Modeling Pharmacokinetics in Rat Pups

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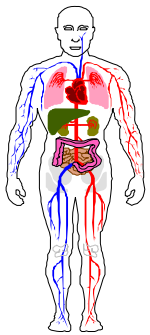
Overview

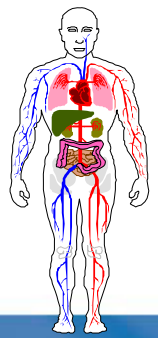
- Background
- Predictive modeling for VOCs
- Predictive modeling for lactational transfer
- Conclusions

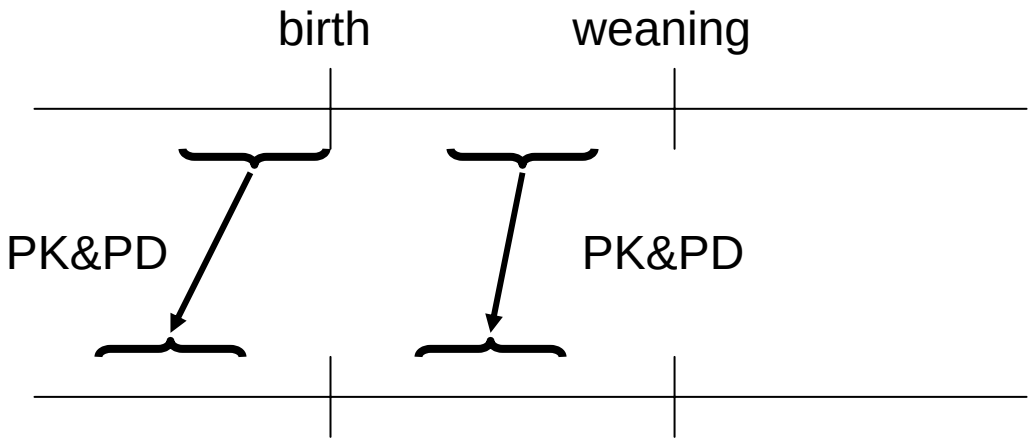
Evaluating Risks to Early Ages

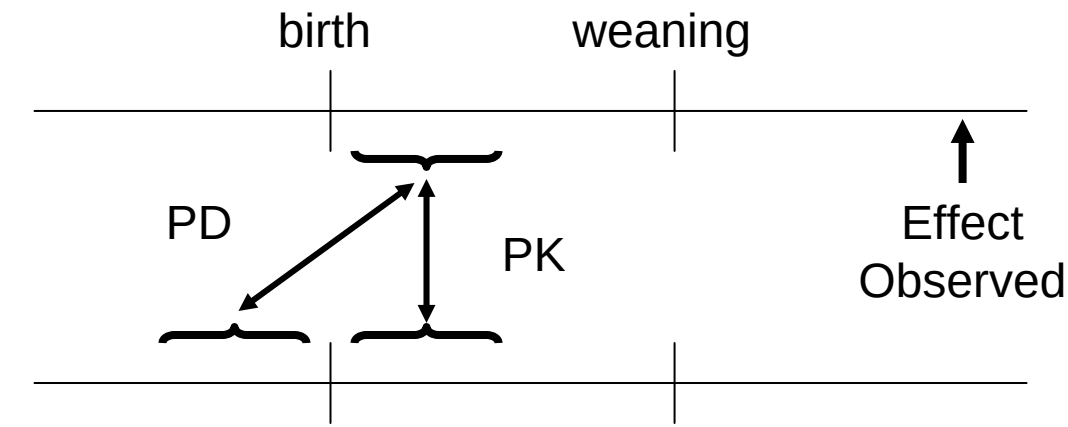
- Extrapolation from adult to children
  - Changes in exposure
  - Changes in pharmacokinetics/toxicokinetics
  - Changes in pharmacodynamics/toxicodynamics
- Extrapolation across-species
  - Toxicity studies
    - developmental (in utero),
    - 2-generation reproductive/developmental,
    - developmental neurotoxicity
  - Exposure, PK, PD (window of susceptibility, critical period)

Mapping Cross-species









Windows of Suceptibility

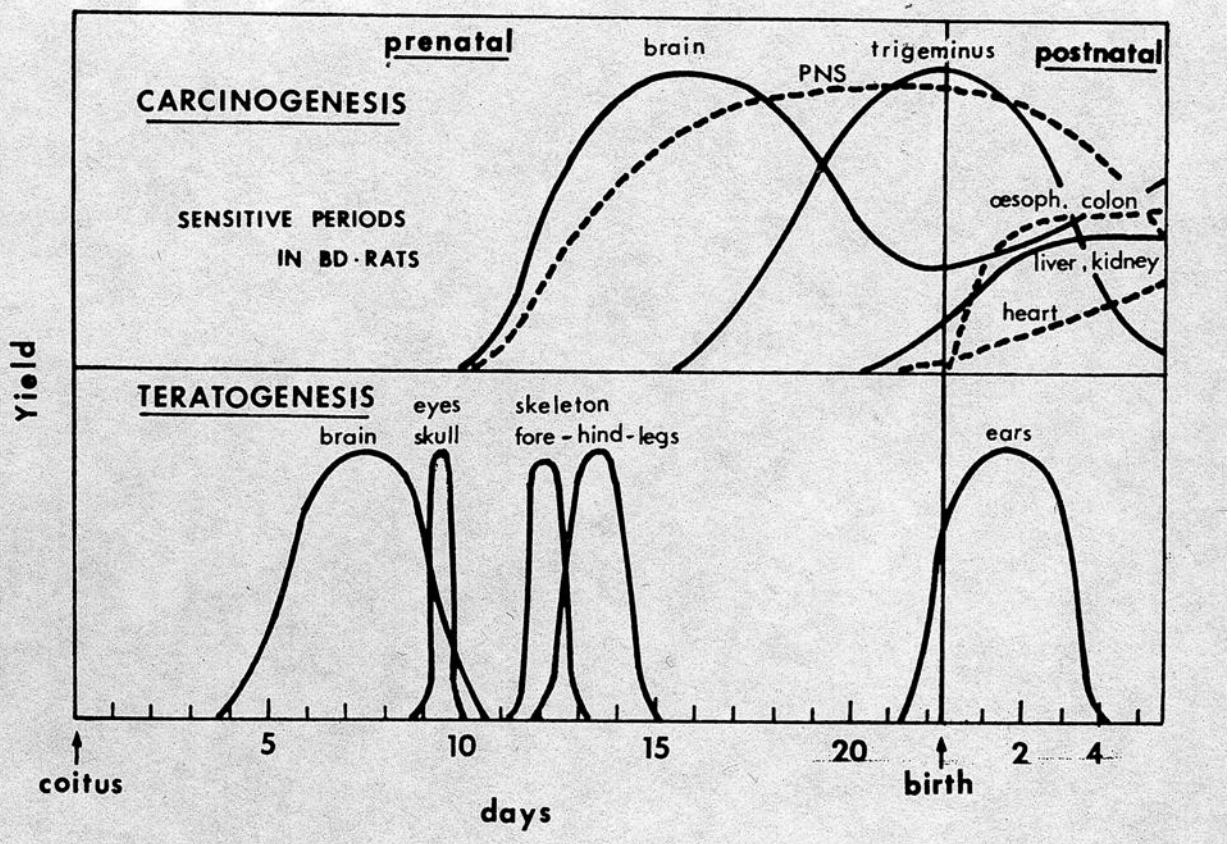
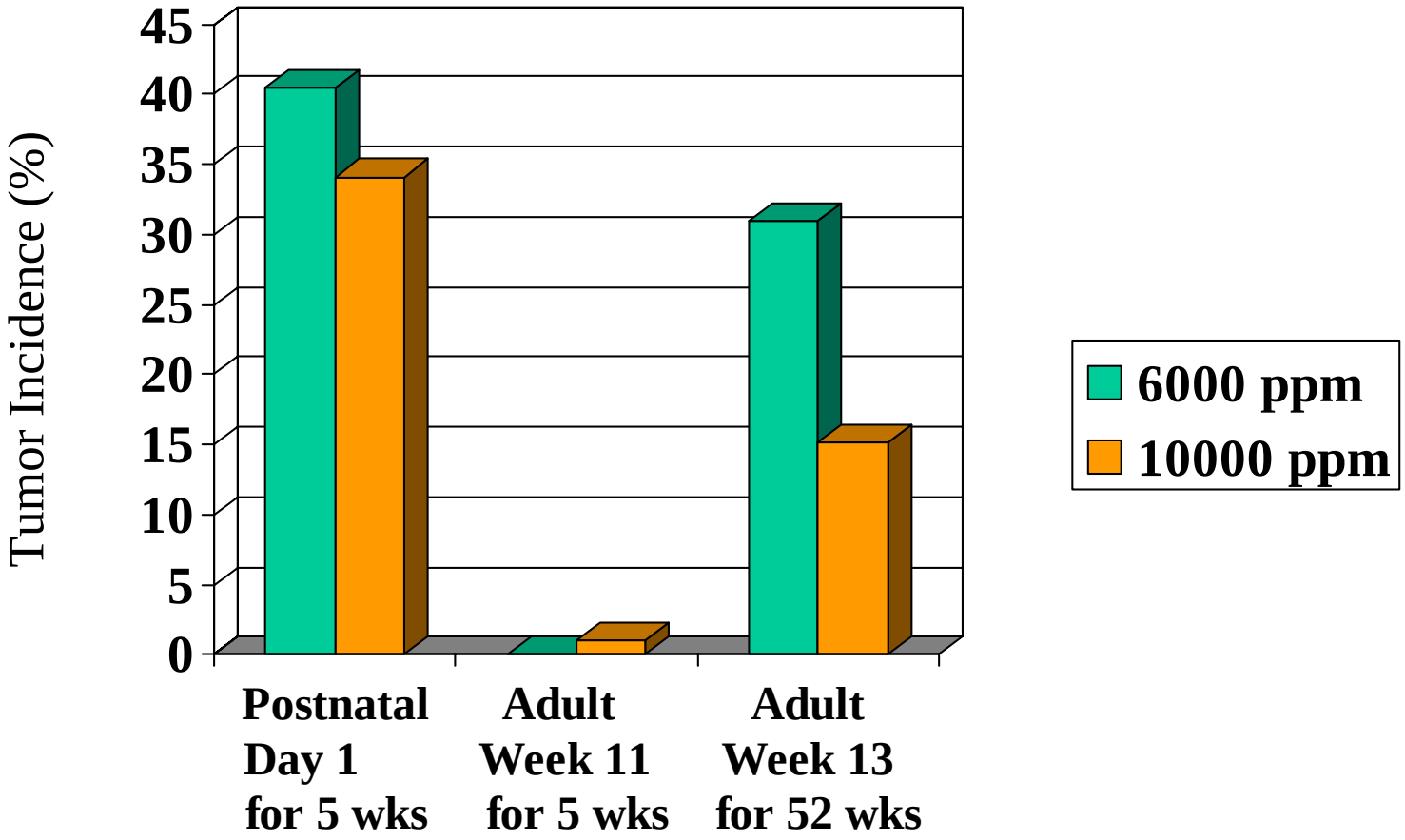


Fig. 4. Sensitive periods of various organs of BD rats in transplacental and neonatal carcinogenesis and teratogenesis caused by direct and indirect alkylating substances. Malformations of the auricles induced by cyclophosphamide, 20 mg/kg. Abscissa: days after observed coitus and birth respectively; ordinate: yield.

Druckrey H
IARC Sci Pub
4, 45-57, 1973

Vinyl Chloride and Life Stage – Sprague Dawley rat liver angiosarcomas



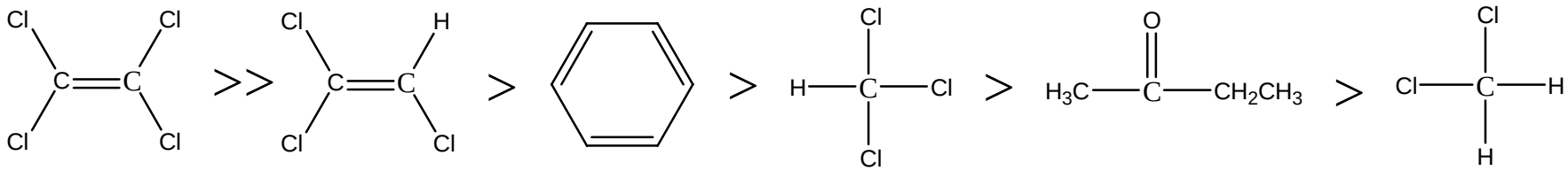
Maltoni C. *et al.*, 1984.

