Estimating Human Risk from Exposure to VC

Quantification with PB-PK Modeling

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for
CMA Vinyl Chloride Panel
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Collaborators

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VC History

Low Acute Toxicity

Occup. Expos. Limits - 500 ppm

Viola (1970, 1971)

- Rats, Increased Tumor Incidence

Maltoni (1974)

- Confirmed Viola's Results
- Identified Rare Liver Angiosarcoma
- Dose Response Flat > 1,000 ppm

Creech & Johnson (1974)

- Found Same Cancer Type (Liver Angiosacroma) in Humans

Human Tumor Registry (to Present)

- 14,000 Subjects, 19 VC Plants

Objectives / Opportunity

- Develop A Process for Quantitatively Estimating Risk in Humans
  - + Low, Non-Occupational Exposures
    - Superfund Sites
    - Fugitive Emission
    - Drinking Water
- Test the Utility of our Cancer Risk Assessment Procedures
  - + Rich Animal Data Set in Rats and Mice
  - + Unique Opportunity to Compare Risk Assessment with Actual Results in Humans

Expectations for Pharmacokinetic Modeling

Modeling Cannot Eliminate ALL Uncertainty from Risk Assessments

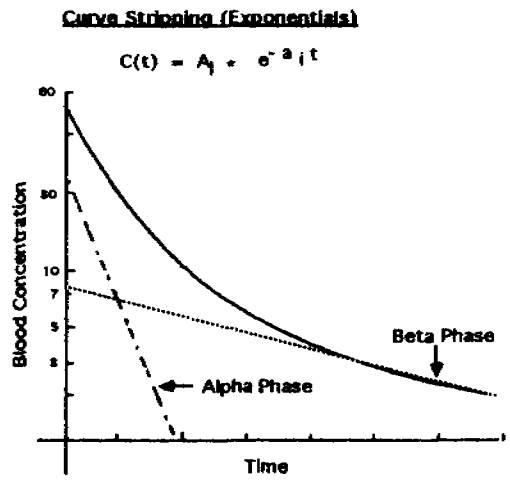
Modeling Can Quantitatively Describe:

- **Metabolic Saturation**
- **Changes in Dose Route**
- **Physiological Differences in Species**

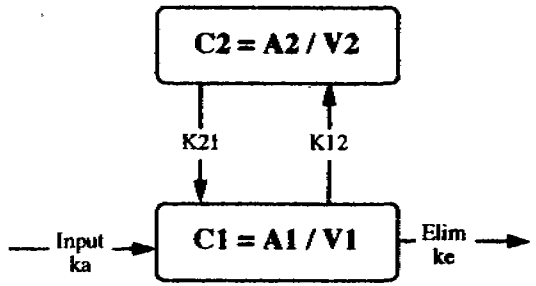
PREMISE:

- **Risk Assessments based on Estimates of "Delivered Dose" will be More Reliable than Risk Assessments based Only on Administered Dose**

Classical Pharmacokinetics: "Stripping the Curve"



Classical Pharmacokinetics: Compartmental Models



Differential Equations:

```
dA0/dt = -ka*Dose
dA1/dt = ka*Dose - K12*C1 + K21*C2 - ke*C1
dA2/dt = +K21*C1 - K21*C2
dElim/ t = -ke*C1
```


Advantages of PB-PK Models:

Compound Specific Information

- Vapor Pressure
- Solubilities (Partitioning) in Tissues

Species Specific Information

- Physiology
- Metabolism

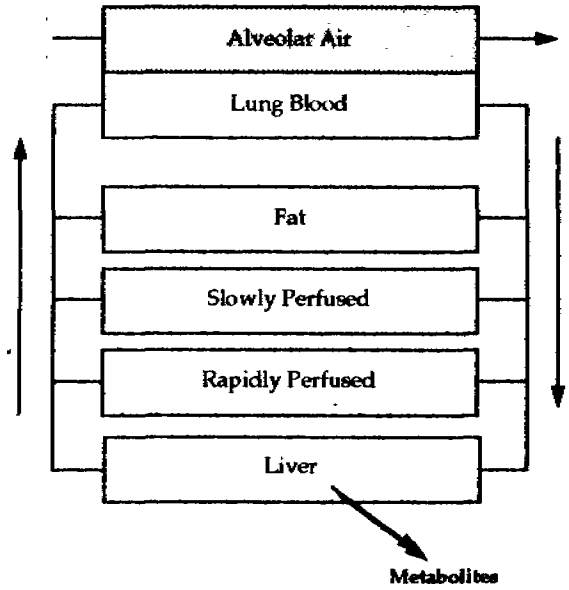
Route Specific Information

- Oral Route, 1st Pass Through Liver

Allow Extrapolations

- Between Dose Routes
- Between High Dose / Low Dose
- Between Species

A PB-PK Model for VC



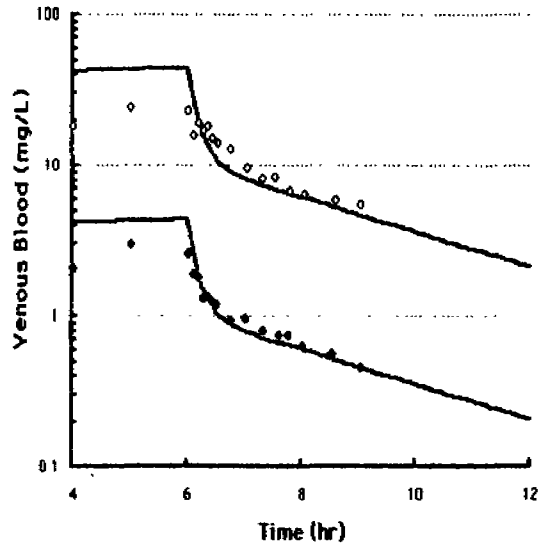
Based on Ramsey & Andersen, 1984.

Capabilities of PB-PK Models

- **Will use examples from studies of Reitz et al., at Dow Chemical Co., with 1,1,1-trichloroethane (Methylchloroform, MC)**
- **Data used to illustrate potential applications for VC PB-PK Model.**

MC Rat Inhalation
(Blood Levels)

Methylchloroform, (MC) used as an example of the technique.



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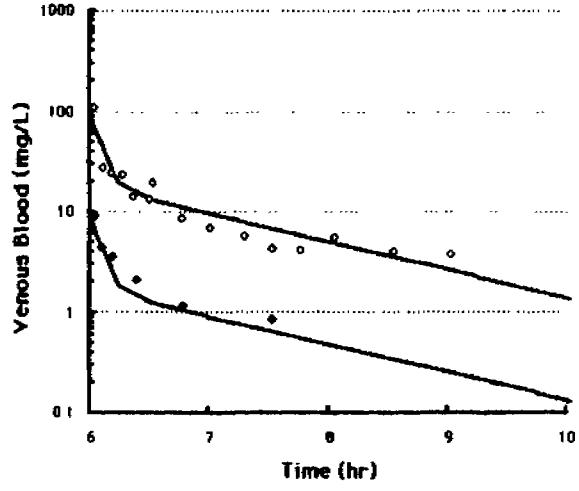
MC Mouse Inhalation
(Blood Levels)



Methylchloroform, (MC) used as an example of the technique.

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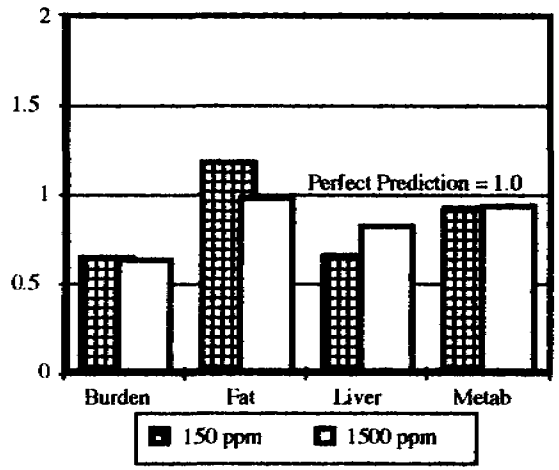
MC Mouse Inhalation
(Other Endpoints)



