Experimental Data Used with PBPK Models

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Disclaimer: This presentation does not present official Agency Policy.

Overview

- Data types
  - Physiological
    - Anatomy, physiology, endogenous biochemistry
  - Chemical specific
    - In vivo
    - In vitro & Ex vivo
- Data Themes
  - Study design
  - Model analyses

Physiological Parameters

- Physiological, anatomical, endogenous biochemical
- Body mass (weight, volume, lean mass)
- Blood flows (cardiac output, tissue flows)
- Tissue volumes
- Tissue structure (e.g., liver acinus, liver enzyme locationalization)
- Glutathione concentrations (diurnal rhythms), synthesis & basal degradation rates
- Protein turnover rates

MEMOIRS

OF

THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY

No. 6

THE RAT

DATA AND REFERENCE TABLES

FOR

THE ALBINO RAT

(MUS NORVEGICUS ALBINUS)

AND

THE NORWAY RAT

(MUS NORVEGICUS)

— Second Edition —

Revised

COMPILED AND EDITED BY

HENRY H. DONALDSON

Physiological Parameters

2^{nd} Edition

Philadelphia

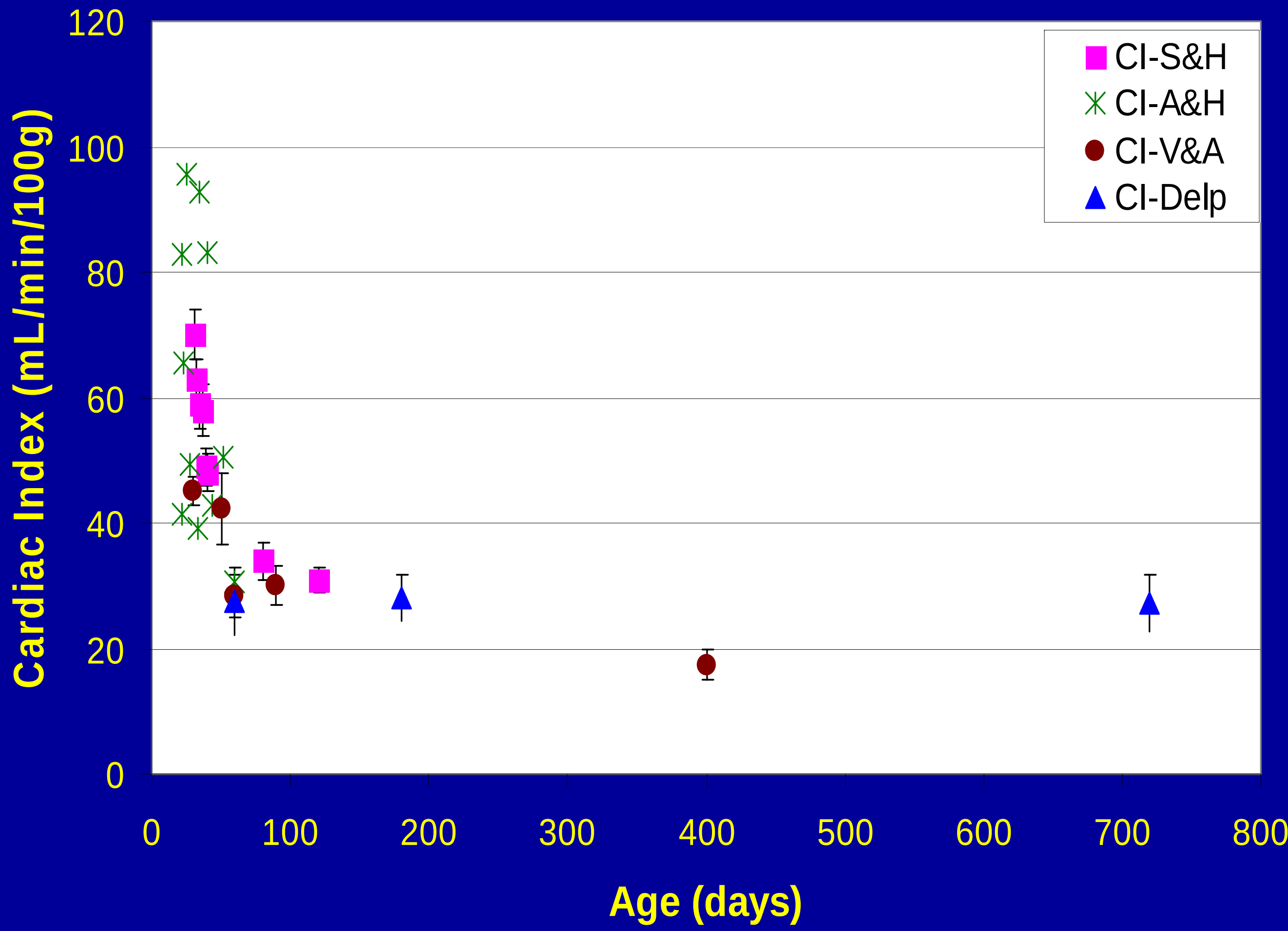
1924

Tissue weights

Organ Volumes and Percent Body Fat in 2 month old male, Sprague Dawley rats											
WEIGHT (g)	Rat #1	Rat #2	Rat #3	Rat #4	Rat #5	Rat #6	Rat #7	Rat #8	Rat #9	Mean	SD
Total Body	358.3	343.6	329.5	337.4	313.7	335.2	314.8	325.6	340.4	333.1667	14.15053
Liver	14.64	13.7	12.799	13.125	11.551	11.58	11.76	12.212	14.418	12.865	1.191473
Spleen	0.729	0.828	0.719	0.783	0.97	0.894	0.783	0.674	0.84	0.802222	0.092285
Stomach	1.55	1.463	1.423	1.437	1.53	1.444	1.293	1.617	1.704	1.495667	0.120306