Predictive Modeling for VOCs for Rats

Ages simulated

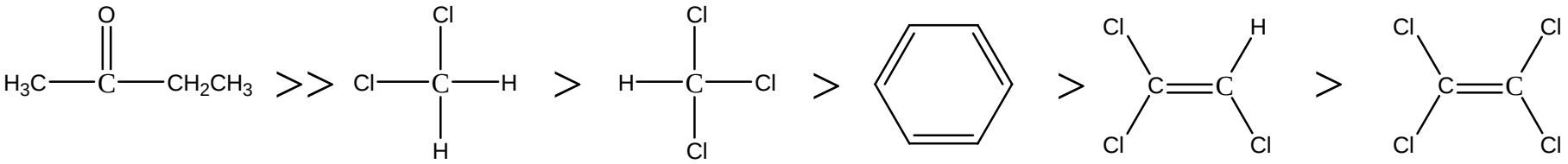
Post-natal day 10 (PND10), 60 day old (adult), and 2 year old (aged)

Ranked by Lipophilicity



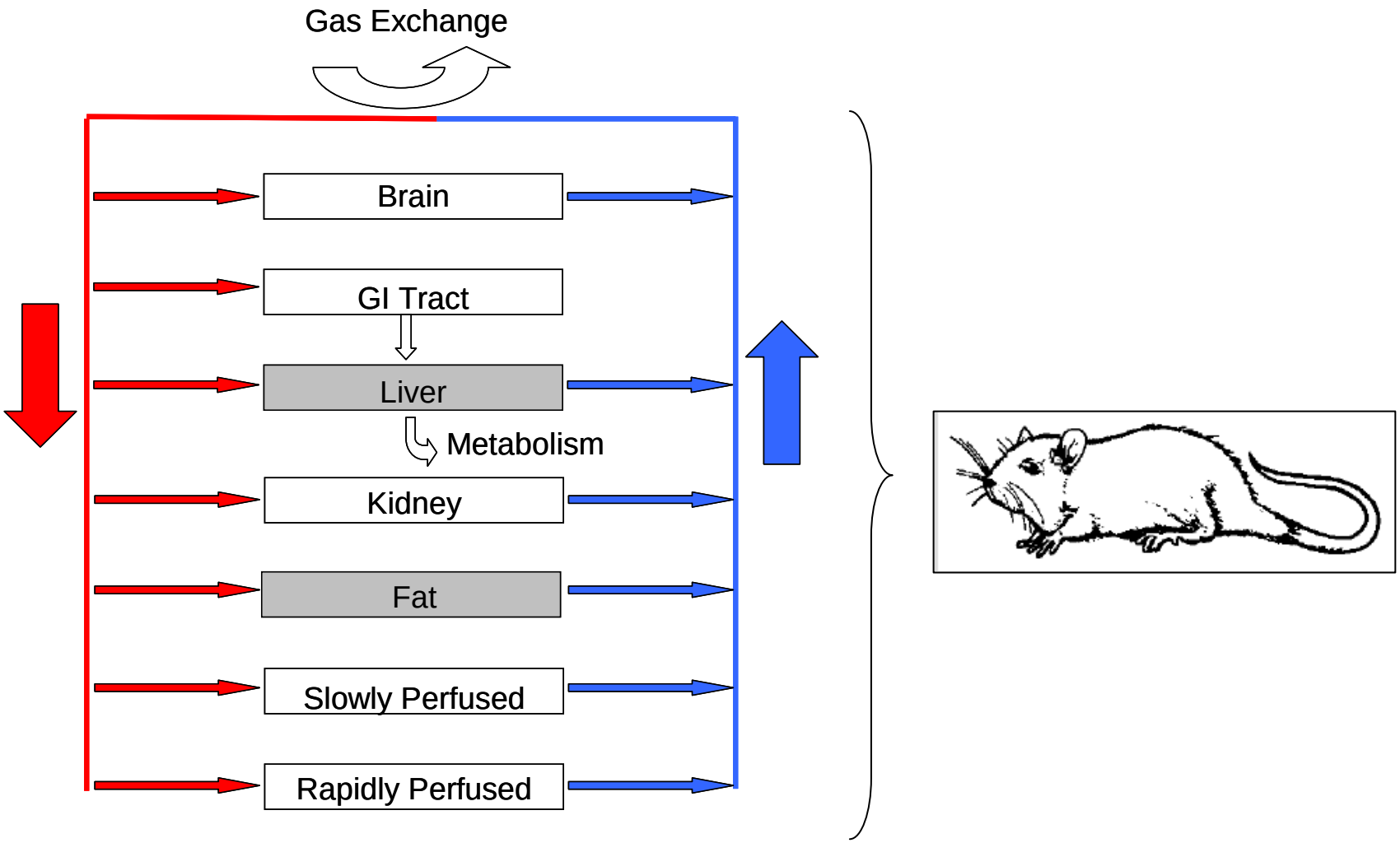
Perchloroethylene >> **Trichloroethylene** > **Benzene** > **Chloroform** > **Methylethylketone** > **Methylene Chloride**

Ranked by Water Solubility



Methylethylketone >> **Methylene Chloride** > **Chloroform** > **Benzene** > **Trichloroethylene** > **Perchloroethylene**

VOC Model Structure



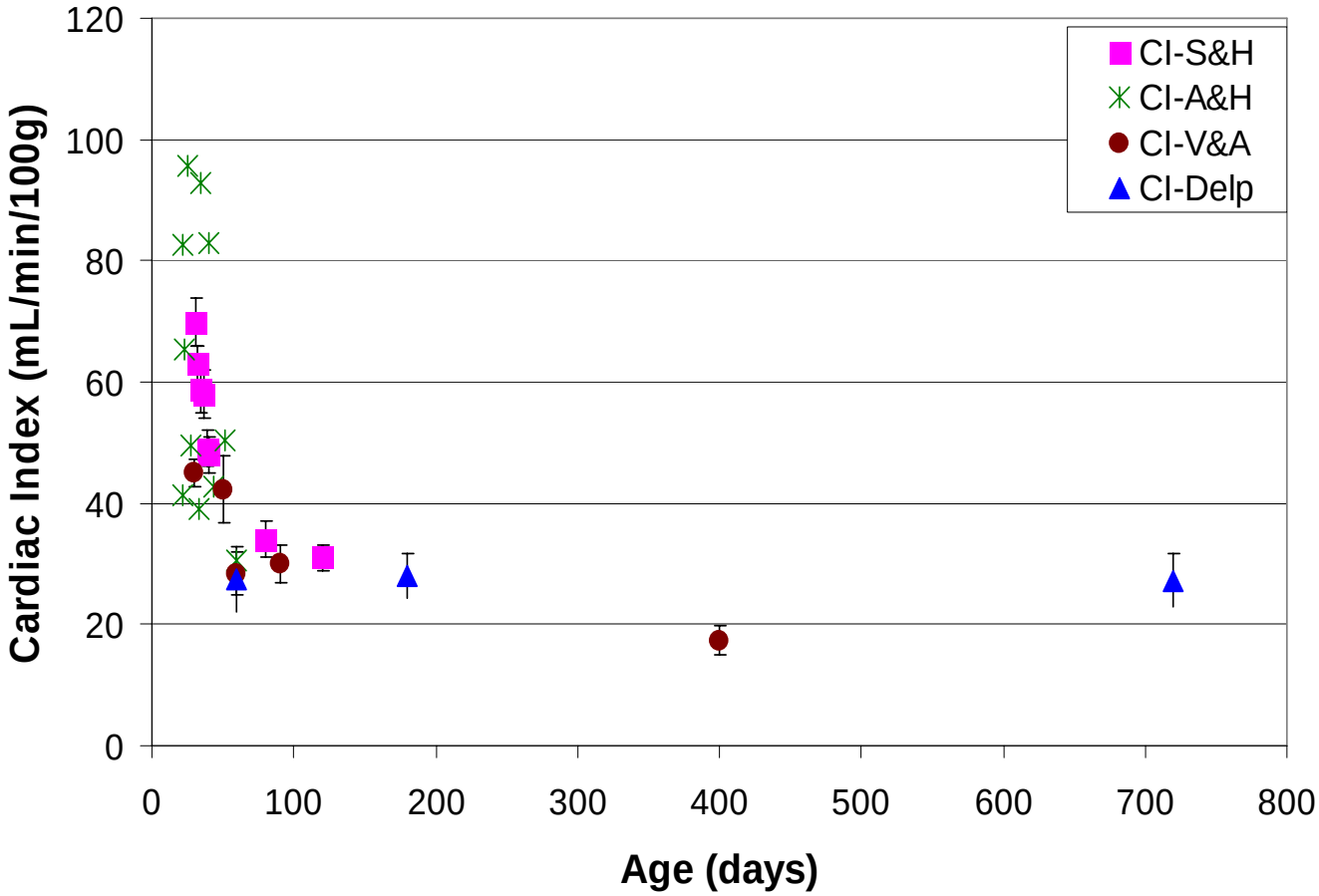
Physiological Parameters

- Tissue Volumes
  - What tissues go where?
  - What does the available data measure?
- Fractional flow to tissues
- Alveolar ventilation rate
- Cardiac Output

Cardiac Output

- Cardiac output normalized to body weight (Cardiac Index) is constant for 2, 6, and 24 month old rats (Delp et al. 1998), which is inconsistent with $BW^{0.75}$ scaling
- No studies prior to weaning in rats
- Studies after weaning show a large pubertal decrease in Cardiac Index
- Post-weaning trend similar to $BW^{0.75}$ scaling, but pubertal changes greater than predicted
- Substantial datagap for modeling pnd 0 – pnd 21, the lactational period in rats

