



CHEMICAL MANUFACTURERS ASSOCIATION

July 5, 1994

James Cogliano
Chairman, Carcinogen Review Assessment
Verification Endeavor
U.S. EPA (8602)
401 M Street, S.E.
Washington, D.C. 20460

Dear Mr. Cogliano:

It has come to my attention that EPA's Carcinogen Review Assessment Verification Endeavor currently is reassessing human health risk for vinyl chloride. The Chemical Manufacturers Association Vinyl Chloride Panel applauds EPA's efforts to review the latest health effects information to determine risks posed by specific chemicals.

Dr. Richard Reitz, formerly of Dow Chemical, has developed a physiologically-based pharmacokinetic model for vinyl chloride risk assessment. Dr. Reitz recently presented his model to the Vinyl Chloride Panel and has agreed to present his model to EPA prior to its publication, if the Agency provides an opportunity for the presentation. Therefore, the Vinyl Chloride Panel requests a meeting with appropriate EPA and/or contractor staff to discuss the new vinyl chloride risk assessment model. Dr. Reitz's abstract of the model is enclosed with this letter.

Also, the Panel conducted an epidemiologic study of vinyl chloride workers covering a period of time from 1942-1982. The final report on the study was submitted to the EPA Administrator in 1986. A copy of the report is enclosed with this letter just in case the report did not reach CRAVE or CAG personnel. The following articles related to the CMA-sponsored vinyl chloride epidemiology study also are enclosed:

1991 An Industry-Wide Epidemiologic Study of Vinyl Chloride Workers, 1942-1982;

1993 Letter to the Editor, Diagnostic Bias in Occupational Epidemiologic Studies (H. Shah); and,

1993 Response to Letter to the Editor, Diagnostic Bias in Occupational Epidemiologic Studies: An Example Based on the Vinyl Chloride Literature (O. Wong).

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I will call you in the next few weeks to discuss the possibility of meeting to examine scientific issues related to the vinyl chloride risk assessment. Meanwhile, if you have any questions or need additional information, please contact me at (202) 887-1192.

Sincerely,



Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Enclosures

cc: William Farland, Director, Office of Health
and Environmental Assessment, EPA

Hugh McKinnon, M.D., Director, Human Health
Assessment Group, EPA

Estimating Human Risk from Exposure to VC

Quantification with PB-PK Modeling

**Richard H. Reitz
Michael L. Gargas**

McLaren/Hart, ChemRisk Division

**for
CMA Vinyl Chloride Panel
May 19, 1994**

S/20/94

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Collaborators

McLaren/Hart:

**R. H. Reitz
M. L. Gargas**

ICI Toxicology Lab (Zeneca)

**T. L. Green
W. M. Provan**

U. S. E. P. A. (Res Tri Park)

M. E. Andersen

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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 Angiosarcoma) in Humans

Human Tumor Registry (to Present)

- 14,000 Subjects, 19 VC Plants

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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

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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

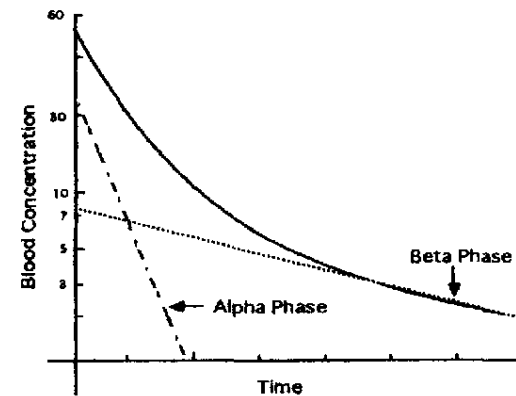
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Classical Pharmacokinetics: "Stripping the Curve"

Curve Stripping (Exponentials)

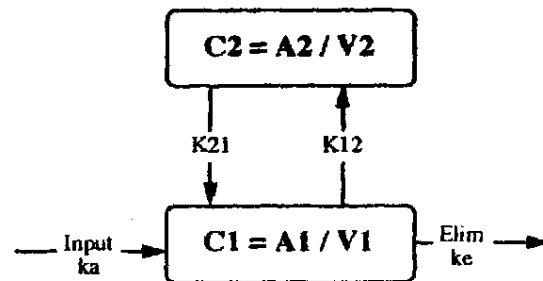
$$C(t) = A_1 + e^{-\alpha t}$$



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Classical Pharmacokinetics: Compartmental Models