Sm. intestine	9.553	9.16	8.668	8.878	8.383	8.257	7.618	8.507	9.11	8.681556	0.574638
Lg.intestine	3.449	3.185	2.785	3.196	3.023	3.513	2.843	3.209	3.579	3.198	0.281714
Kidneys	2.912	2.535	2.464	2.707	2.737	2.424	2.5	2.571	3.068	2.657556	0.21832
Heart	1.08	1.115	1.032	1.055	1.044	0.955	1.078	1.129	1.187	1.075	0.065863
Lung	1.607	1.678	1.16	1.346	1.33	1.416	1.354	1.275	1.715	1.431222	0.191702
Brain	1.947	1.916	1.88	2.063	1.911	1.907	1.852	1.901	2.033	1.934444	0.06975
Total organ wt.	37.467	35.58	32.93	34.59	32.479	32.39	31.081	33.095	37.654	34.14067	2.329921
Carcass	320.833	308.02	296.57	302.81	281.221	302.81	283.719	292.505	302.746	299.026	12.24128
Dry carcass	94.87	84.96	92.05	90.33	85.24	86.07	86.54	87.54	90.49	88.67667	3.428462
Carcass % water	70.4301	72.41738	68.9618	70.16941	69.68932	71.57624	69.49799	70.07231	70.11026	70.32498	1.062733
LIPID RECOVERY (g)											
Extraction 1	16.86	16.48	22.18	15.78	17.1	16.03	19.303	17.435	18.2	17.70756	1.999657
Extraction 2	3.13	4.5	4.23	4.73	3.63	2.58	4.078	3.48	4	3.817556	0.682176
Total lipid extracted	19.99	20.98	26.41	20.51	20.73	18.61	23.381	20.915	22.2	21.52511	2.262422
% Recovery Extra.1	84.34217	78.551	83.98334	76.93808	82.48915	86.13649	82.55849	83.36122	81.98198	82.26021	2.868876
% Recovery Extra.2	15.65783	21.449									
Total % recovery	100	100									
L(% carcass wt.)	6.230656	6.811246									
L(% body wt)	5.58	6.11									

Schoeffner DJ, Warren DA, Muralidara S, Bruckner JV, Simmons JE. Organ weights and fat volume in rats as a function of strain and age. J Toxicol Environ Health A. 1999 Apr 9;56(7):449-62