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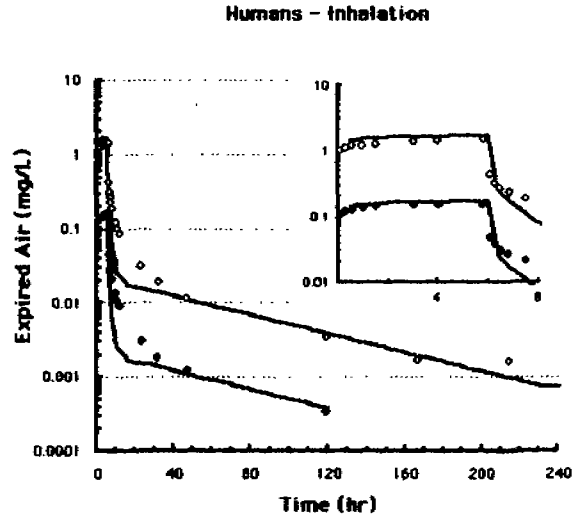
MC Human Inhalation
(Exhaled Air)



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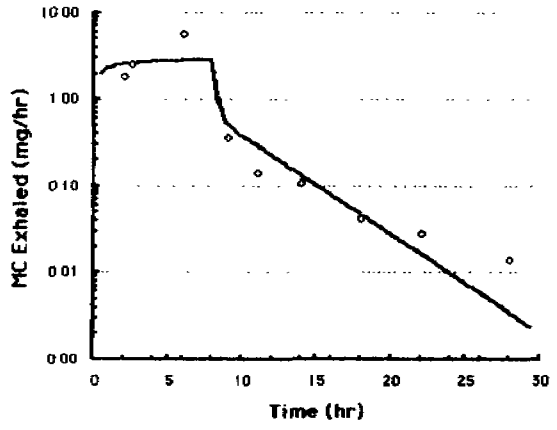
MC Rat Water
(Exhaled Air)



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Approach: VC PBPK Model

(1) Parameterize Model

- **Physiological Constants**
  - Andersen et al., 1987
- **Partition Coefficients**
  - Vial Equilibration
  - Fat, Liver, Muscle, Blood
- **Metabolic Rate Constants**
  - In Vivo (Rats, Mice)

(2) Validate Model

- **Independent Rat, Mouse and Human In Vivo Studies**

(3) Extrapolate Risks

- **Rats to Mice**
- **Rats to Humans**

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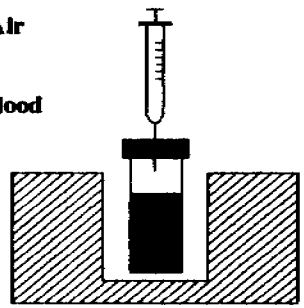
VC Partition Coefficients Vial Equilibration

Measure:

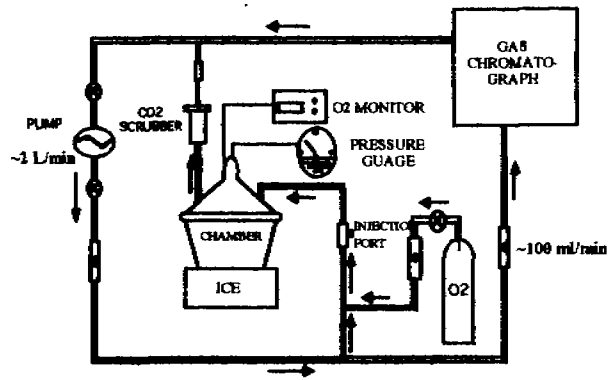
- **Blood/Air**
- **Liver/Air**
- **Fat/Air**
- **Muscle/Air**

Calculate:

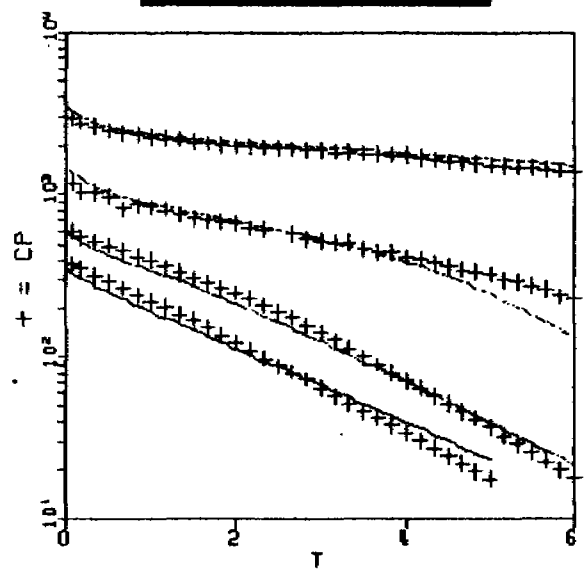
- **Tissue/Blood**



VC Metabolic Rate Constants Gas Uptake Apparatus



Gas Uptake Data
(Male Rats)



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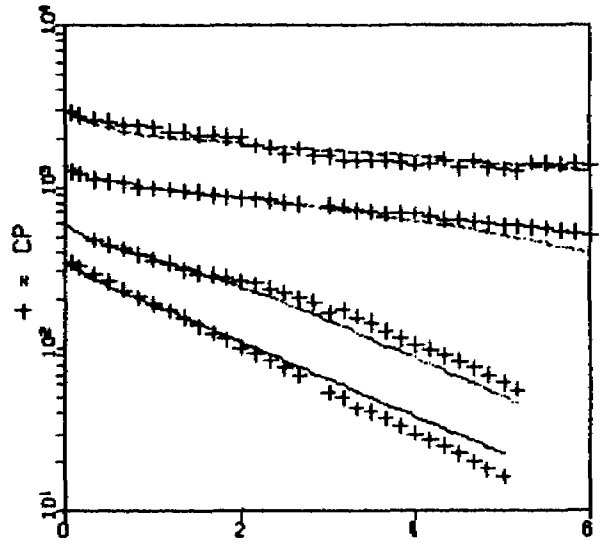
Gas Uptake Data
(Female Rats)



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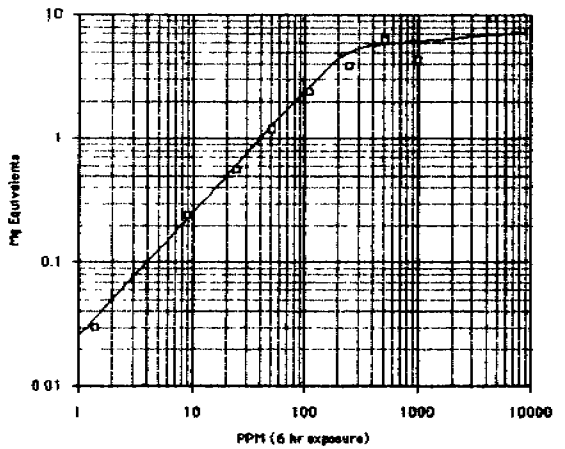
Validation of Rat Model
(Watanabe et al., 1976)



