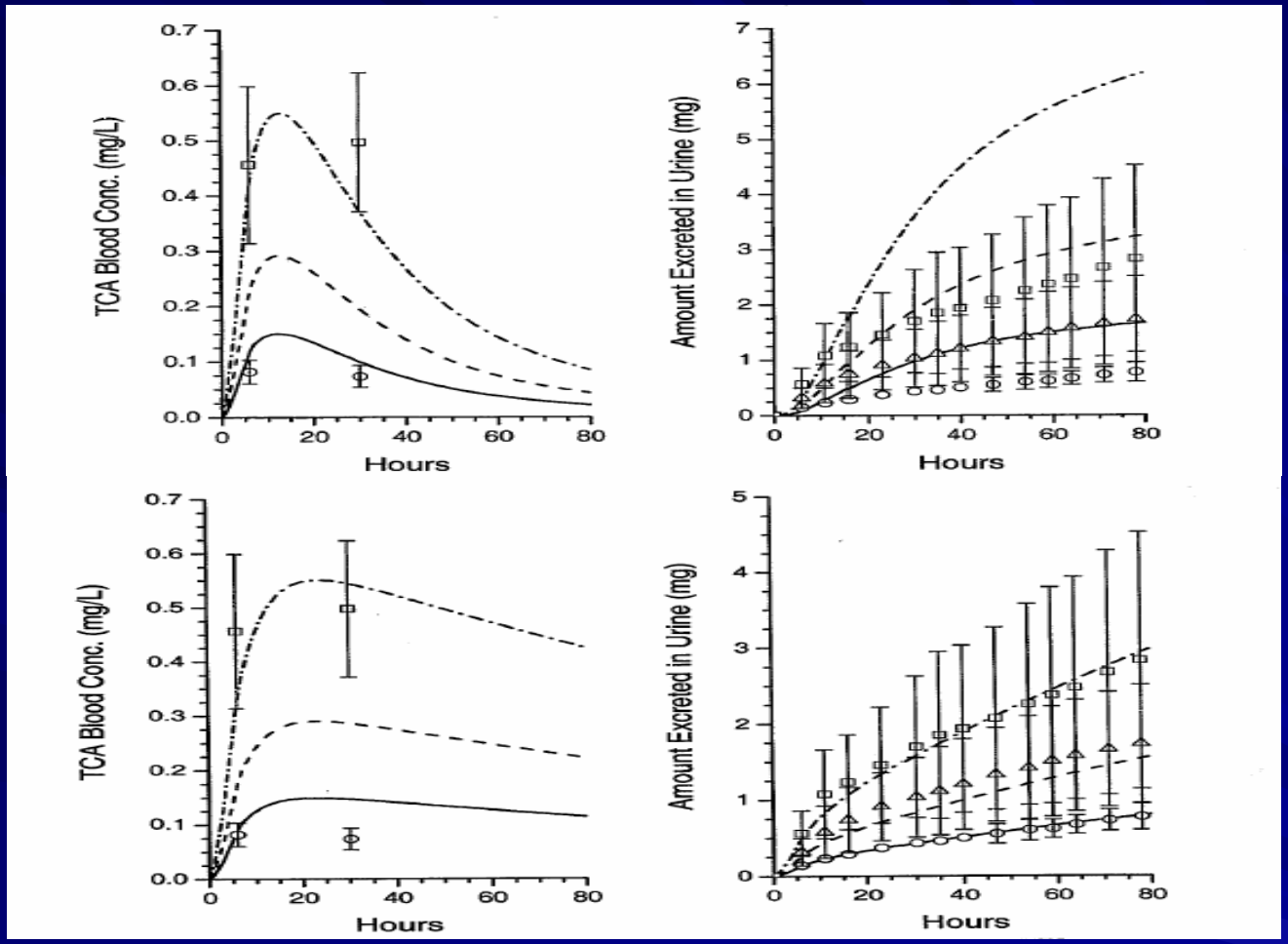
Perfluorooctane sulfonate

Elimination appears to be enhanced as blood concentration increases with suspected involvement of transporters.

Consistent with saturation of renal uptake.