Cardiac Index vs Rat Age



Rat Strains

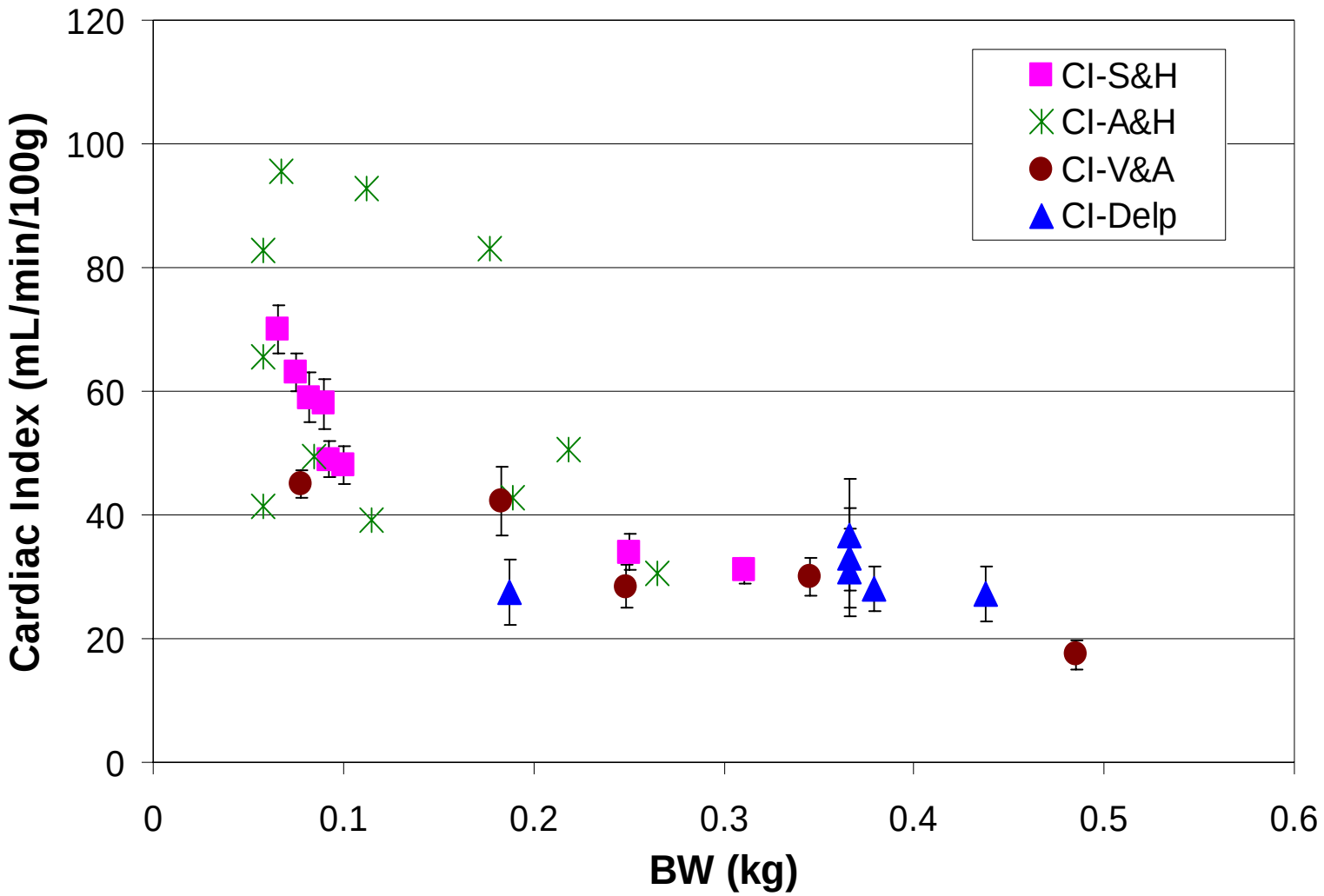
S&H: Wistar Kyoto

A&H: Sprague Dawley

V&A: Wistar

Delp: F344 (S-D)

Cardiac Index vs Rat Body Weight



Tissue:blood partition coefficients

VOC	PB	PL	PK	PF	PBR	PR	PS	PG
Methylene Chloride								
PND10	14	0.9	0.7	6.0	0.6	0.9	1.1	1.1
Adult	18	1.2	0.7	7.7	0.6	1.2	0.5	0.5
Aged	21	1.3	0.7	7.5	0.6	1.3	0.6	0.6
Methyl ethyl ketone								
PND10	208	1.0	0.9	1.0	0.9	1.0	0.9	0.9
Adult	196	1.1	1.2	1.2	0.8	1.1	0.8	0.8
Aged	197	1.2	1.1	1.1	0.8	1.2	0.8	0.8
Perchloroethylene								
PND10	15	2.8	2.2	63	1.7	2.8	6.2	6.2
Adult	14	2.6	2.4	112	3.0	2.6	1.8	1.8
Aged	21	3.2	1.8	96	3.0	3.2	2.9	2.9

Mahle DA, Gearhart JM, Grigsby C, Mattie DR, Barton HA, Lipscomb JC, Cook RS. (2007) Age-Dependent Partition Coefficients for a Mixture of Volatile Organic Solvents in Sprague-Dawley Rats and Humans. J Toxicol Environ Health (in press) [(2005) AFRL-HE-WP-TR-2005-0012]

Age-Adjustments for Metabolism

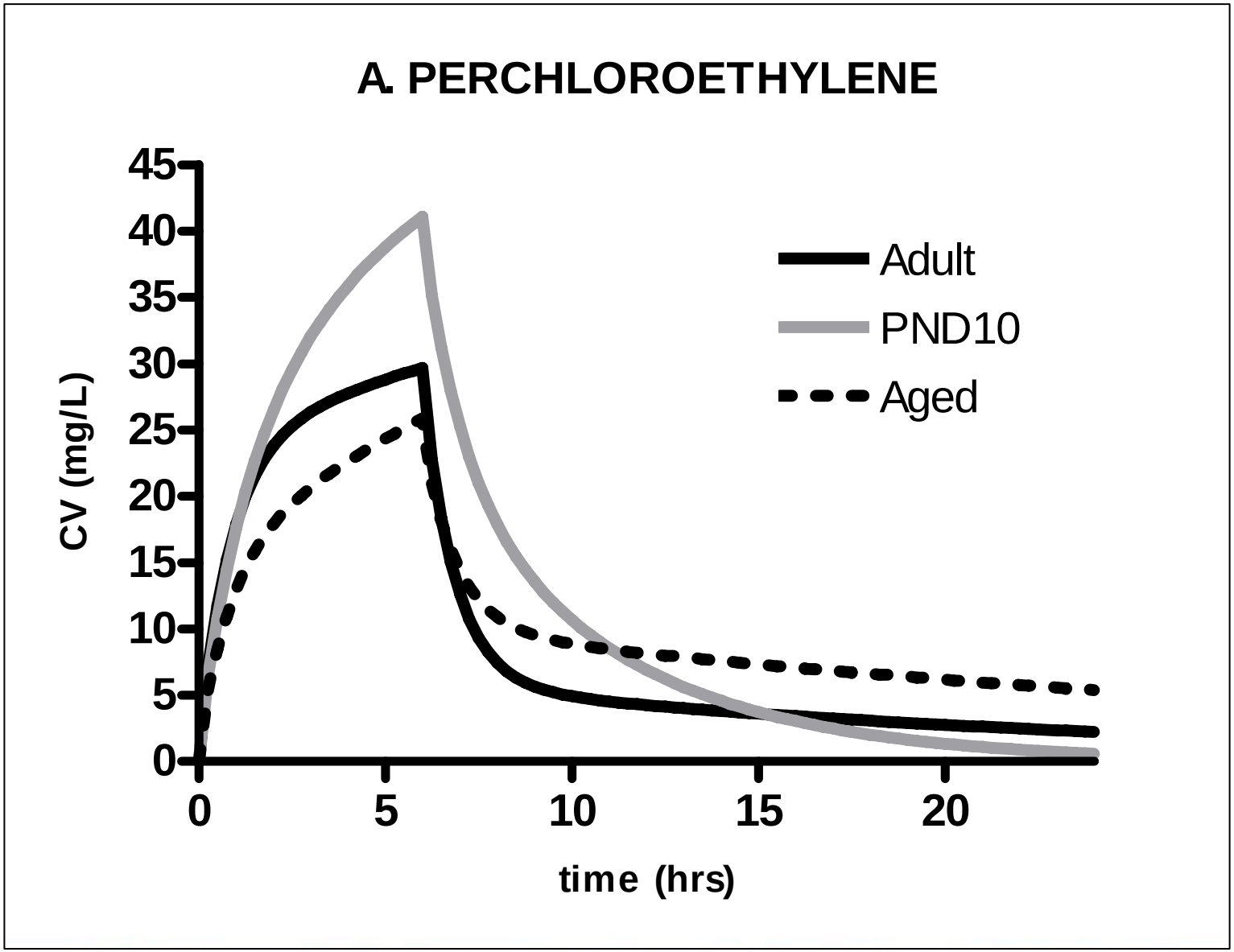
- Vmax & Km from PBPK models for adult rats
- Adjust to appropriate ages using in vitro data for substrates specific to enzymes (e.g., CYP, GST)

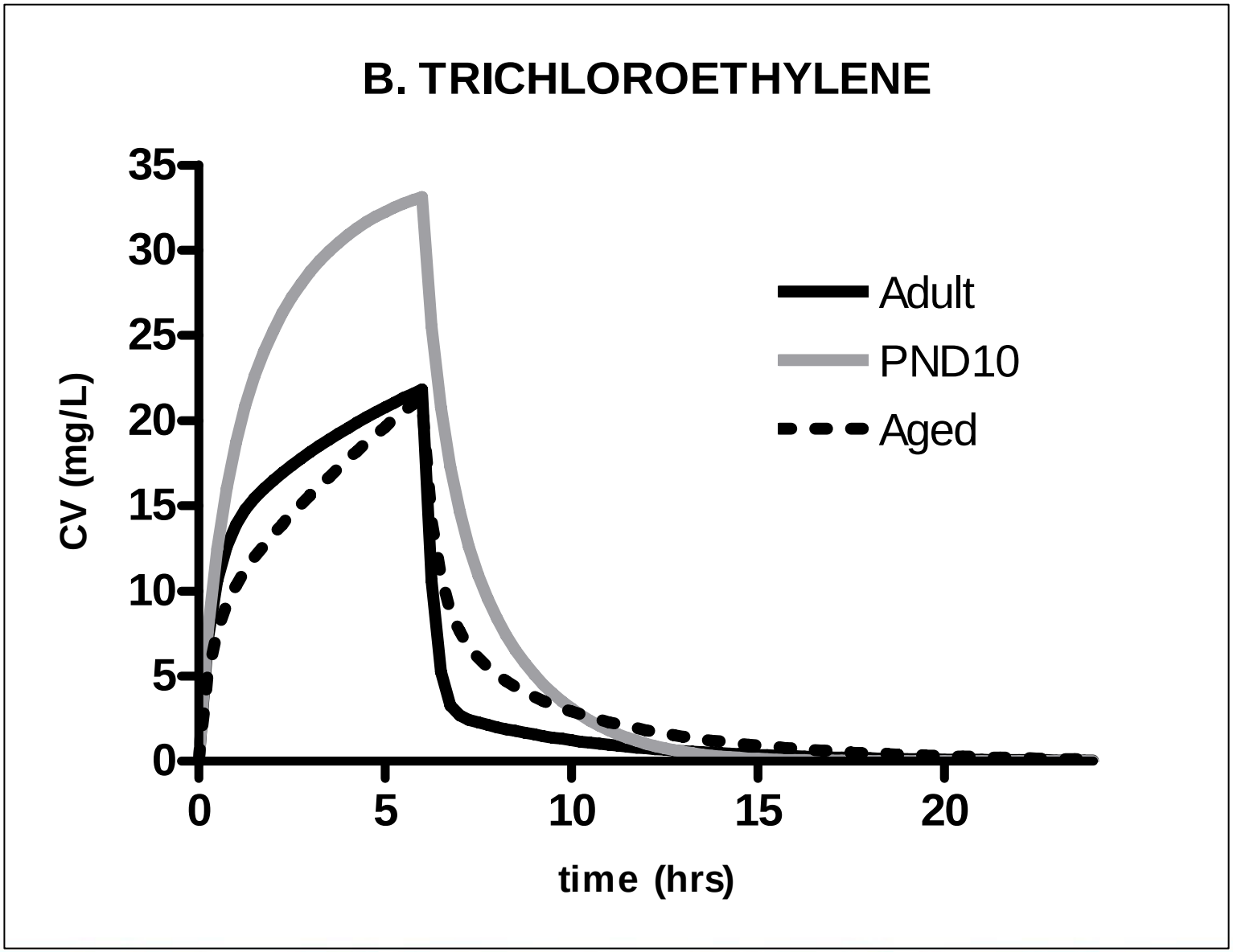
$$Vmax = Vmax(\text{in vitro})^{*}\ Cmp\ ^{*}VL$$