Estimating Mouse Metabolic Rate Constants

Small, Halogenated Hydrocarbons Metabolized by CyP450 2E1

<u>In Vivo</u> VMax's from Experiments

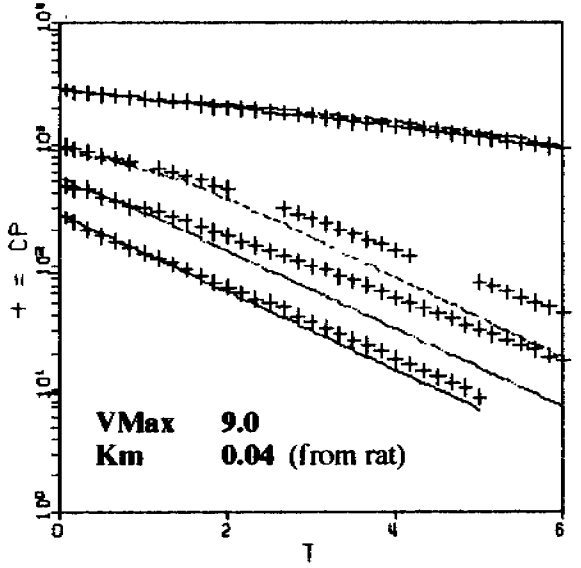
- **Methylene Chloride ($MeCl_2$) (Rats, Mice, Humans)**
- **Chloroform ($CHCl_3$) (Rats, Mice)**

Calculate VMax / gram Liver

Normalize to Rat <u>In Vivo</u>

	Mouse	Human
$MeCl_2$	2.57	0.21
$CHCl_3$	2.71	-
Average	2.64	0.21

Testing Estimated Mouse Metabolic Constants



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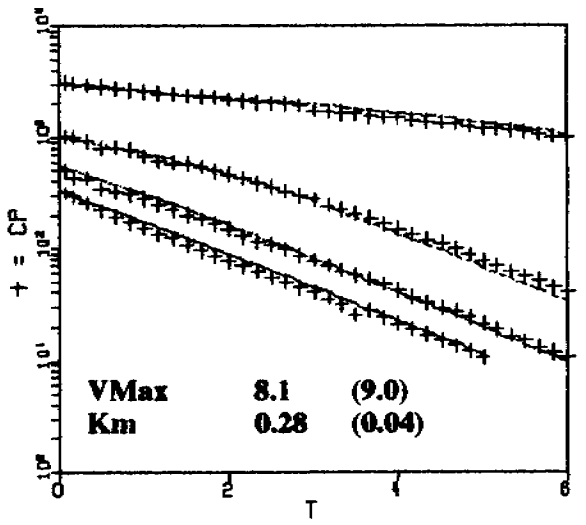
Optimized Mouse Data



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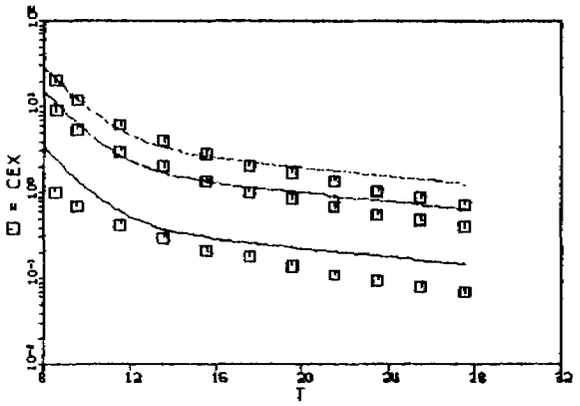
CMA 119759

Validation of Human Model
(Baretta et al., 1969)



Deriving Rat Potency

Based on Maltoni's Experiments

- 12 Months Exposure
- 0, 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2500, 6000, 10000, 30000 ppm tested
- Poor Survival 10000 and 30000; Use Remaining 13 Dose Groups

Use PB-PK Model to Calculate Dose

- Average Amount VC Metabolites per day per Liter of Liver Tissue

Howe & Crump's GLOBAL83 Multistage Model Dose Response (Maximum Likelihood Estimate)

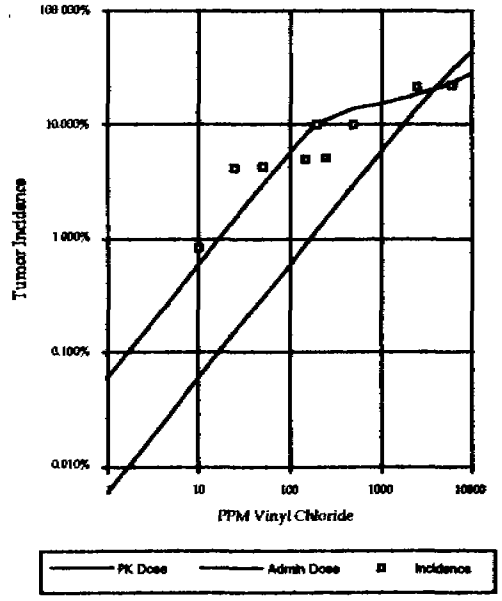
Comparison: Linear Model Fitted to Top Two Doses (MTD, MTD/2)