Differential Equations:

$$dA_0/dt = -k_a \cdot \text{Dose}$$

$$dA_1/dt = k_a \cdot \text{Dose} - K_{12} \cdot C_1 + K_{21} \cdot C_2 - k_e \cdot C_1$$

$$dA_2/dt = +K_{21} \cdot C_1 - K_{12} \cdot C_2$$

$$d\text{Elim}/dt = -k_e \cdot C_1$$

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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

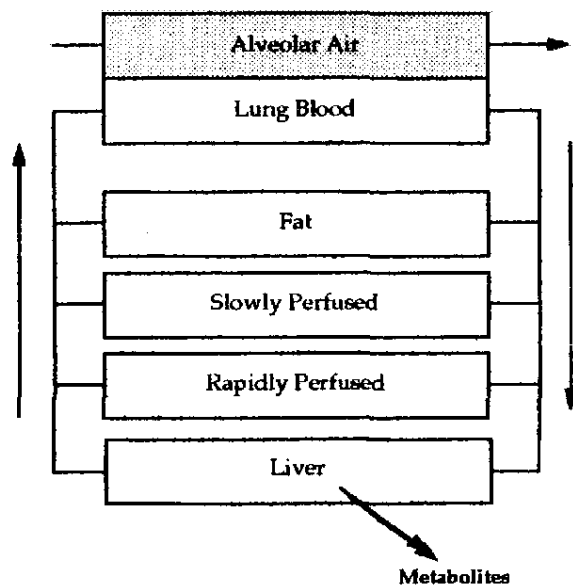
Allow Extrapolations

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

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A PB-PK Model for VC



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Based on Ramsey & Andersen, 1984

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Capabilities of PB-PK Models

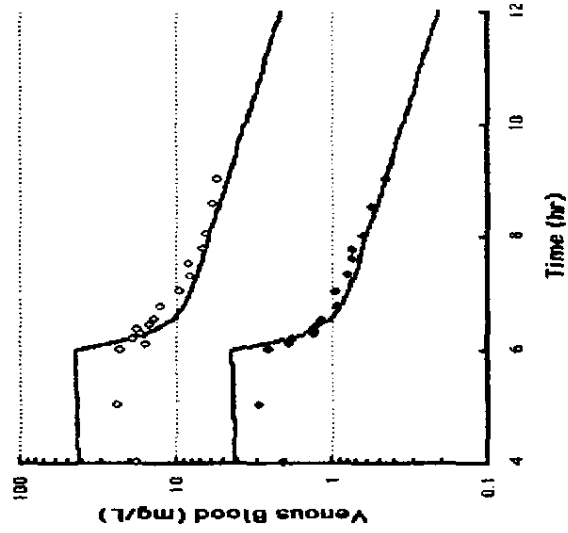
- Will use examples from studies of Reitz et al., at Dow Chemical Co., with 1,1,1-trichloroethane (Methylchloroform, MC)
- Data used to illustrate potential applications for VC PB-PK Model.

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MC Rat Inhalation (Blood Levels)

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

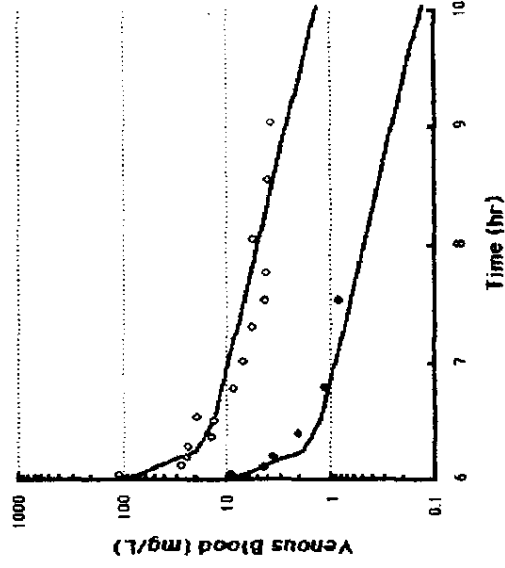


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MC Mouse Inhalation (Blood Levels)