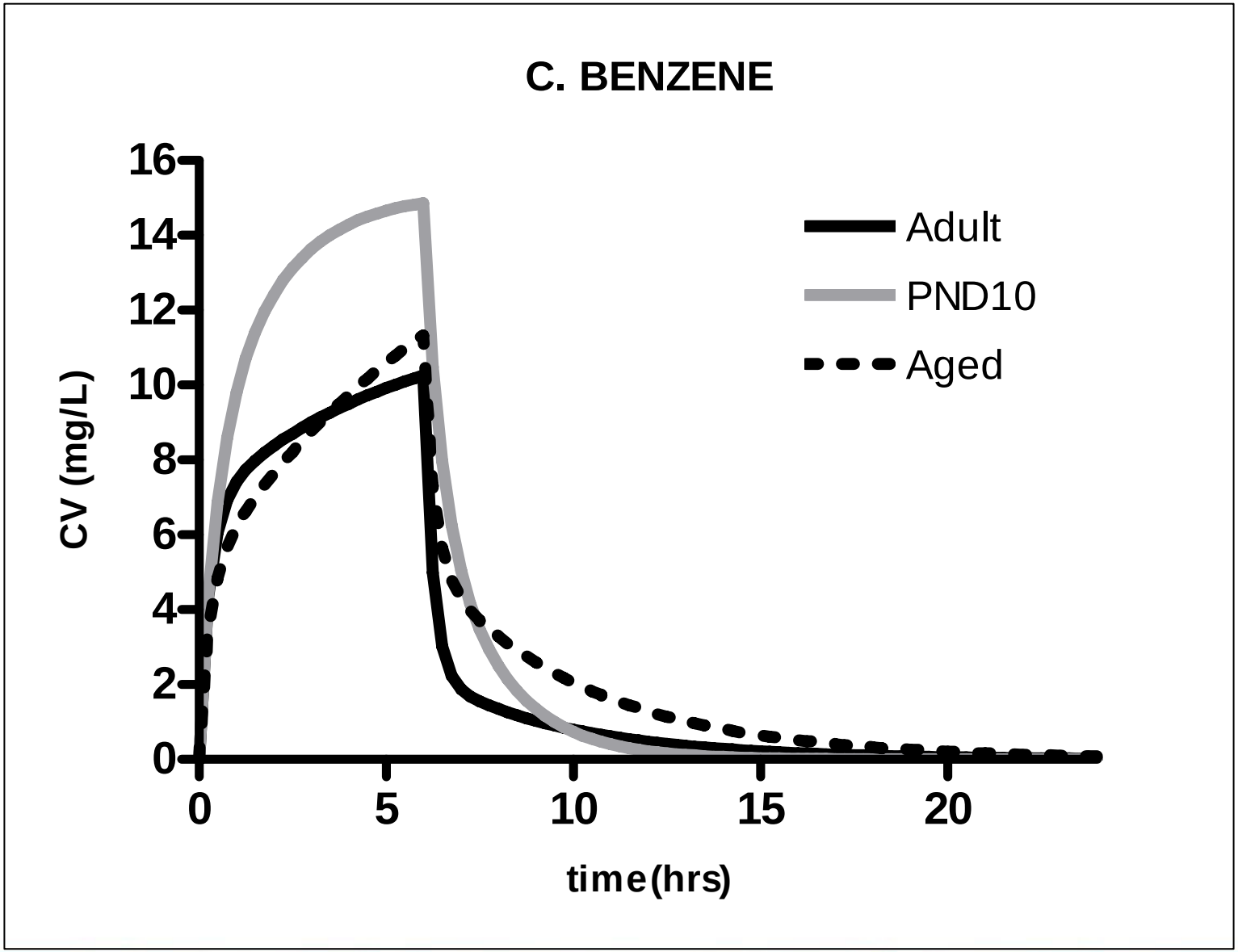
$$Vmax_{x} = Ra^{*}Rmp^{*}Rvl\ ^{*}Vmax_{adult}$$

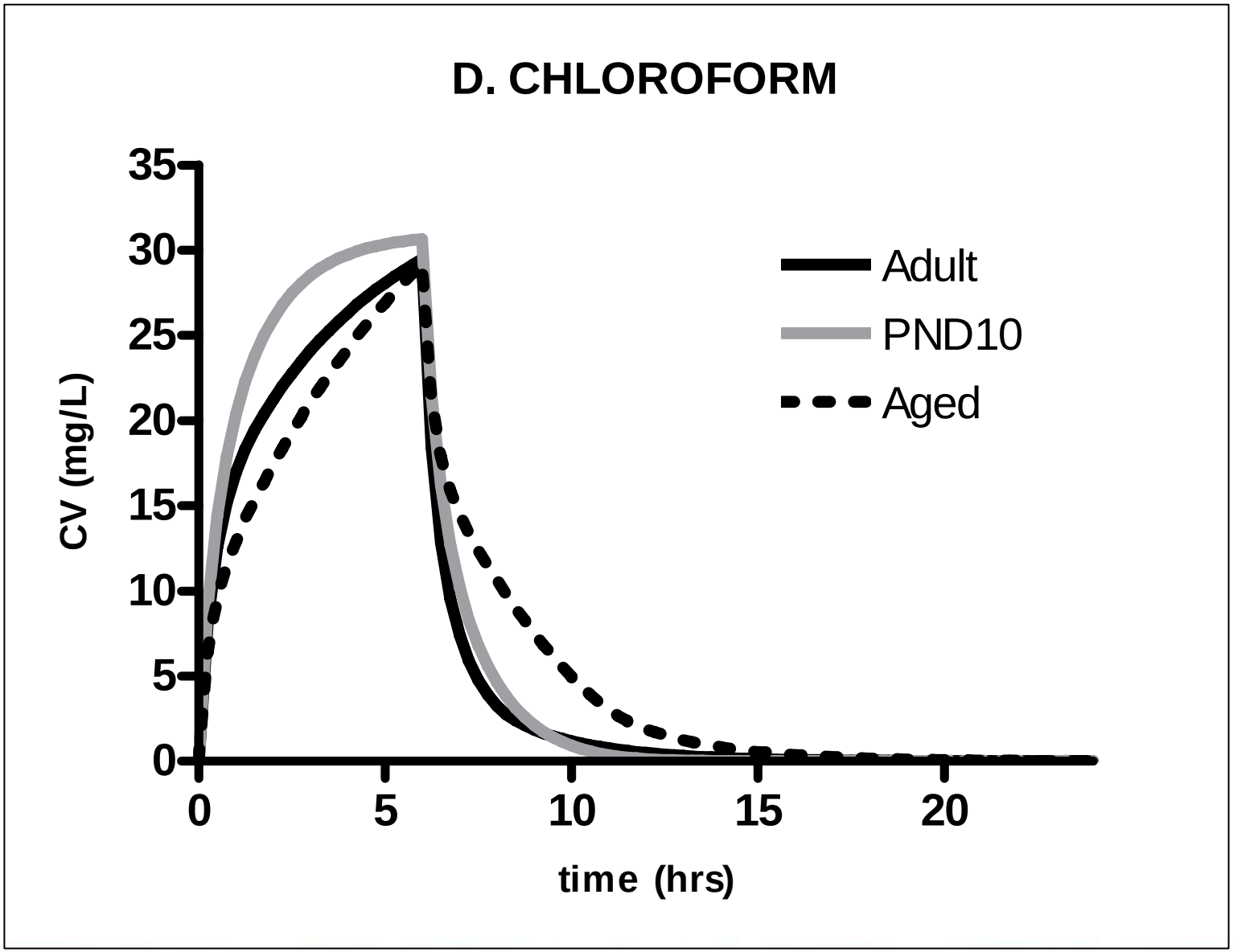
$$Ra = \frac{(\text{CYP2E1 activity})_{x}}{(\text{CYP2E1 activity})_{adult}} \qquad Rmp = \frac{Cmp_{x}}{Cmp_{adult}} \qquad Rvl = \frac{VL_{x}}{VL_{adult}}$$

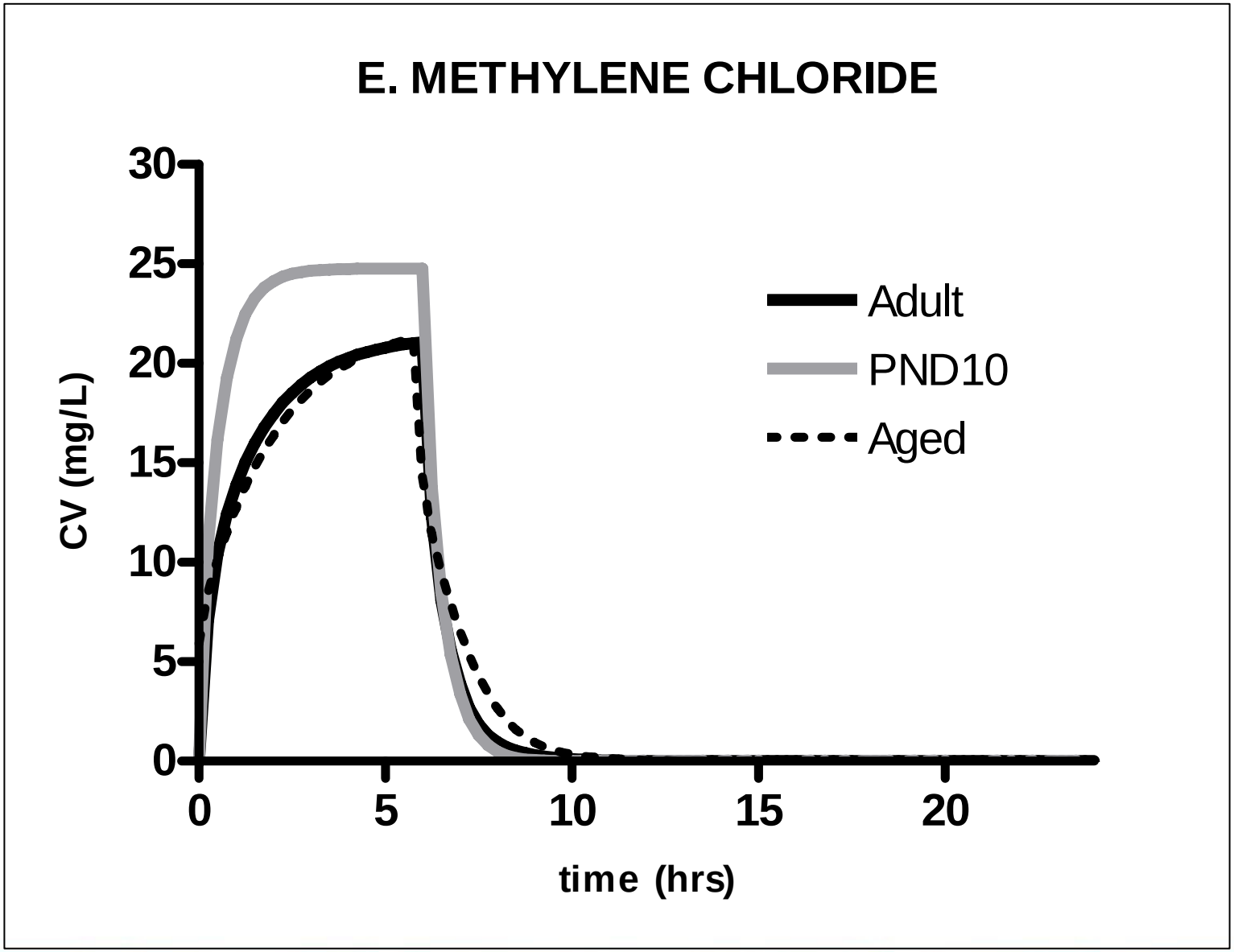
Ra*Rmp*Rvl = 0.042 and 1.09 for PND10 and aged rats