Predicted Tumor Incidence in Rats

Administered and PB-PK Dose Scales

Risk Specific Dose (10^{-4}) = 1.77×10^{-1}

(mg metabolite/liter/day)



Extrapolating Rat -> Mouse

(Maltoni, Swiss Albino Mice)

Conc	Males	Females	LADD
0	0/80	0/70	0.0
50	1/30	0/30	38.4
250	9/30	9/30	173.1
500	6/30	8/30	265.2
2,500	6/29	10/30	331.0

- Equivalent Amounts of Metabolite produce Equivalent Tumor Yields
- No Surface Area Correction Factor Used.
- The 10^{-4} RSD = 0.80×10^{-1}

Comparing RSD's

Maltoni et al., (Rat)	**0.177**
Maltoni et al., (Mouse)	**0.080**
Lee et al., (Mouse)	**0.120**
Drew et al., (B6 Mouse)	**0.0032**

Diagnostic Criteria?

Drew et al. reported angiosacromas in controls. Lee and Maltoni saw none.

B6C3F1 Ultrasensitive?

Reported to have partial oncogene activation in absence of any chemical treatment.

Extrapolating Rat -> Humans

(Maltoni, Rat Potency)

Equivalent Amounts of Metabolite produce Equivalent Tumor Yields

No Surface Area Correction Factor Used.

Calculated "Unit Risk", Lifetime Exposure to 1$\mu g/m^3$, 24 hr/day.

- PBPK MLE = 4×10^{-7}
- PBPK UCL = 6×10^{-7}
- IRIS Number = 840×10^{-7}

VC Tumor Registry
(Simonato et al., 1991)

- **12,706 Individuals from Population of 14,351**
- **Completeness of Followup = 97.7%**
- **Cohort has > 25 Years since 1st Exposure to VC**
- **Exposure Groupings:**
  - **+ 0 - 2,000 ppm years**
  - **+ 2,000 - 6,000 ppm years**
  - **+ 6,000 - 10,000 ppm years**
  - **+ > 10,000 ppm years**
- **Absolute Risks Estimated to Range from 6.2/100,000 to 280/100,000**

PBPK Risk Assessment Versus Simonato et al (1991)

PPM	PPM Years	PB-PK LADD	PB-PK Prediction per 100,000	Observed Cases per 100,000
Ten Years Exposure				
50	500	3.33	188	—
100	1,000	6.63	374	(6.2)[a]
200	2,000	13.06	736	—
—	4,000	—	—	42.2
500	5,000	26.68	1,497	—
—	8,000	—	—	152.3
1000	10,000	31.28	1,753	—
—	>10,000	—	—	(280.0)[b]
2000	20,008	36.03	2,532	—
Twenty Years Exposur				
50	1,000	6.66	376	(6.2)[a]
100	2,000	13.26	747	—
200	4,000	26.11	1,465	42.2
—	8,000	—	—	152.3
500	10,000	53.35	2,971	
—	15,000	—	—	(280.0)[b]
1000	20,000	62.57	3,476	
2000	40,000	72.07	3,993	

Summary

- Straight-Forward Modification of Existing PBPK Model
- Based on Rat In Vivo Studies, Validated with Mouse and Human Data
- Described Tumor Data 1-6,000 ppm in Rats and Predicted Tumor Data in Mouse Studies
- Unit Risk Based on PBPK Principles 150 Fold Lower than Current IRIS Value.
- Tumor Predictions Most Accurate WITHOUT Surface Area Correction Factor

- **When Mechanism is Known, PBPK Procedures Should Be Capable of Giving Much More Accurate Estimates of Risk.**