Andersen et al. (2006). Toxicology, doi:10.106/j.tox.2006.08.004

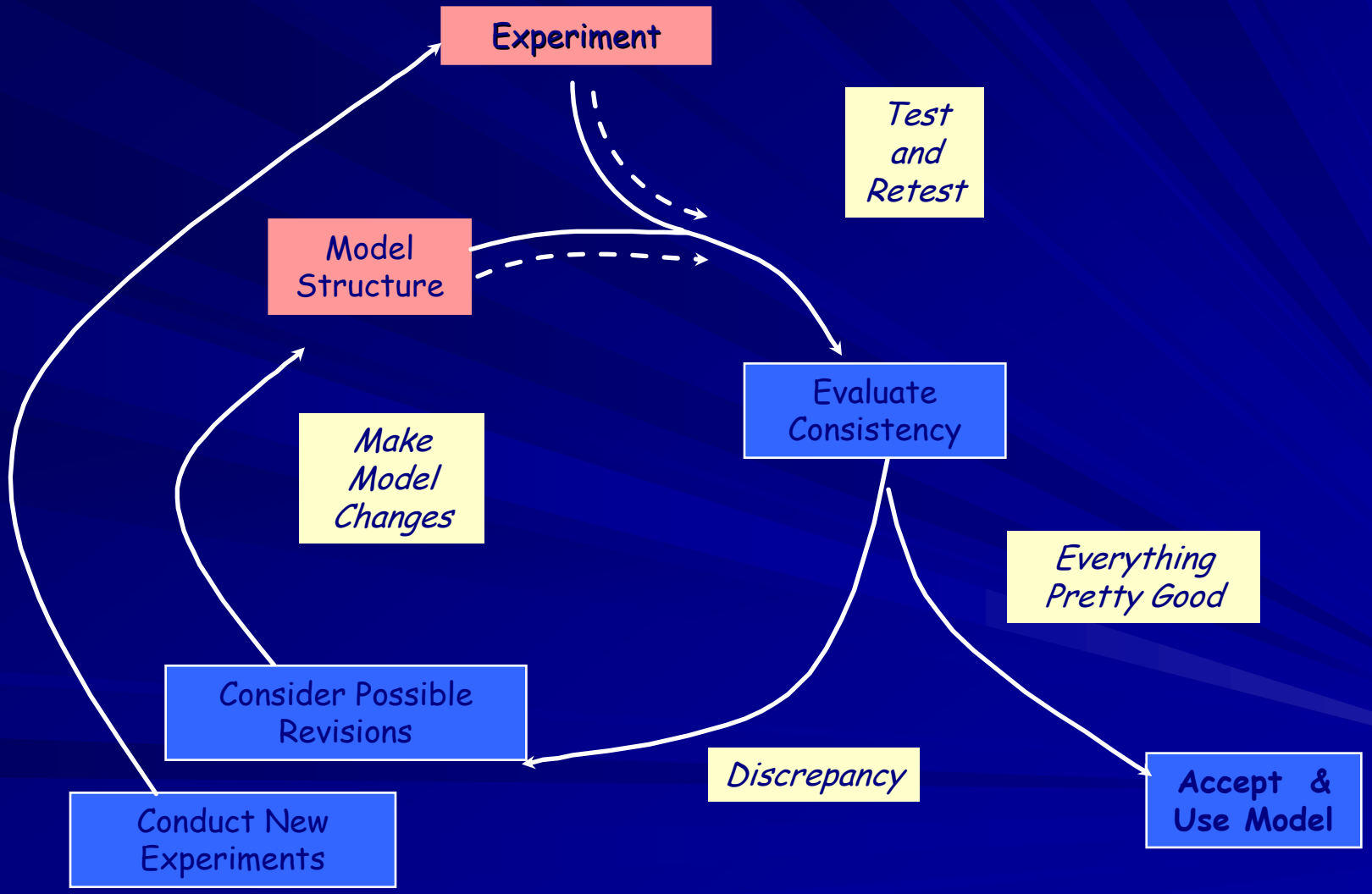




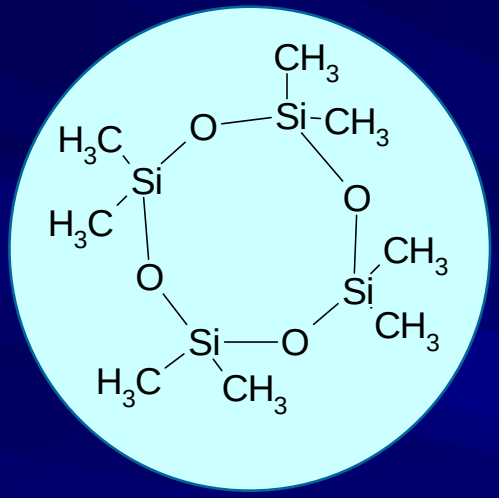
TCA Elimination from Humans after Exposure to 10, 20 or 40 ppm Perchloroethylene. Top Panel with TCA moving into a volume of distribution before renal excretion. Bottom –TCA from kidney metabolism directly excretion to urine.

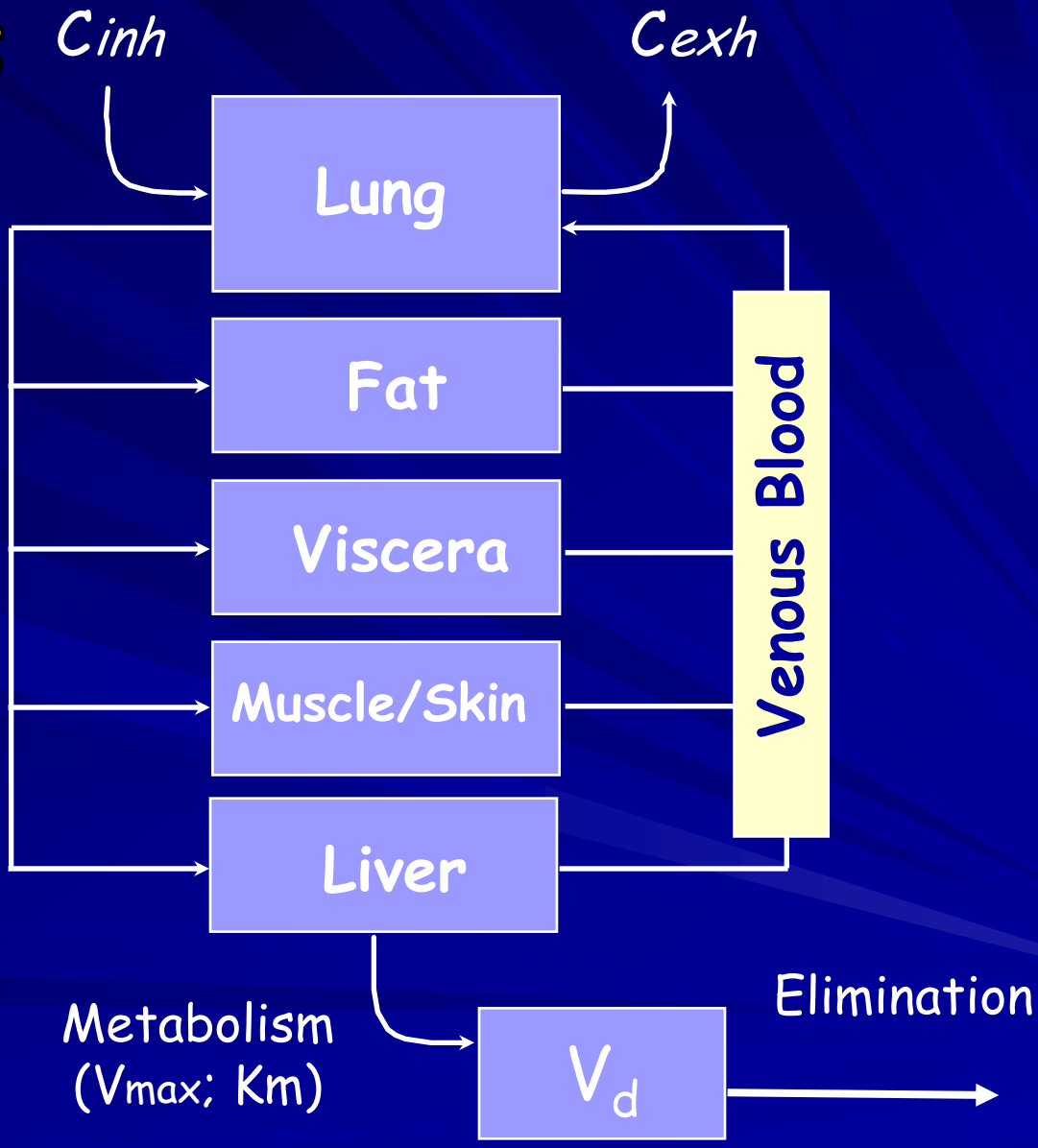
Clewell, et al., Crit. Rev. Toxicol., 35, 413-433, 2005