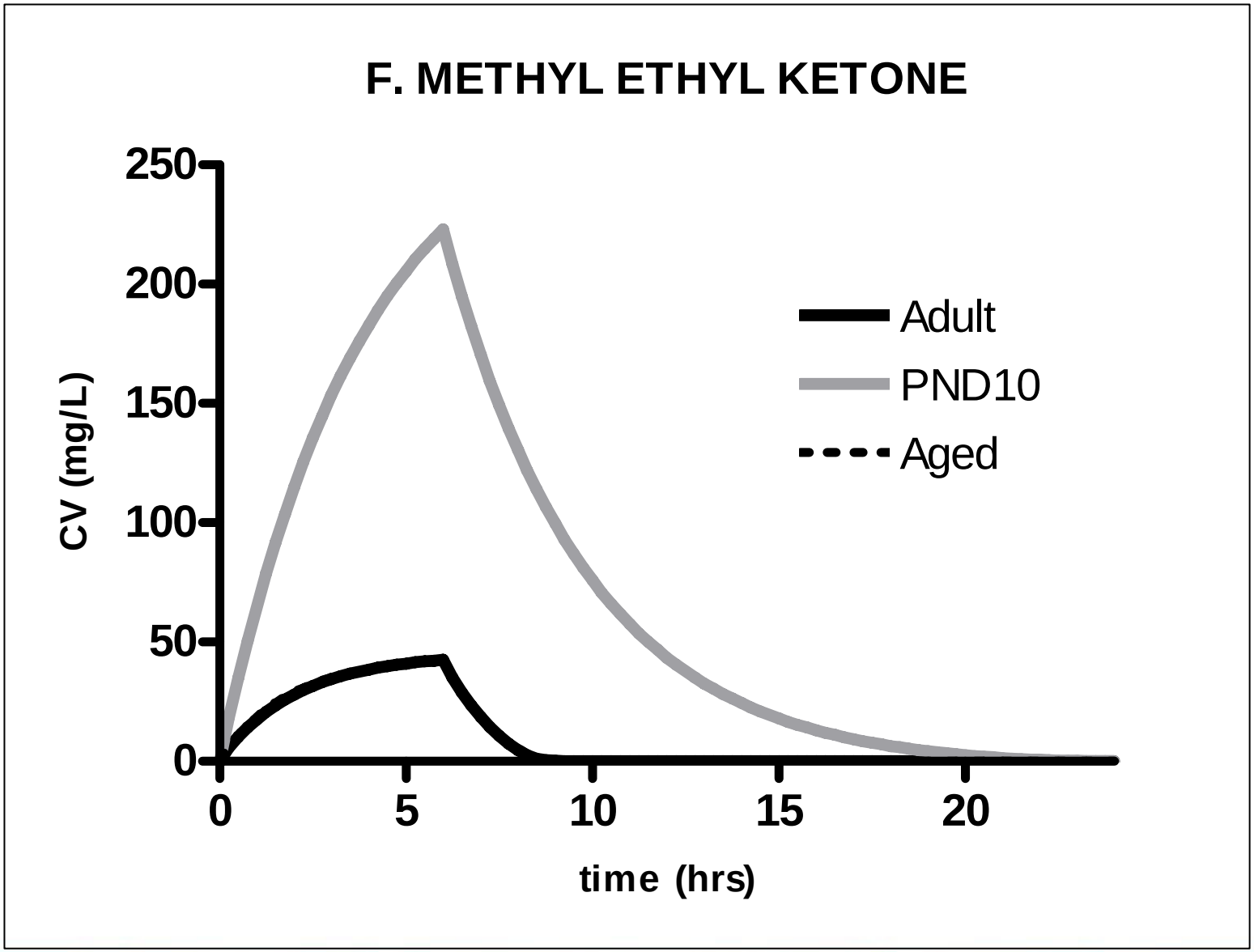

A. PERCHLOROETHYLENE
CV (mg/L)
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
time (hrs)
Adult
PND10
Aged


B. TRICHLOROETHYLENE
CV (mg/L)
35
30
25
20
15
10
5
0
0
5
10
15
20
time (hrs)
Adult
PND10
Aged


C. BENZENE
16
14
12
10
8
6
4
2
0
CV (mg/L)
0
5
10
15
20
time(hrs)
Adult
PND10
Aged

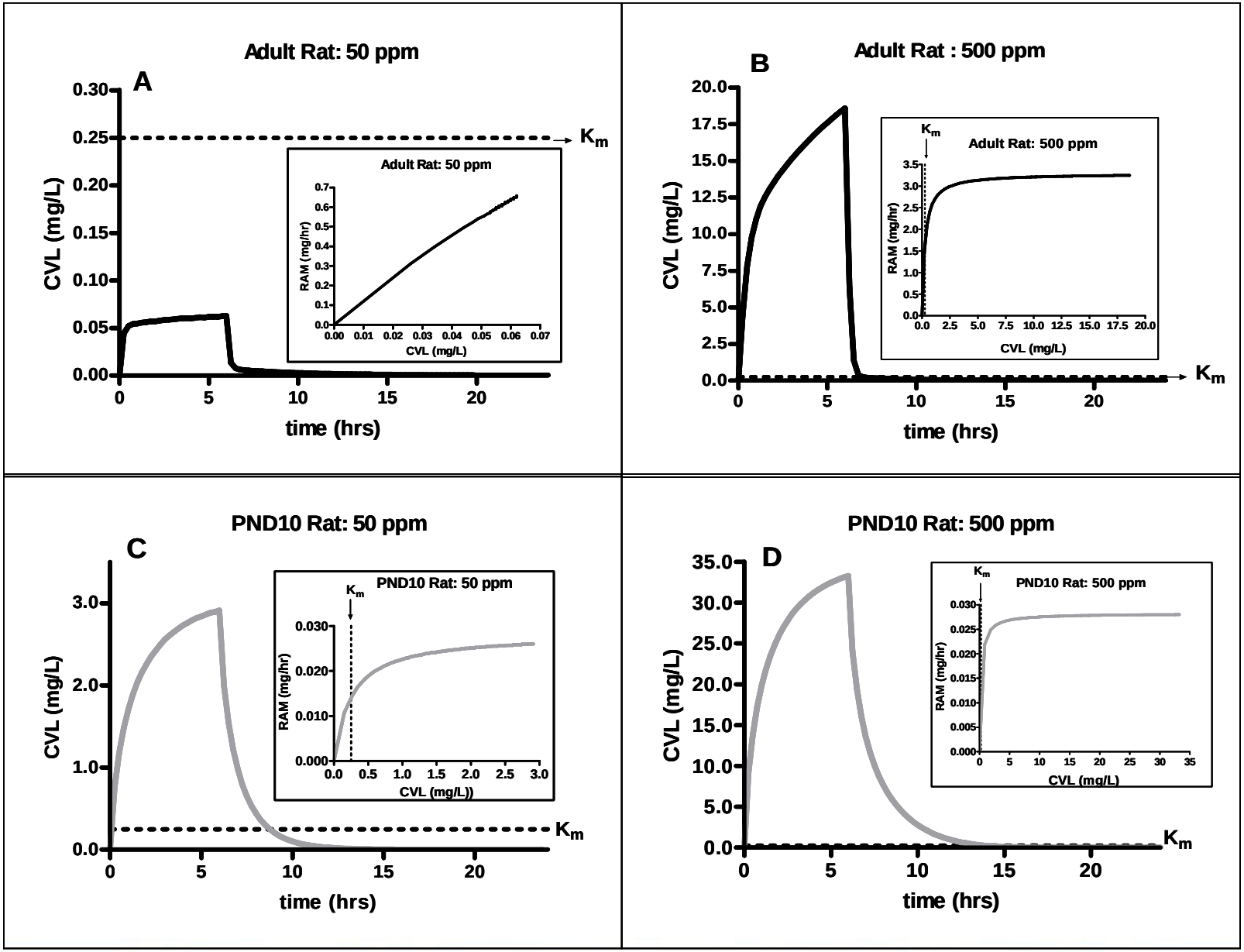

D. CHLOROFORM
35
30
25
20
15
10
5
0
CV (mg/L)
0
5
10
15
20
time (hrs)
Adult
PND10
Aged


E. METHYLENE CHLORIDE
CV (mg/L)
30
25
20
15
10
5
0
0
5
10
15
20
time (hrs)
Adult
PND10
Aged


F. METHYL ETHYL KETONE
250
200
150
100
50
0
CV (mg/L)
0
5
10
15
20
time (hrs)
Adult
PND10
Aged

Predicted Amount of VOC Metabolized per Unit Liver Volume (mg/L) for Different Ages of the Rat at 24 h following a 50 or 500 ppm Inhalation Exposure for 6 h

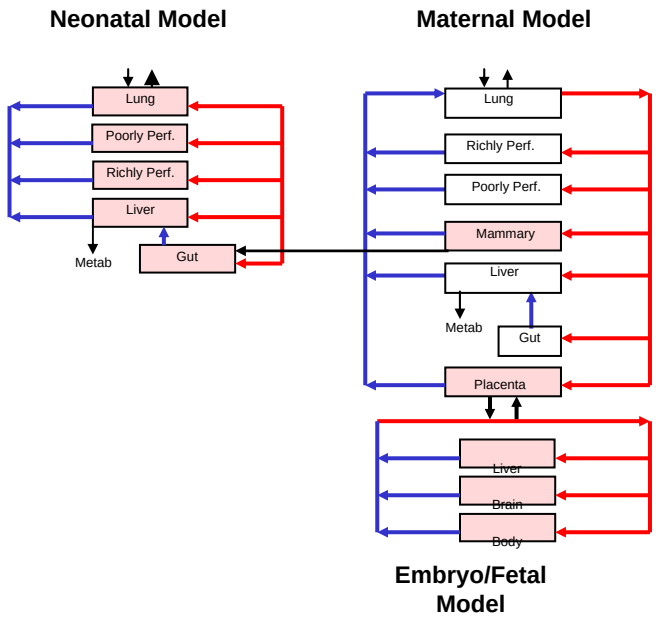
VOC		PND10	Adult	Aged	Aged /Adult	PND10 /Adult
Perchloroethylene	500 ppm	12	104	97	0.9	0.1
	50 ppm	1.2	10.4	9.7	0.9	0.1
Trichloroethylene	500 ppm	635	2900	3909	1.3	0.2
	50 ppm	390	420	506	1.2	0.9
Benzene	500 ppm	273	1530	1954	1.3	0.2
	50 ppm	66	195	240	1.2	0.3
Chloroform	500 ppm	317	2004	2661	1.3	0.2
	50 ppm	215	386	460	1.2	0.6
Methylene Chloride	500 ppm	143	1257	1772	1.4	0.1
	50 ppm	99	259	308	1.2	0.4
Methyl ethyl ketone	500 ppm	1461	2557	2987	1.2	0.6
	50 ppm	376	286	333	1.2	1.3


Adult Rat: 50 ppm
A
CVL (mg/L)
time (hrs)
Km
Adult Rat: 50 ppm
RAM (mg/hr)
CVL (mg/L)
Adult Rat : 500 ppm
B
CVL (mg/L)
time (hrs)
Km
Km
Adult Rat: 500 ppm
RAM (mg/hr)
CVL (mg/L)
PND10 Rat: 50 ppm
C
CVL (mg/L)
time (hrs)
Km
Km
PND10 Rat: 50 ppm
RAM (mg/hr)
CVL (mg/L))
PND10 Rat: 500 ppm
D
CVL (mg/L)
time (hrs)
Km
Km
PND10 Rat: 500 ppm
RAM (mg/hr)
CVL (mg/L)