Cardiac Index vs Rat Age



Rat Strains

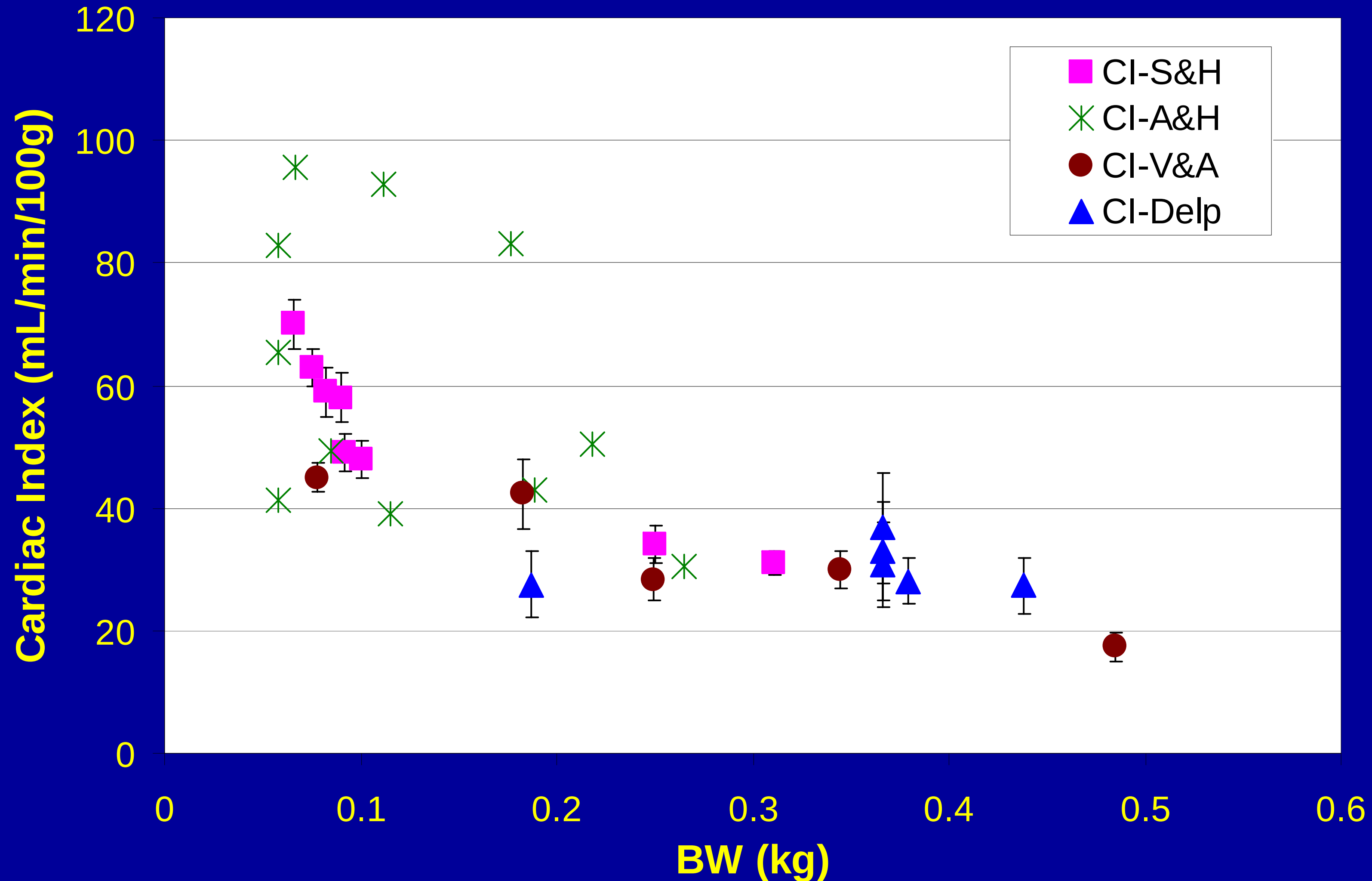
S&H: Wistar Kyoto

A&H: Sprague Dawley

V&A: Wistar

Delp: F344 (S-D)

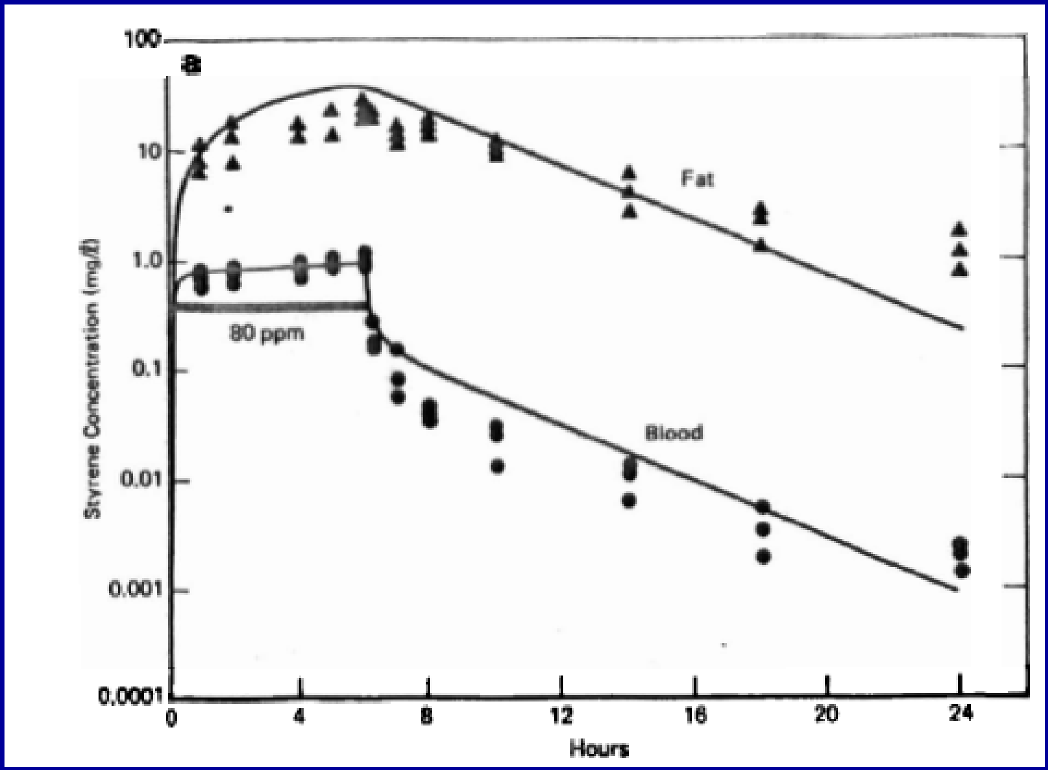
Cardiac Index vs Rat Body Weight



In vivo pharmacokinetics

- PK = ADME (absorption, distribution, metabolism, excretion)
- Chemical levels over time and doses
  - Single or repeated exposures
  - Exposure (dosing) regimens: intravenous bolus or infusion, oral bolus, inhalation, dermal
  - Serial determinations in multiple animals (e.g., tissue or blood concentrations)
  - Repeated measures in same animal/human (e.g., serum, urine, feces, exhaled breath, closed chamber atmosphere)

In Vivo Time Course: Styrene



Data: Young JD et al. (1979) In Toxicology and Occupational Medicine. Proceedings of Tenth Inter-American Conference on Toxicology and Occupational Medicine. pp 297-310. Elsevier