Testing Ideas and Assumptions



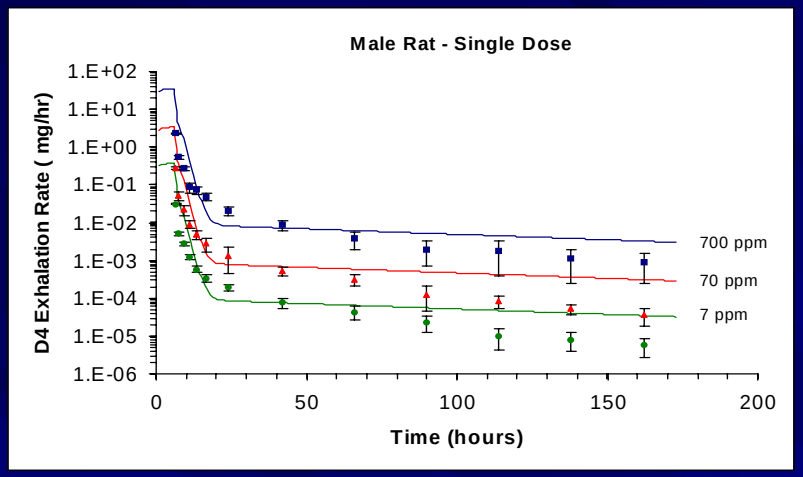
Cyclic Siloxanes

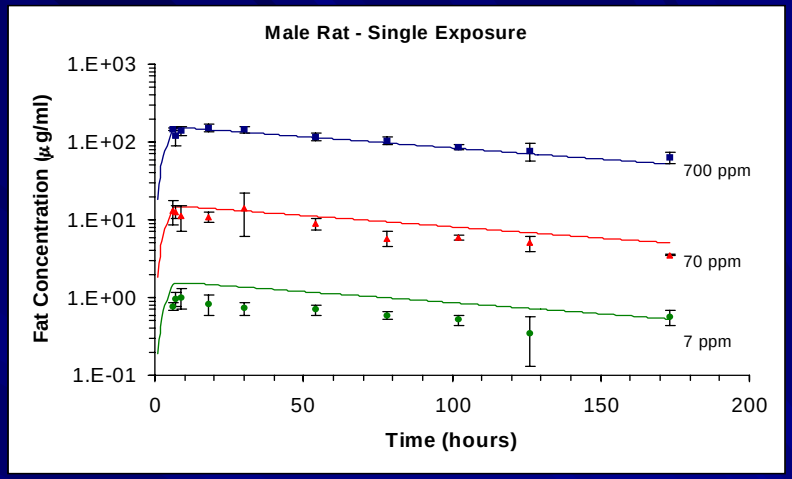


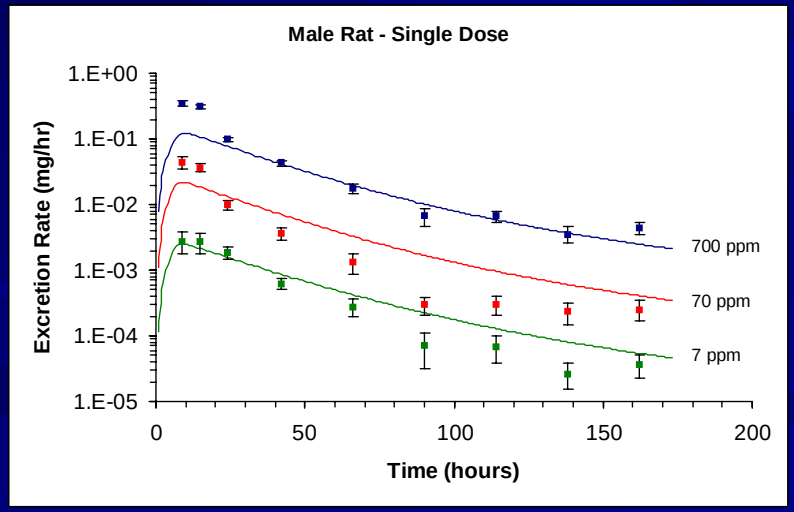


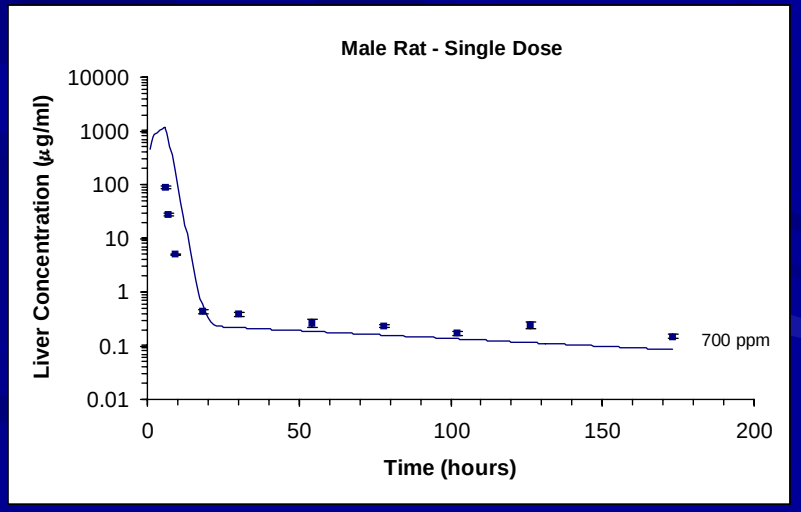
Andersen et al. (2001). Toxicol. Sci. 60, 214-231.