Developmental Pharmacokinetics

- Lactation (mother & preweaning offspring)
- Post-weaning juvenile/child

- Challenges
  - Physiological parameters
  - Chemical specific parameters

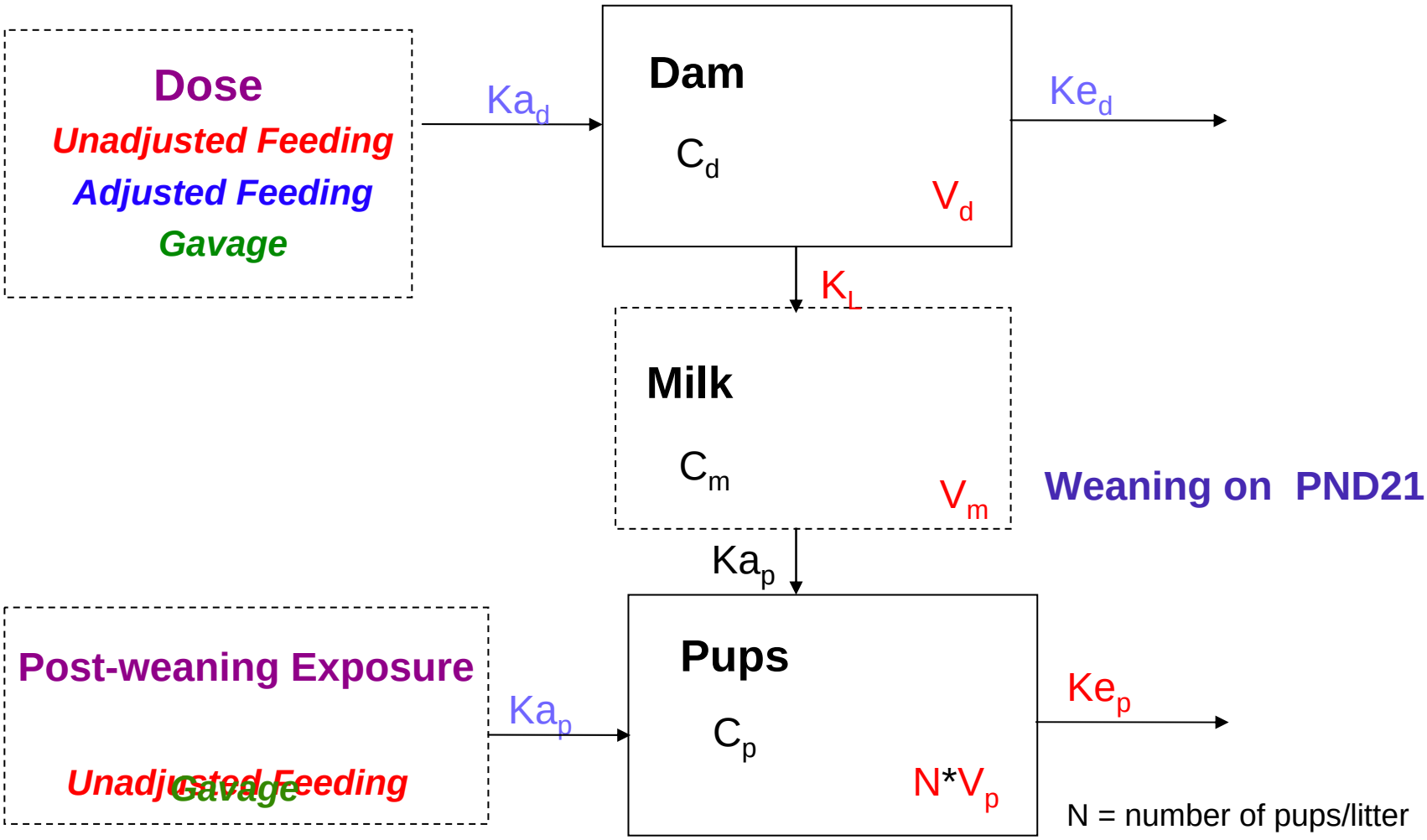


Biologically Based Lactational Modeling

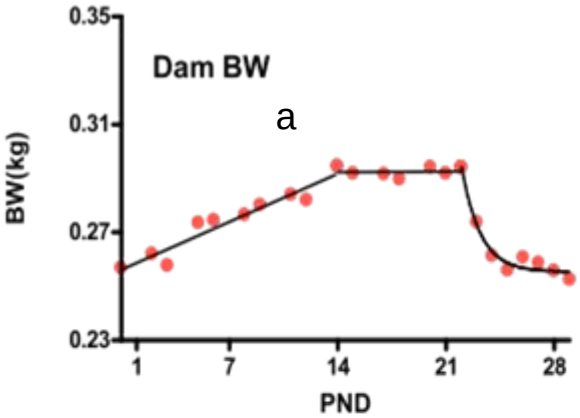
Develop methods to predict dosimetry in the young during lactational and early post-weaning periods

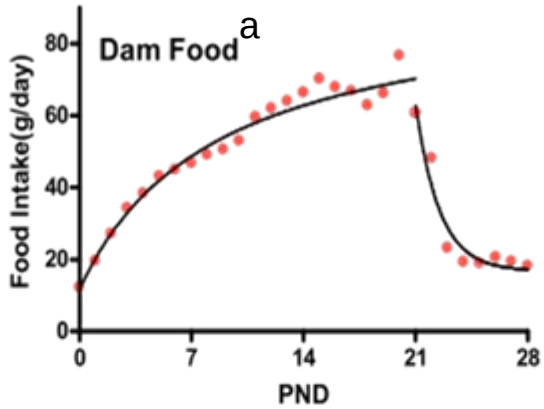
- Use only limited biological and pharmacokinetic information
- Evaluate impacts on postnatal dosimetry according to
  - Dosing approaches
    - **Gavage:** constant mg/kg/day to dam
    - **Diet or drinking water: Unadjusted** constant ppm
      up to 3-fold increased mg/kg/day during lactation
    - **Diet: Adjusted** ppm during lactation
      ~constant mg/kg/day during lactation to dam
  - Chemical's pharmacokinetic properties
    - **Half life**
    - **Milk to plasma partition**
    - **Volume of distribution**

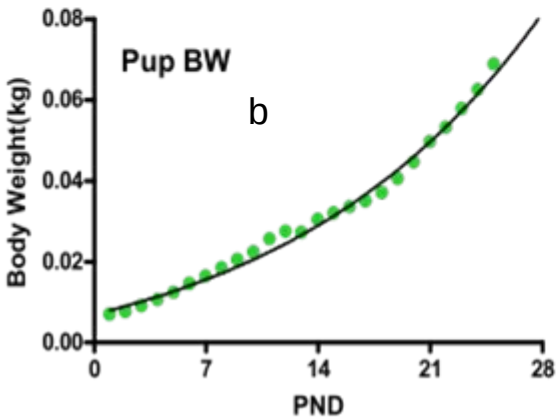
BBPK Model for Lactational and Early Post-Weaning Exposure

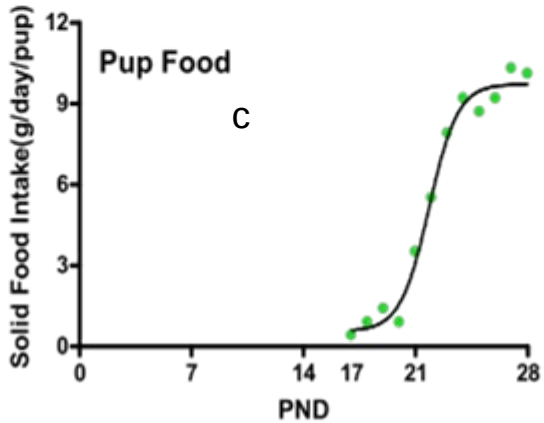


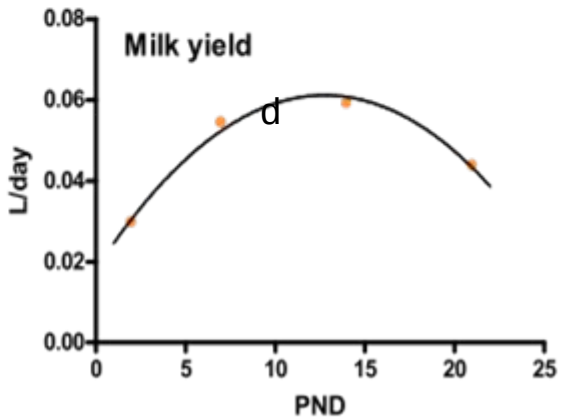
Biological Data Incorporated











[a] Shirley, 1984
Lab. Animal Sci. 34:169-172

[b] Doerflinger and Swithers, 2004
Dev. Psychobiol. 45:72-82

[c] Redman and Sweney, 1976
J. Nutr. 106:615-626

[d] Knight et al., 1984
J. Dairy Res. 51:29-35

Current Assumptions on Chemical Properties

- Lactational transfer of parent chemical only
- Volume of distribution same in the dam and pup
- Milk concentration (Pm, milk:blood partition coefficient)

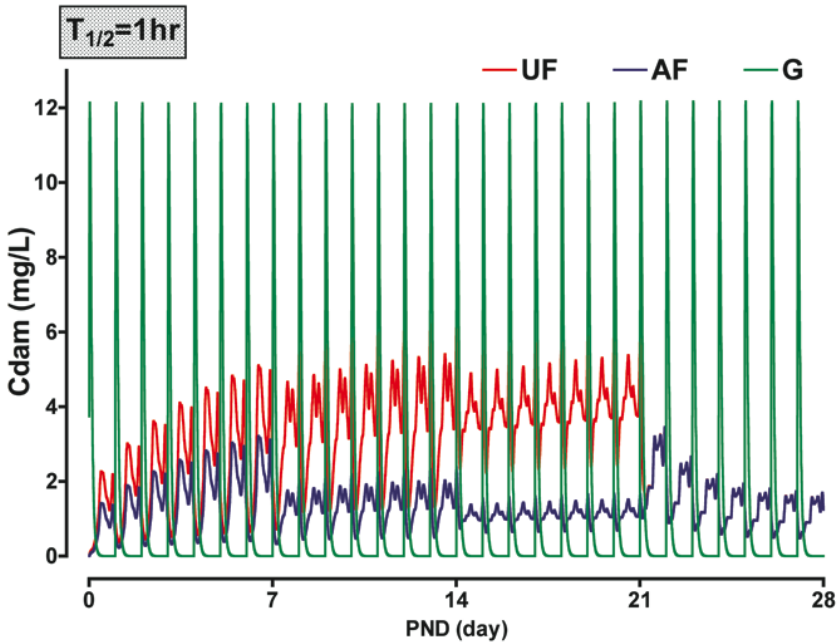
  - constant through out lactation
- Absorption same in the dam and pup
- Base case of theoretical chemical properties

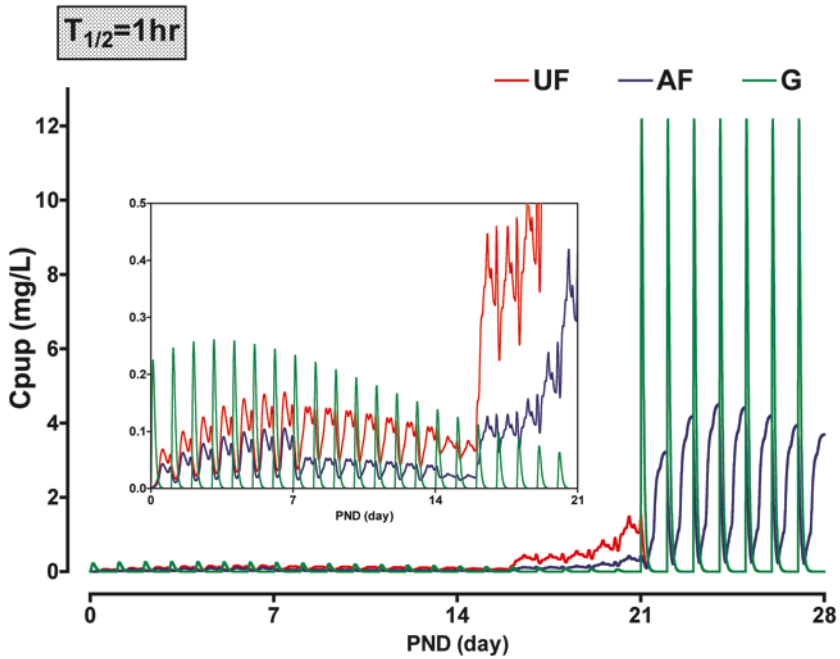
  Vd = 0.7 L/kg, Pm=1, $t_{1/2}$=1hr or 24 hr
- Chemical properties varied from base case one at a time

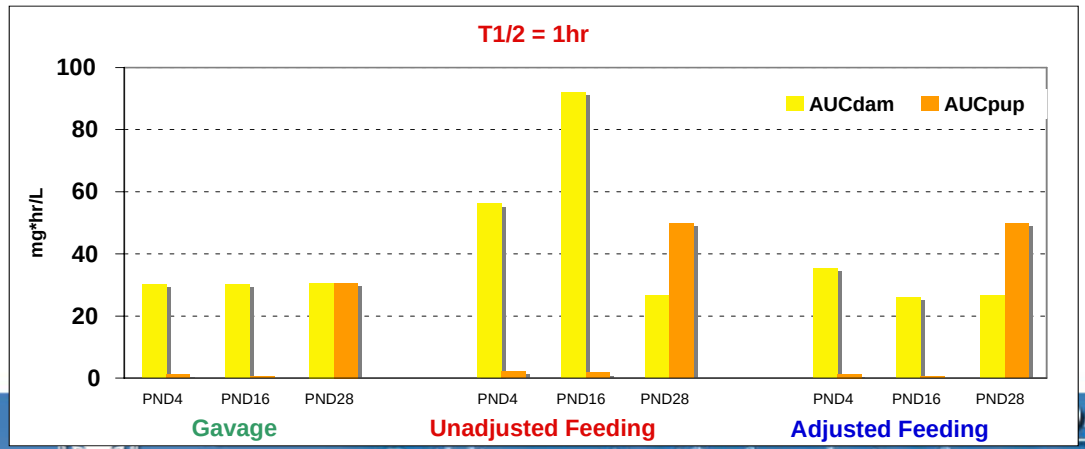
  Pm or Vd
- Half-life

  - same in the dam and pup for base case -> no developmental changes in elimination capacity, already at adult level at birth in base case