Model: Ramsey JC, Andersen ME. Toxicol Appl Pharmacol. 1984 Mar 30;73(1):159-75

Study Design: 4 concentrations, 3 rats/time – sampled blood, fat, liver, kidney

6 hr constant conc – 5 time points

18 hr post-exposure – 7 time points

In vivo: Plasma Concentration in Chronic Toxicity Study

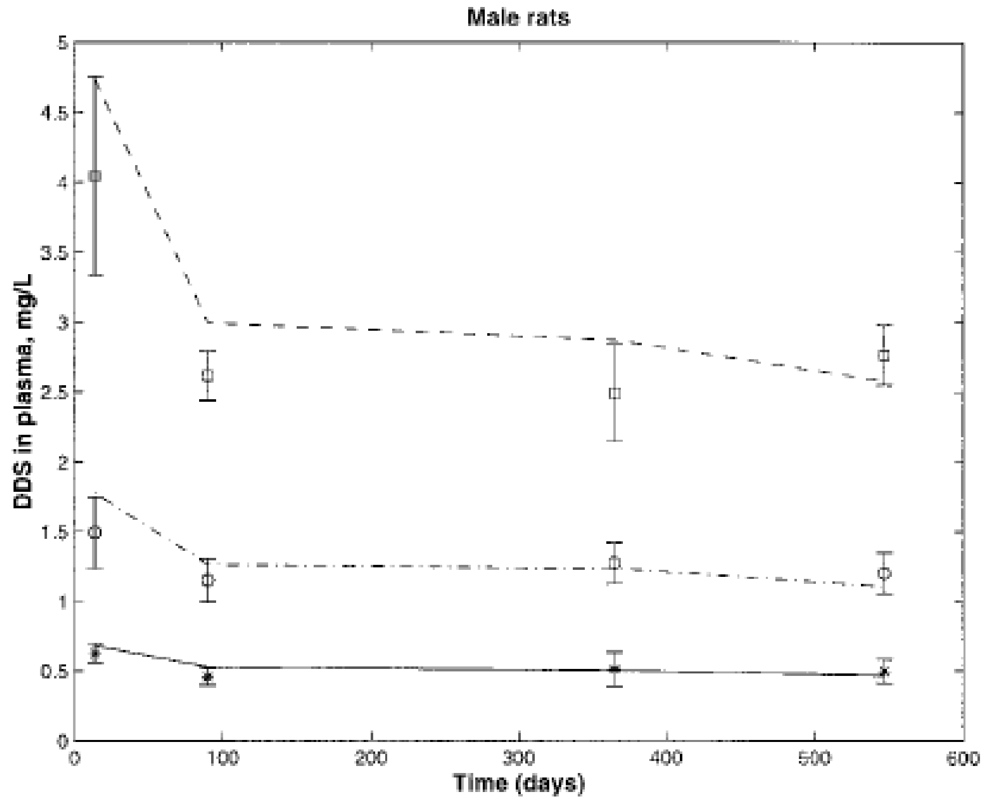


FIG. 13. Model predictions (plasma concentration in mg/L) vs data for male rats, chronic study: solid line (model) and asterisks (data), 10 ppm; dot-dash line (model) and circles (data), 30 ppm; dashed line (model) and squares (data), 100 ppm.

Data: NTP Tech Rep 501 (2000)

Model: Parham FM, Matthews HB, Portier CJ. A physiologically based pharmacokinetic model of p,p'-dichlorodiphenylsulfone. Toxicol Appl Pharmacol. 2002 Jun 15; 181(3):153-63

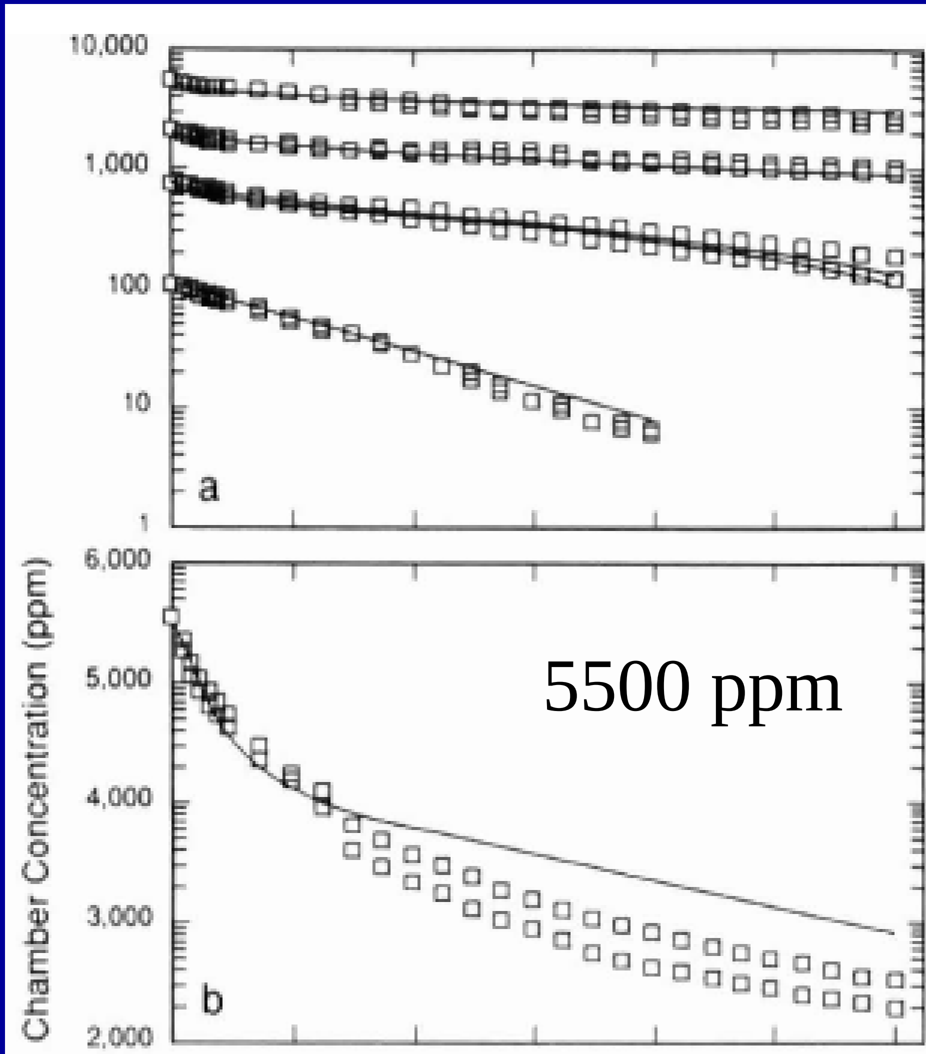
Study:

p,p'-dichlorodiphenylsulfone

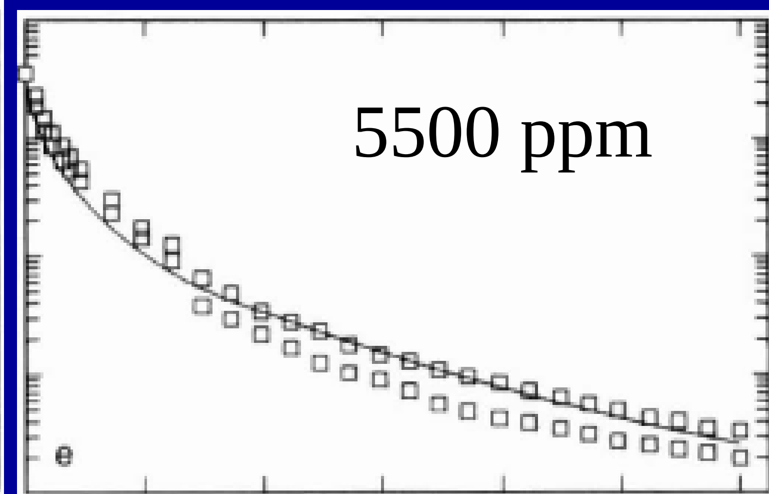
Dietary daily exposure

Rats sampled at 9am, 12noon, 3 pm

In vivo: Closed Chamber: Chloroform



Gearhart JM, Seckel C, Vinegar A. In vivo metabolism of chloroform in B6C3F1 mice determined by the method of gas uptake: the effects of body temperature on tissue partition coefficients and metabolism. Toxicol Appl Pharmacol. 1993 Apr; 119(2):258-66



Estimate Vmaxc, Km, Kfc

With temperature dependent metabolism

Chloroform – physiology, metabolism

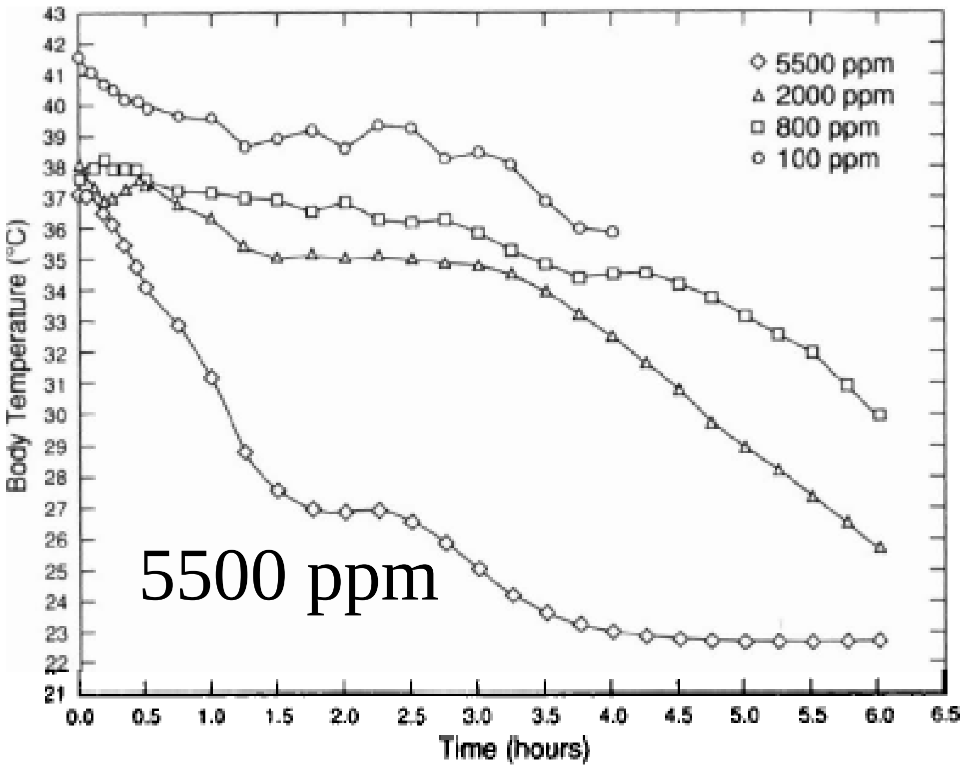


FIG. 1. Changes in absolute core body temperature during exposure to different starting concentrations of $CHCl_3$ as a function of time during a gas uptake exposure in B6C3F1 mice. Each curve represents the average temperature for the two mice exposed at each concentration.