Initial Fits – Some Good

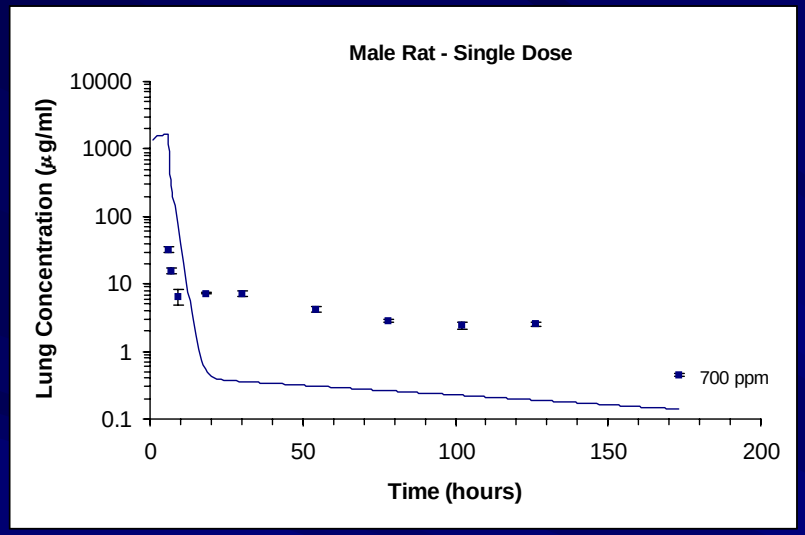


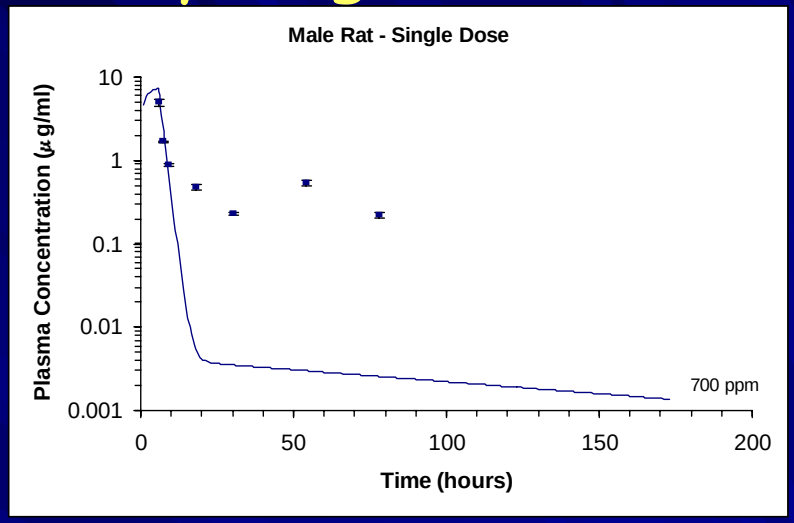


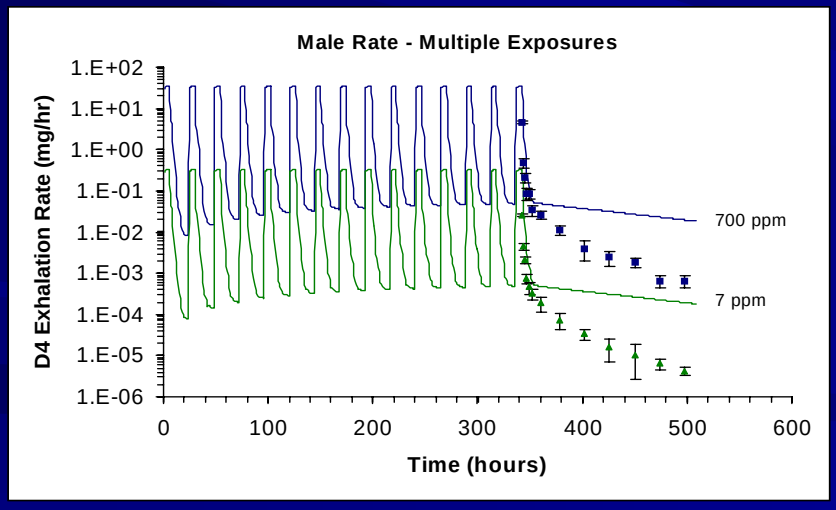


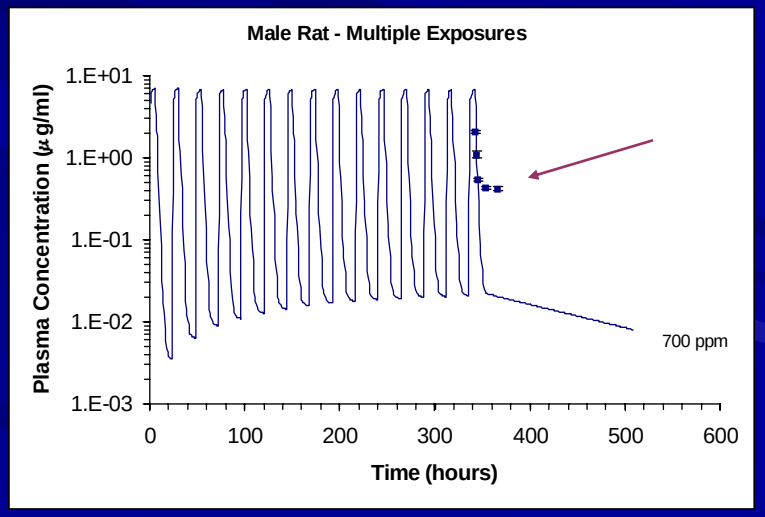


Initial Fits – Some not nearly as good