Predicted Concentration
for Short Half life Compound



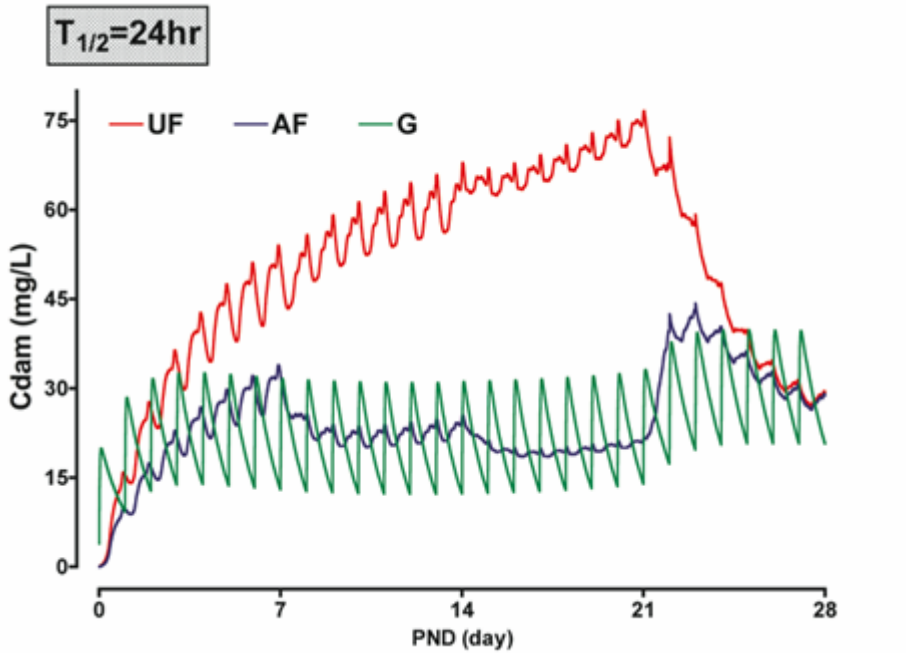


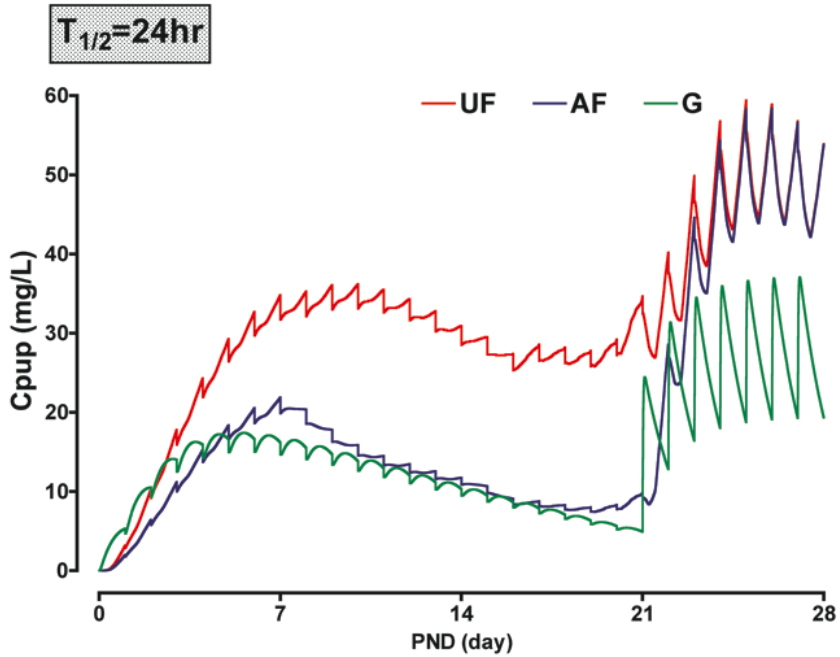


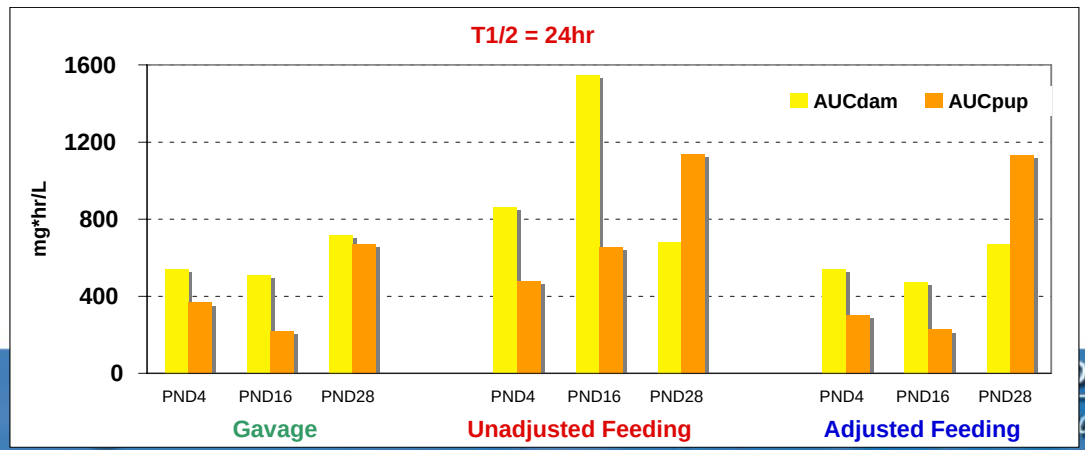
- Gavage, 15mg/kg/day
- Unadjusted Feeding
- Adjusted Feeding

✓ Chemical was mixed in food to produce ~15mg/kg/day based on food consumption during gestation

Predicted Concentration
for Long Half life Compound







- Gavage, 15mg/kg/day
- Unadjusted Feeding
- Adjusted Feeding

✓ Chemical was mixed in food to produce ~15mg/kg/day based on food consumption during gestation

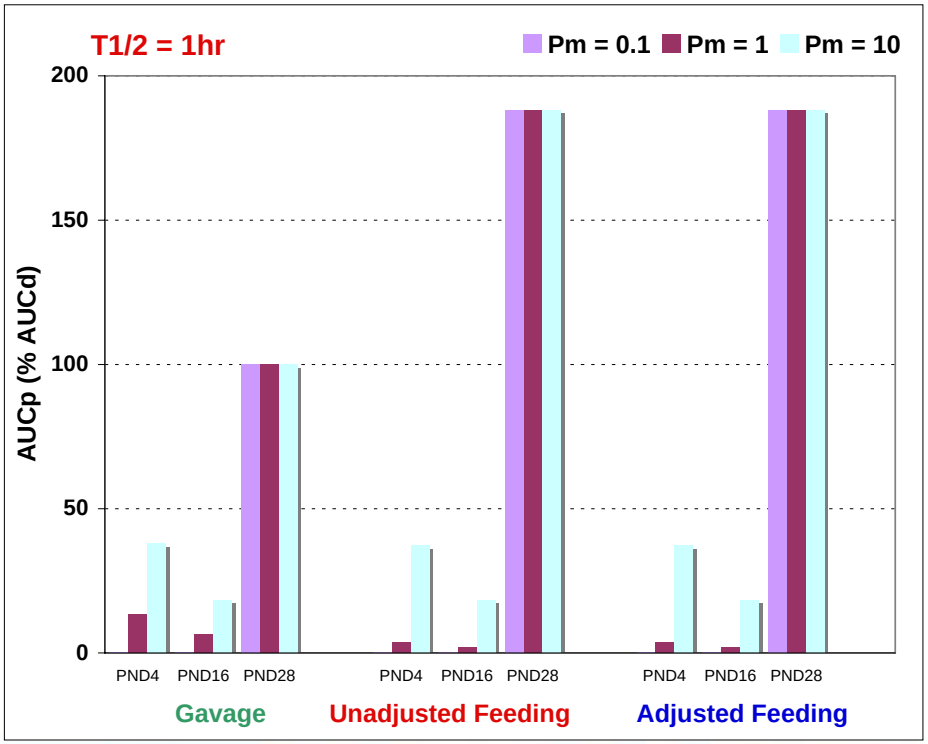
Comparison of AUC values in Dam and Pup
with Varying Milk Partition

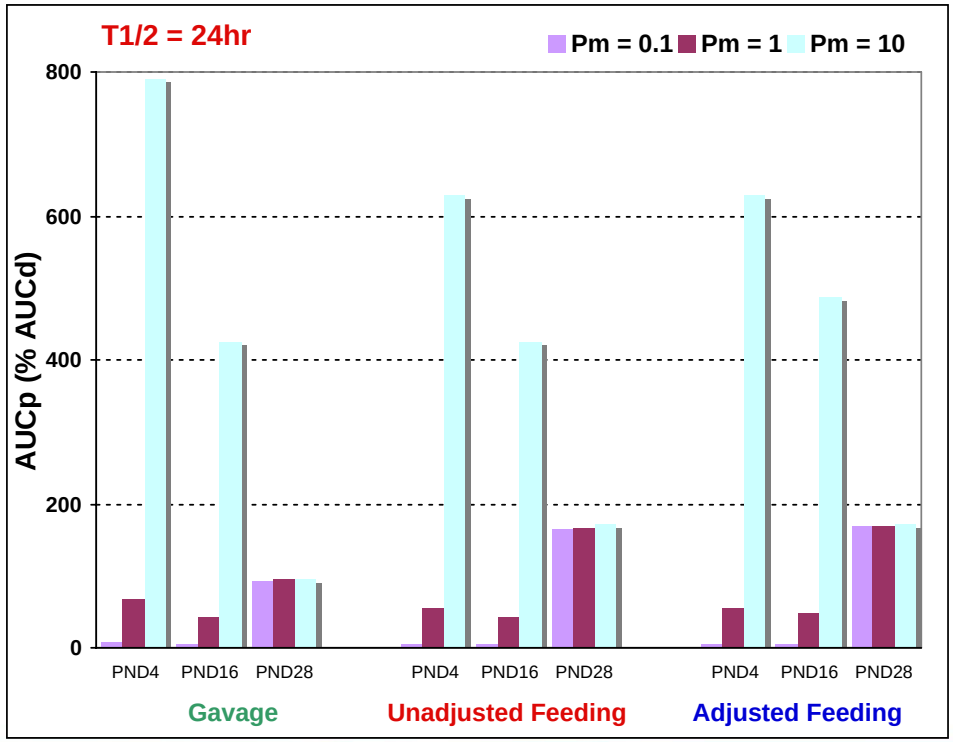
- Chemical transfer level through milk varied from base case

- Pm=0.1, lower than dam's blood (ex. PFOA ≈ 0.1 in rat)

- Pm= 1, equals dam's blood concentration (ex. 2,4-D ≈1 in rat)

- Pm=10, higher than dam's blood (ex. PERC ≈10)





Factors with Limited Impacts on Pup Dosimetry

- Delay in development of elimination capacity
  - Simulated example: renal function development