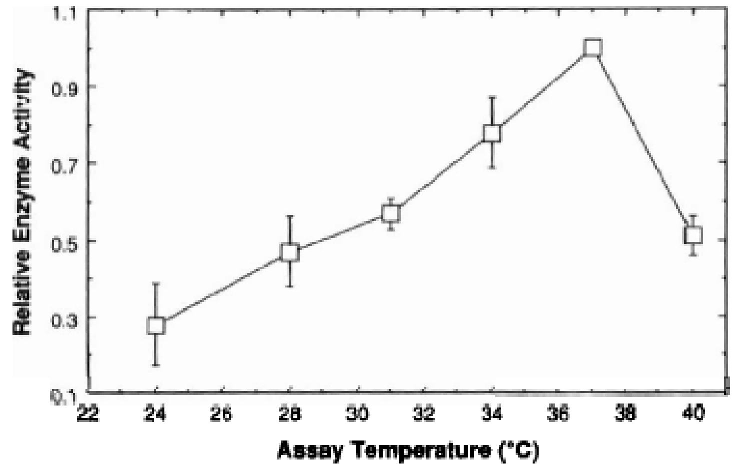
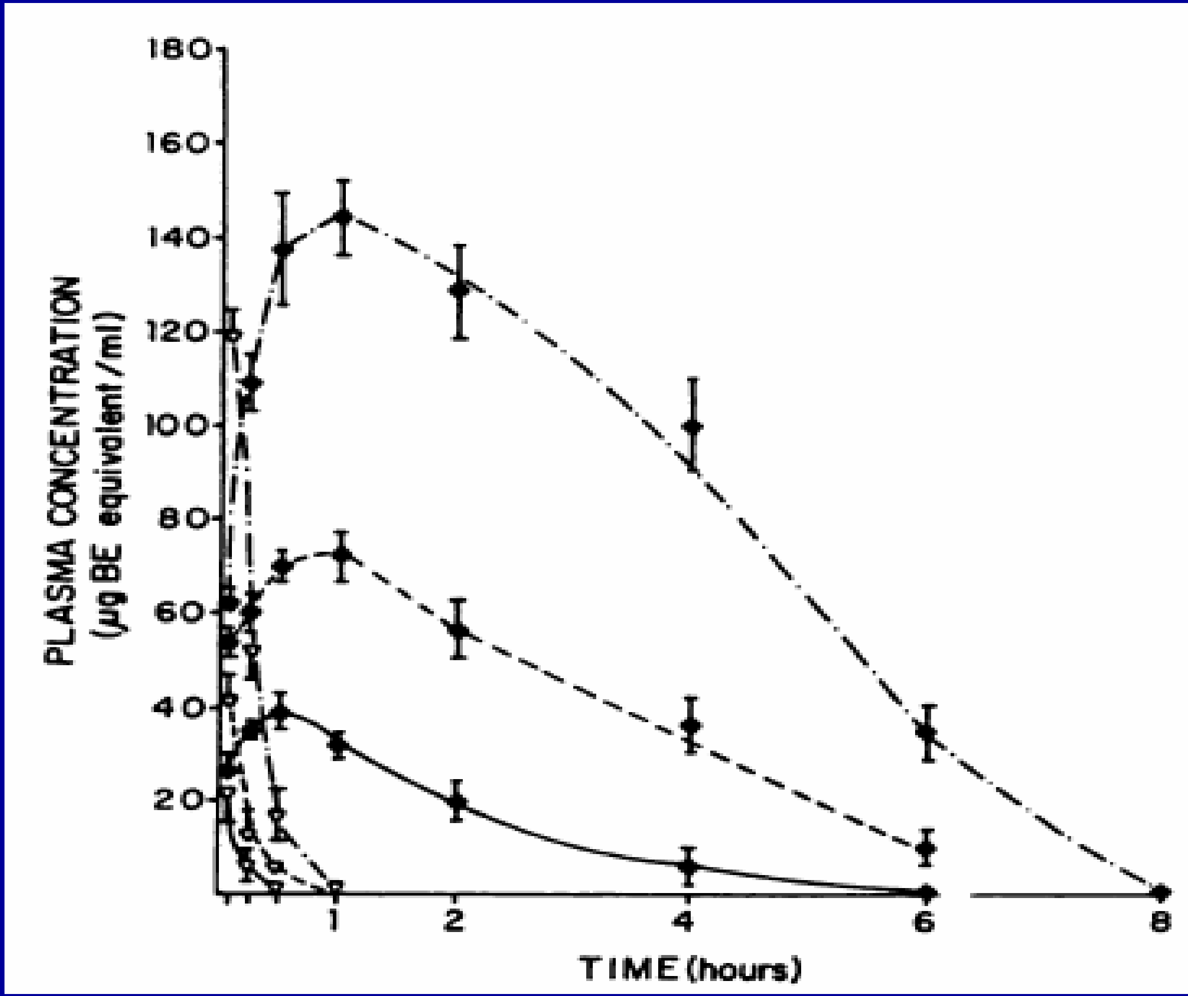


FIG. 2. Changes in the mean (±SD) relative ratio of 7-ethoxycoumarin *O*-deethylase in mouse liver homogenates at different assay temperatures. The enzyme activity ratio for each individual animal at each temperature was calculated with respect to the enzyme activity at 37°C for that animal.

Gearhart JM et al Toxicol Appl Pharmacol. 1993 Apr; 119(2):258-66

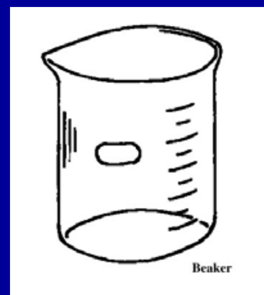
In vivo: Intravenous & Oral



Ghanayem BI, Sanders JM, Clark AM, Bailer J, Matthews HB. Effects of dose, age, inhibition of metabolism and elimination on the toxicokinetics of 2-butoxyethanol and its metabolites.J Pharmacol Exp Ther. 1990 Apr;253(1):136-43.

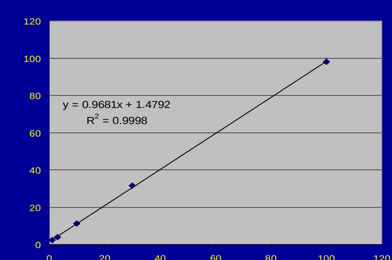
Fig. 1. Mean plasma concentration-time profiles of BE (∇) and BAA (◆) in 3- to 4-month-old (left) and 12- to 13-month-old (right) rats treated with 125 (-·-·-), 62.5 (- - -) and 31.25 (——) mg/kg ^{14}C-BE. Values are presented as the means ± S.E. of three rats, except old rats treated with 125 µg, where $n = 2$.