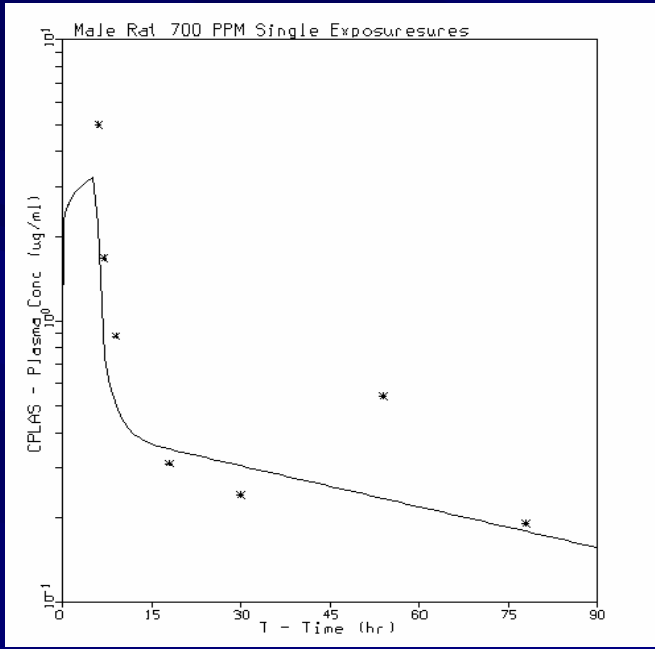


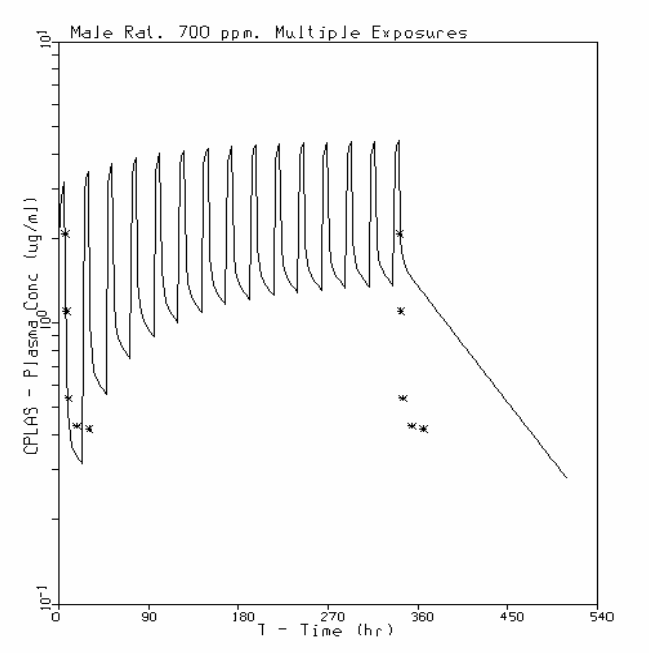




Accounting for Discrepancies

Some ideas don't work.

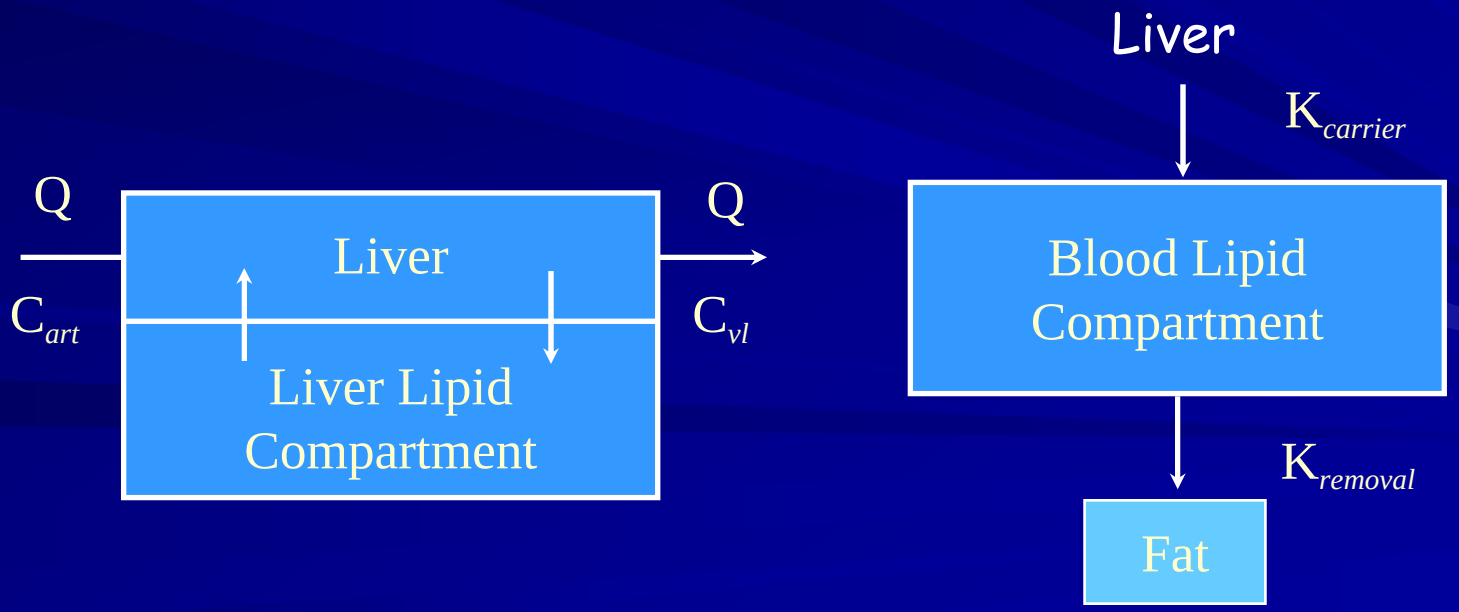




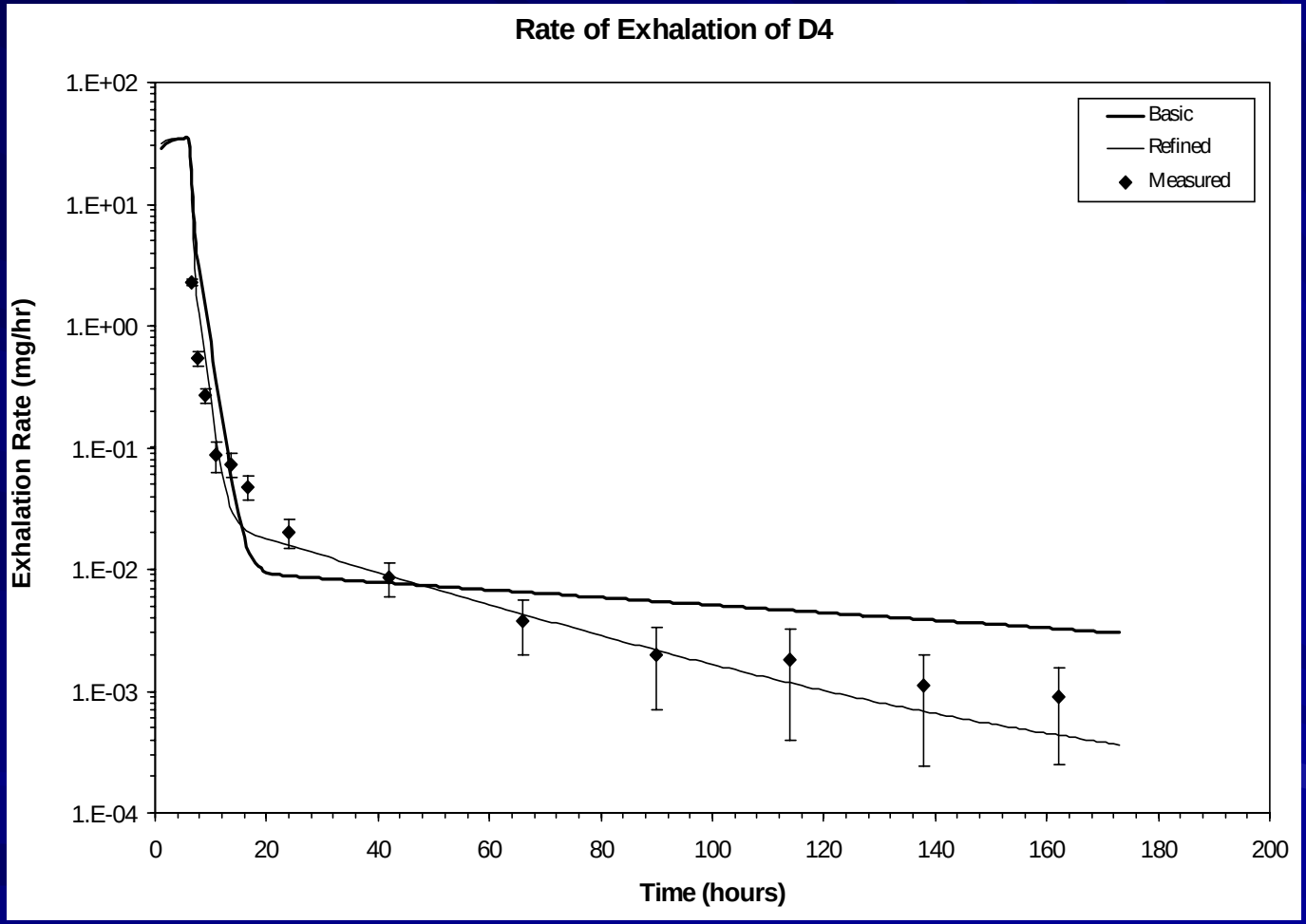
REVERSIBLE DIFFUSION INTO BLOOD LIPID STORES