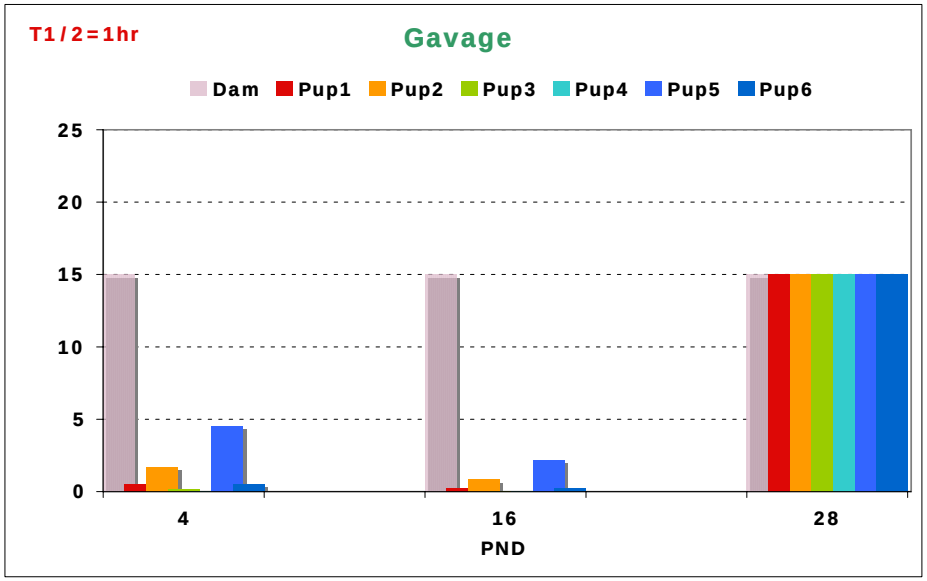
    Assuming rapid maturation during the first week after birth and continue to develop afterwards

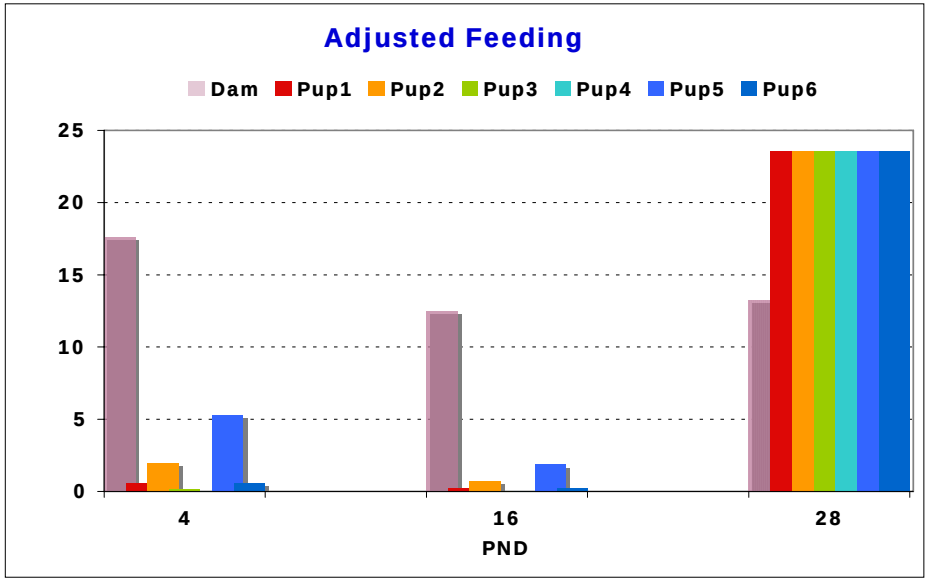
    $Ke_{pup} = R * Ke_{dam}$, $R = 1*PND/(7+PND)$

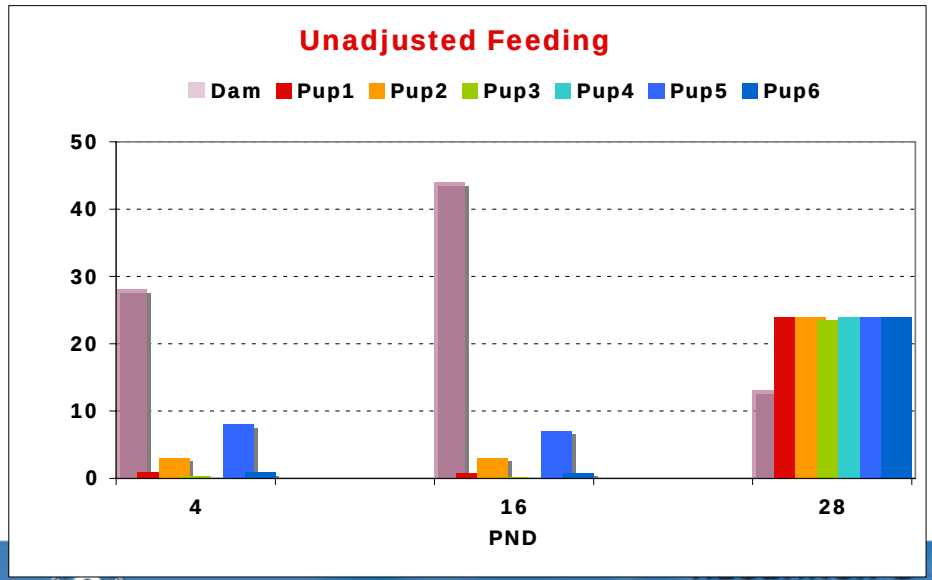
- Excreta recirculation between dam and pups
  - Simulated for two post-natal weeks

Prediction of Daily Dose (mg/kg/day)

for Short Half Life Compound



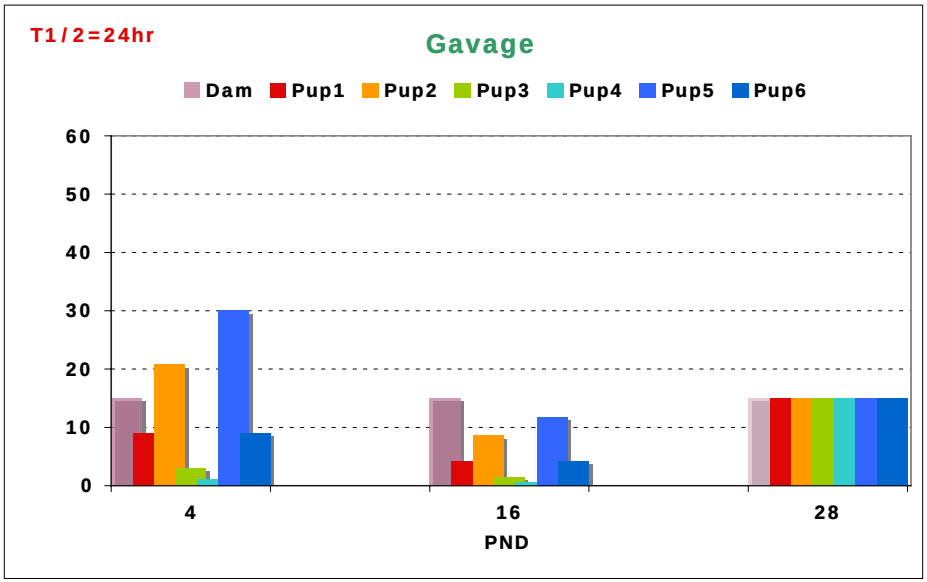


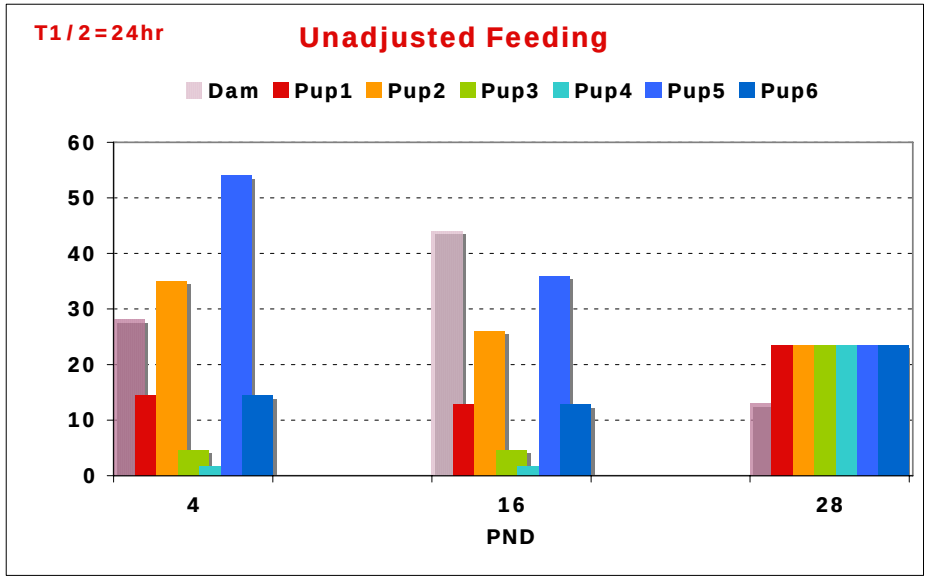


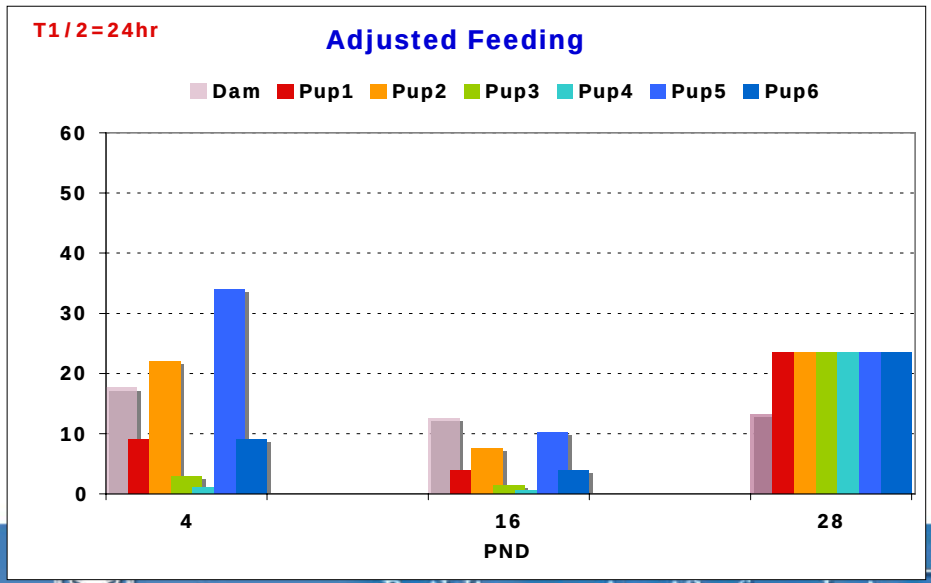
Pup 1	**Base case**	Vd=0.7	Pm=1
Pup 2	**Small Vd**	**Vd = 0.2**	
Pup 3	**Large Vd**	**Vd = 2.5**	
Pup 4	**Low milk transfer**	Vd=0.7	**Pm = 0.1**
Pup 5	**High milk transfer**	Vd=0.7	**Pm = 10**
Pup 6	**Recirculation**	Vd=0.7	Pm=1

Prediction of Daily Dose (mg/kg/day)

for Long Half Life Compound







Pup 1	**Base case**	Vd=0.7	Pm=1
Pup 2	**Small Vd**	**Vd = 0.2**	
Pup 3	**Large Vd**	**Vd = 2.5**	
Pup 4	**Low milk transfer**	Vd=0.7	**Pm = 0.1**
Pup 5	**High milk transfer**	Vd=0.7	**Pm = 10**
Pup 6	**Recirculation**	Vd=0.7	Pm=1

Summary

- For adverse effects following developmental exposures, increasingly need to evaluate dosimetry in tox species and humans for the relevant window of susceptibility
- Absent knowledge of the critical period, evaluate each pharmacokinetically definable period in tox species and humans (characterizes uncertainty)

Summary

- Modeling of VOCs at PND10 predicts higher blood concentrations even though PB is lower (higher QP).
- Modeling of VOCs predicts substantially lower metabolism in PND10 animals.
  - Partially supports that vinyl chloride early life carcinogenesis reflects differences in pharmacodynamics rather than exposure or internal dosimetry

Summary

- Lactational modeling predicts very low exposures in nursing pups for compounds with short half lives (e.g., 1 hr) and larger volumes of distribution (e.g., ≥0.7 fraction of BW)
- Lactational modeling predicts internal exposures in nursing pups approaching or exceeding maternal levels for compounds highly distributed to milk (e.g., PM > 3)
- Post-weaning pup exposures are high due to greater food consumption with dietary dosing.

Summary

- PK comparisons can focus choices of study designs for developmental windows, e.g. cross-fostering study
- Predictive modeling can inform toxicity and pharmacokinetic study designs, interpretation of early-life toxicity studies, and extrapolations for risk assessment.

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