Data Collection for In vivo Studies

Dosing  + 

+  + 

Sample Collection & Processing  +  → 

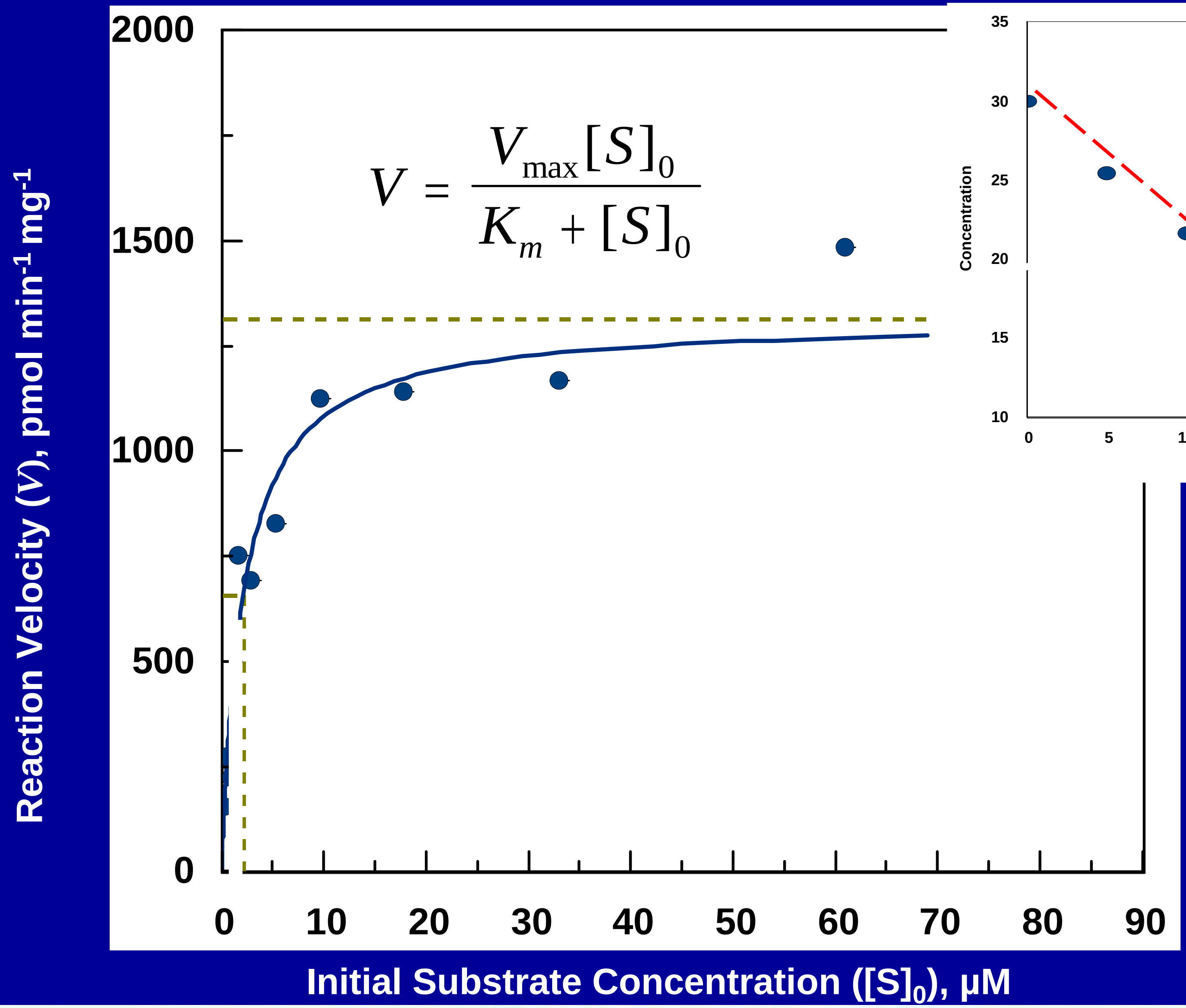
Analytical Chemistry  + 

→ Chemical Concentration & recovery

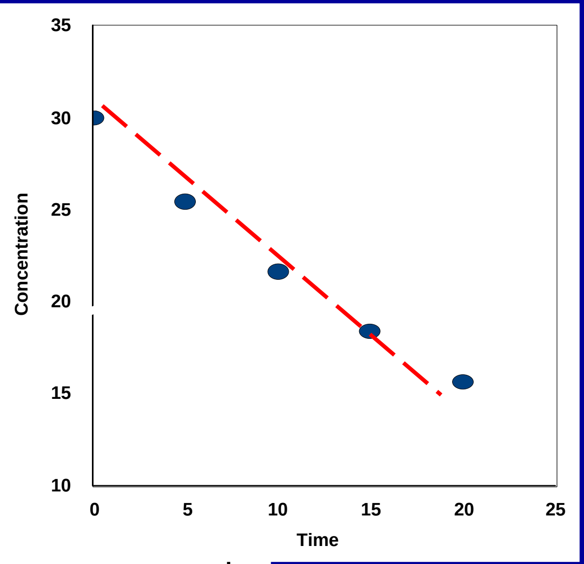
In vitro data

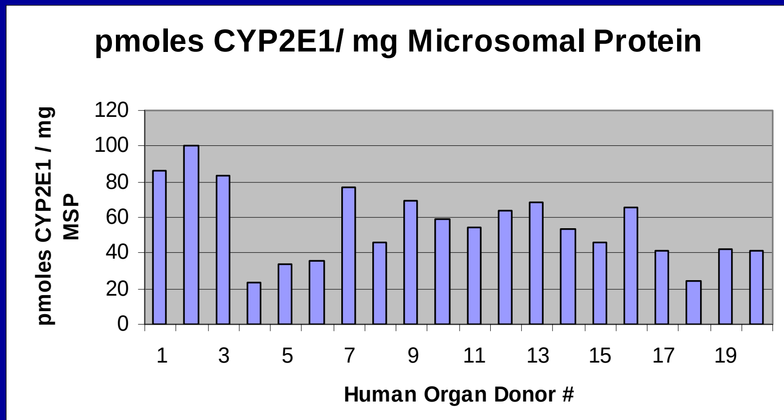
- Partition coefficients: analysis of equilibrium chemical distribution to blood and tissues
- Protein binding rate or equilibrium constants
- In vitro metabolism (e.g., estimates of Km and Vmax)