Accounting for Discrepancies

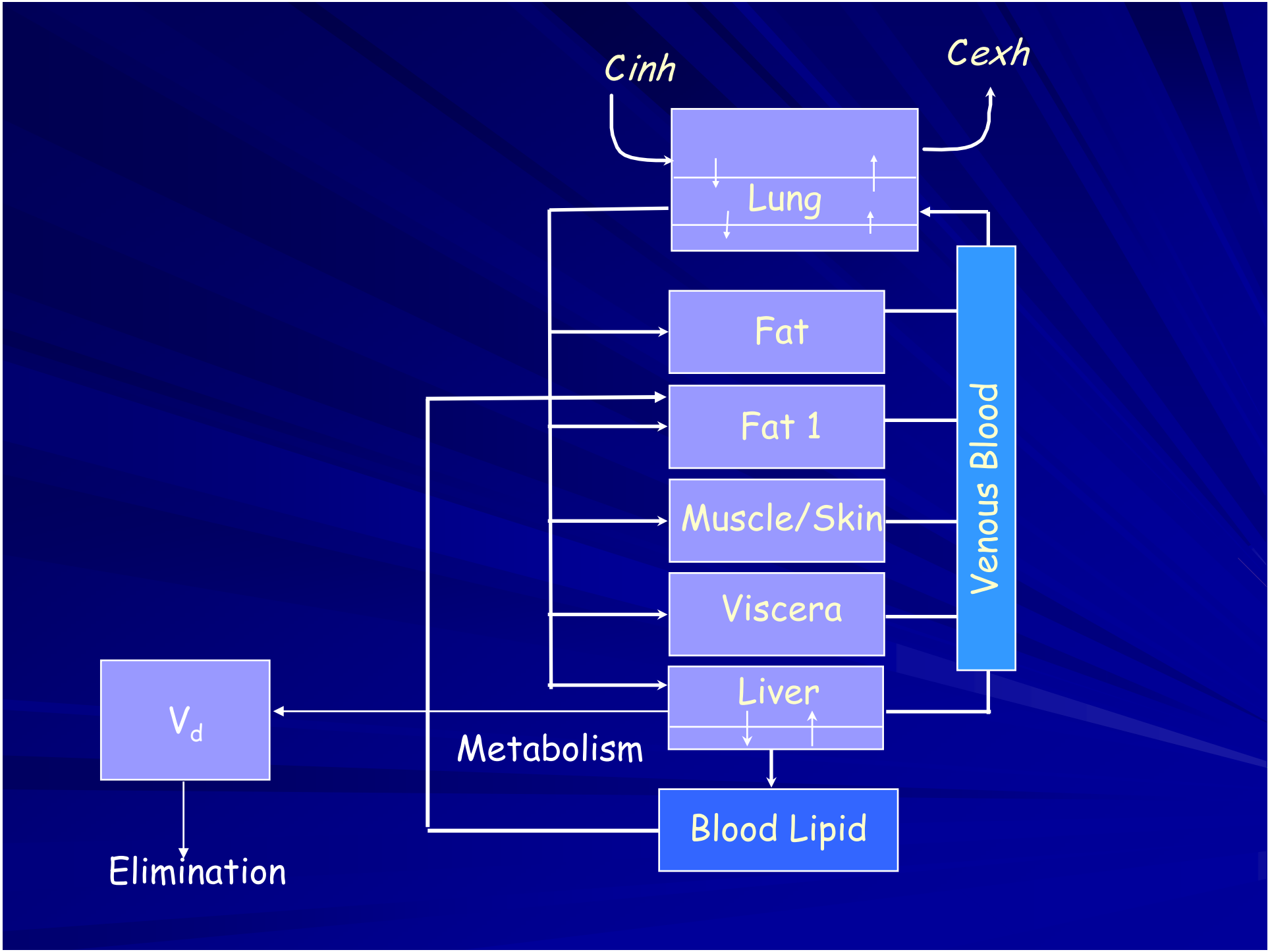
- Deep-lipid compartments within tissues to account for persistence of D4.
- Transported-lipid compartment to blood.



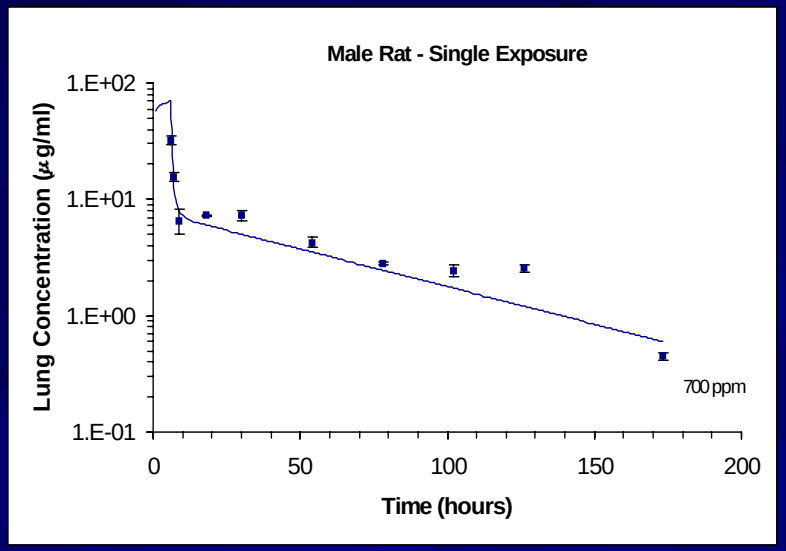
Exhaled Breath is Strikingly Sensitive to Fat Compartment Parameters

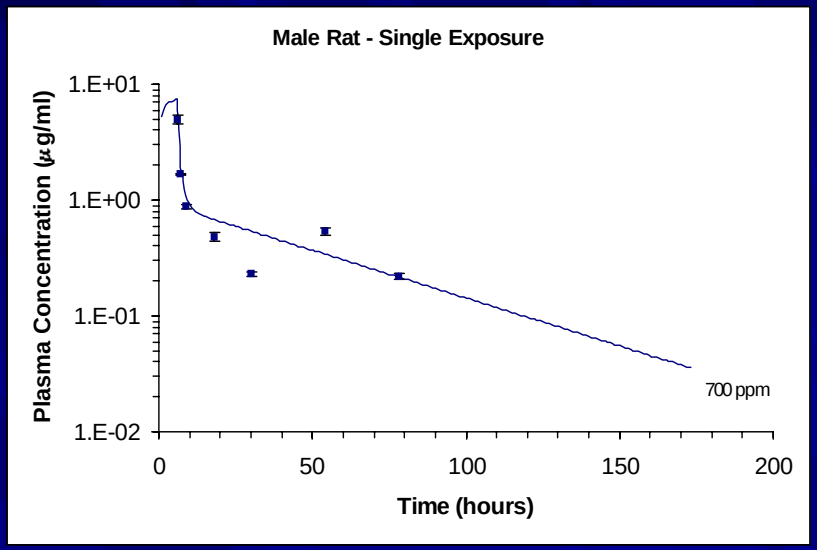


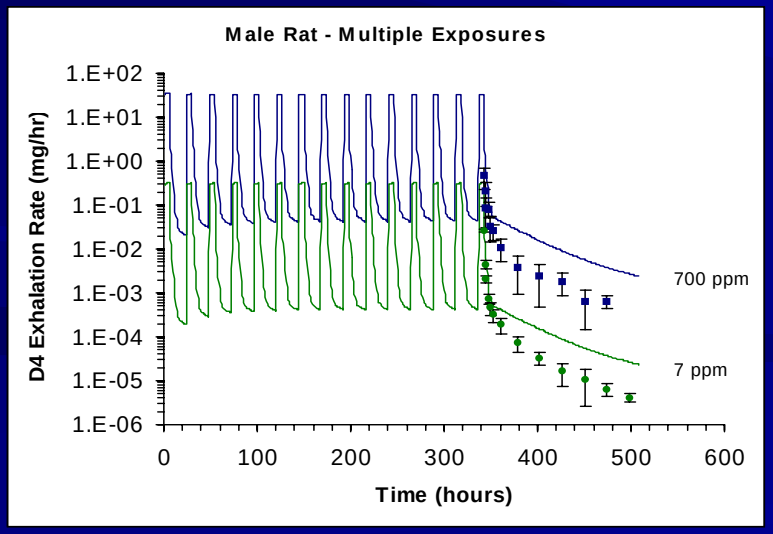
Establish fat tissue parameters from fits to exhalation time course curves where sensitive to fat parameters

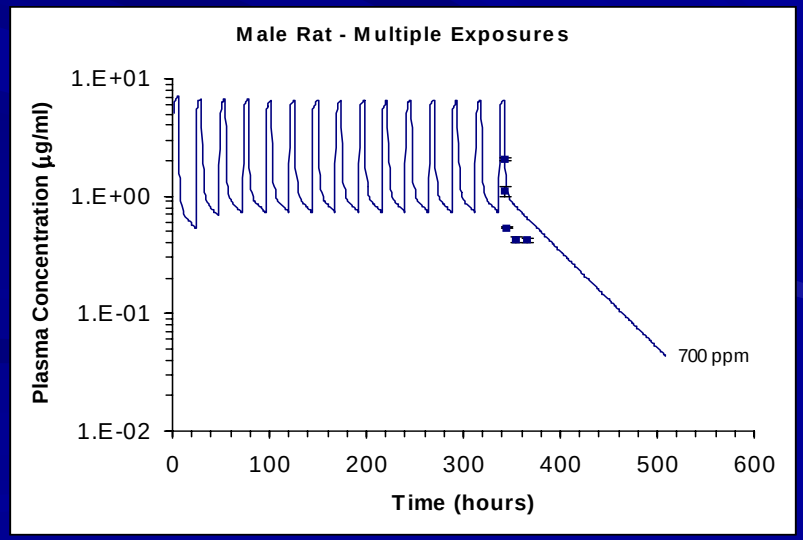

Cinh
Cexh
Lung
Fat
Fat 1
Muscle/Skin
Viscera
Liver
Venous Blood
V_d
Metabolism
Blood Lipid
Elimination

Fits


Male Rat - Single Exposure
Lung Concentration (µg/ml)
1.E+02
1.E+01
1.E+00
1.E-01
0
50
100
150
200
Time (hours)
700 ppm