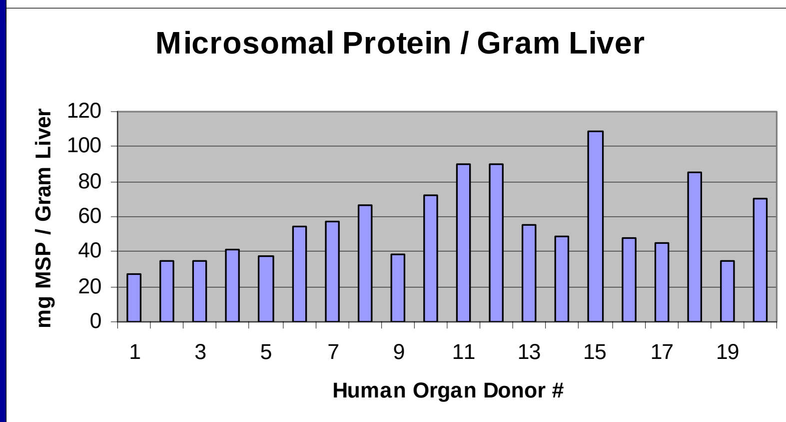
Determination of Kinetic Values

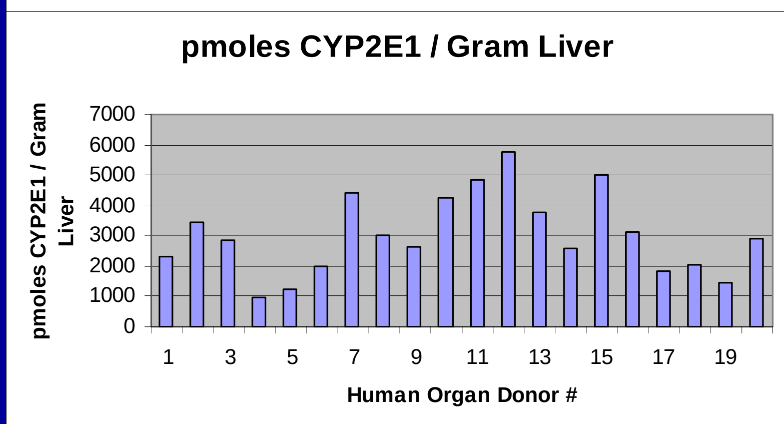


$$V = \frac{V_{\max}[S]_0}{K_m + [S]_0}$$









Human Metabolic Variability

In vitro: CYP2E1 & Microsomal Protein

Lipscomb JC, Teuschler LK, and Swartout JC, Striley CAF, and Snawder JE Variance of Microsomal Protein and Cytochrome P450 2E1 and 3A Forms in Adult Human Liver Toxicol Mech Meth 13:45, 2003

Ex vivo Studies

- Ex vivo: tissues from control and treated animals
- Enzyme induction or destruction (e.g., suicide inhibition)
- GSH depletion
- Other cellular and tissue responses to chemicals

Available Chemical-Specific Data p,p'-Dichlorodiphenylsulfone

- Rats (male & female)
  - Intravenous bolus – 10 mg/kg, 7 times (0.5 – 504 hr), 3-4 rats/time
    - Total radioactivity in blood and 6 tissues
    - Total radioactivity & DDS in urine and feces
    - DDS and total metabolites in blood & liver on day 3
  - Oral bolus – 10, 100, 1000 mg/kg, 1 time (72 hr), 3 – 5 rats
    - DDS and total metabolites in blood and 3 tissues, feces
    - Total radioactivity in 4 tissues & urine
  - Chronic Dietary Study – 3 dose levels
    - Plasma DDS at 9 am, 12 noon, 3 pm at 2 weeks, 3, 12, 18 months
- Mice – generally similar set of studies
- One laboratory, one analytical method, individual animal data

Data: Mathews et al., Drug Metab Dispos. 1996 May;24(5):579-87, NTP Tech Rep 501 (2000)
Model: Parham FM, et al. Toxicol Appl Pharmacol. 2002 Jun 15; 181(3):153-63

Available Chemical-Specific Data Trichloroethylene

- Rats & Mice
  - Gas uptake studies in multiple rat strains & mice
  - Inhalation studies – parent blood & tissues, selected metabolites, time points during & post-exposure
  - Gavage studies – multiple dose levels, radioactivity mass balance, blood & tissue – parent & selected metabolites, urine – selected metabolites
  - Multiple laboratories, multiple analytical methods, published means and variances
- Humans
  - Controlled exposures – parent and selected metabolites
  - In vitro metabolism

Summary

- Data types
  - Physiological
    - Anatomy, physiology, endogenous biochemistry
  - Chemical specific
    - In vivo, In vitro, Ex vivo
- Data Themes:
  - Study design: single & repeated measures, numbers of datapoints, multiple laboratories & analytical methods
  - Model analyses: combining different kinds of data, combining across species or strains