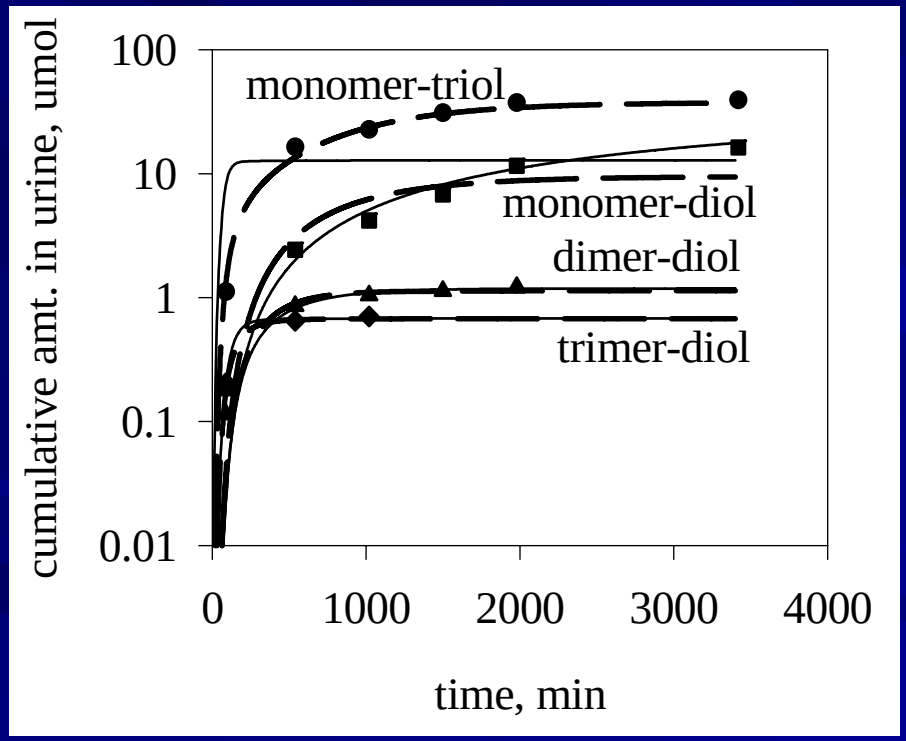

Male Rat - Single Exposure
Plasma Concentration (µg/ml)
1.E+01
1.E+00
1.E-01
1.E-02
0
50
100
150
200
Time (hours)
700 ppm

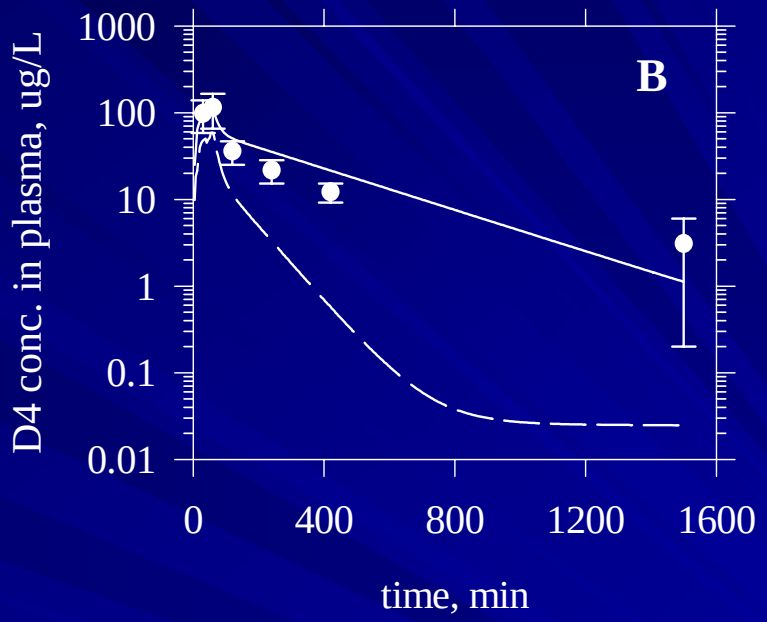

Male Rat - Multiple Exposures
D4 Exhalation Rate (mg/hr)
1.E+02
1.E+01
1.E+00
1.E-01
1.E-02
1.E-03
1.E-04
1.E-05
1.E-06
0
100
200
300
400
500
600
Time (hours)
700 ppm
7 ppm


Male Rat - Multiple Exposures
Plasma Concentration (µg/ml)
1.E+01
1.E+00
1.E-01
1.E-02
0
100
200
300
400
500
600
Time (hours)
700 ppm

Going from the Rat PK Description to the Human

Human Inhalation Studies showed similar PK behaviors and require separate pools of D4 in blood.





Human studies included time-course of metabolites in urine providing opportunity to flesh out the metabolic steps involved.

Reddy et al.(2003). Toxicol.Sci. 72, 3-18.

Comparison with other Structures

- Consistent with Behavior of other Compounds
  - Styrene, methylene chloride (deep tissue stores)
  - Anesthetic gases indicate multiple fat compartments
  - Studies needed to assess plasma distribution of compounds at different times
  - Information should lead to revisions of physiological structures currently used with lipophilic compounds
  - Ideas change with new information and with the expansion of the groups of compounds evaluated – e.g., lung models

Where are we?

- Thirty five years since the PK work began at Dow.
- Twenty years since NRC Meeting on **Pharmacokinetics in Risk Assessment.**
- Lip-service to encourage quantitative descriptions of dosimetry; reluctance to take responsibility for their implementation
- Emphasis on statistical manipulations with existing models rather than on expansion of PK tools to wider suites of compounds, including routine kinetic studies in animals and at low doses in people.

Uncertainty as we look to Future

- PBPK approaches are primarily research tools to see if we really understand processes regulating chemical dosimetry in vivo.
- Prospects for using any of them in risk assessments seem even less likely **to me** today than 10 or 20 years ago.
- My advice recently to someone asking what career track they might take to try to influence risk assessment of environmental chemicals:

Go to law school.

Some Historical References:

Andersen, M.E., Clewell, H.J. III, Gargas, M.I., Smith, F.A., and Reitz, R.H. (1987). Physiologically-based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. 87, 185

Bischoff, K.B., Dedrick, R.L., Zaharko, D.S., and Longstreth, J.A. (1971). Methotrexat pharmacokinetics. J. Pharm. Sci., 60: 1128

Fiserova-Bergerova, V., Vlach, J., and Singhal, K. (1974). Simulation and prediction of the uptake, distribution, and exhalation of organic solvents. Brit. J. industr. Med., 31, 45-52.

Gehring, P. J., Watanabe, P. G., and Blau, G. E. (1976). Pharmacokinetic studies in evaluation of the toxicological and environmental hazard of chemicals. in: New Concepts in Safety Evaluation [Adv. Mod. Toxicol., v. 1, M. A. Mehlman, R. E. Shapiro, and H. Blumenthal, eds., Hemisphere Publishing Corp., New York, 193-270.

Ramsey, J.C. and Andersen, M.E. (1984). A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicol. Appl. Pharmacol. 73, 159.

Rowland, M., Benet, L.Z., and Graham, G.G. (1973). Clearance concepts in pharmacokinetics. J. Pharmacokin. Biopharm., 1, 123.

Teorell, T. (1973a). Kinetics of distribution of substances administered to the body. I. The extravascular modes of administration. Arch. Int. Pharmacodyn., 57, 205

Teorell, T. (1973b). Kinetics of distribution of substances administered to the body. I. The intravascular mode of administration. Arch. Int. Pharmacodyn., 57, 226

Wilkinson, G.R. and Shand, D.G. (1975). A physiological approach to hepatic drug clearance. Clin. Pharmacol. Ther., 18, 377.