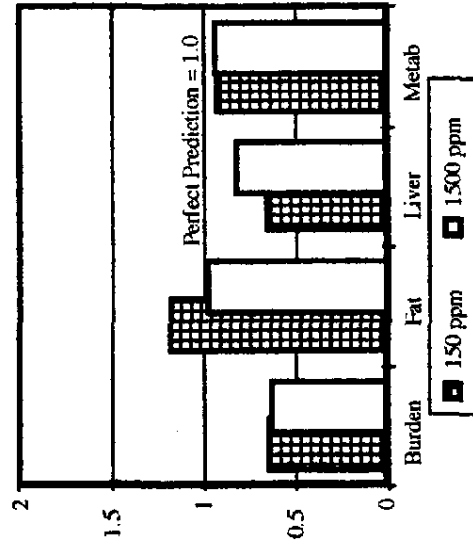
Methylchloroform, (MC) used as an
example of the technique.



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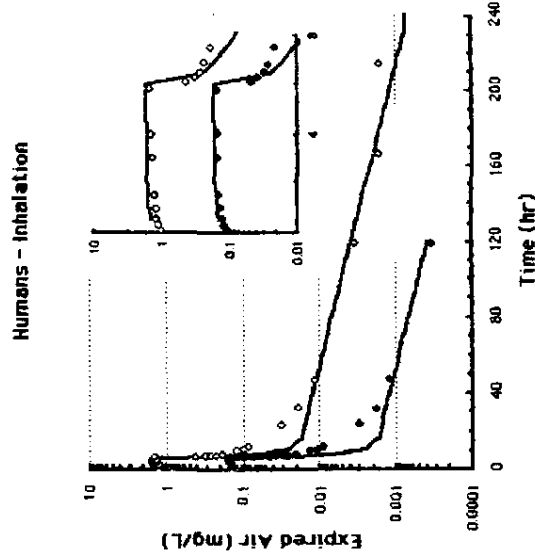
MC Mouse Inhalation (Other Endpoints)



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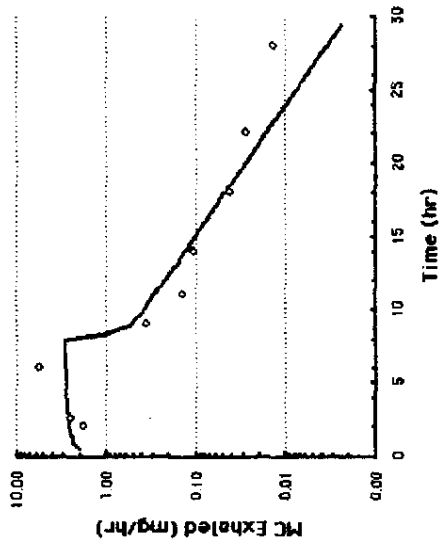
MC Human Inhalation (Exhaled Air)



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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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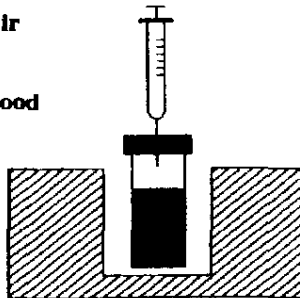
VC Partition Coefficients Vial Equilibration

Measure:

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

Calculate:

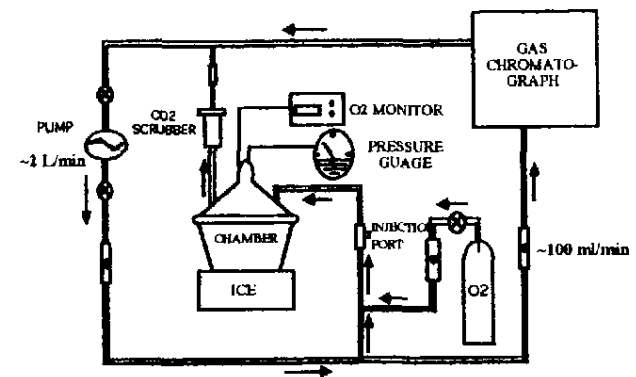
- Tissue/Blood



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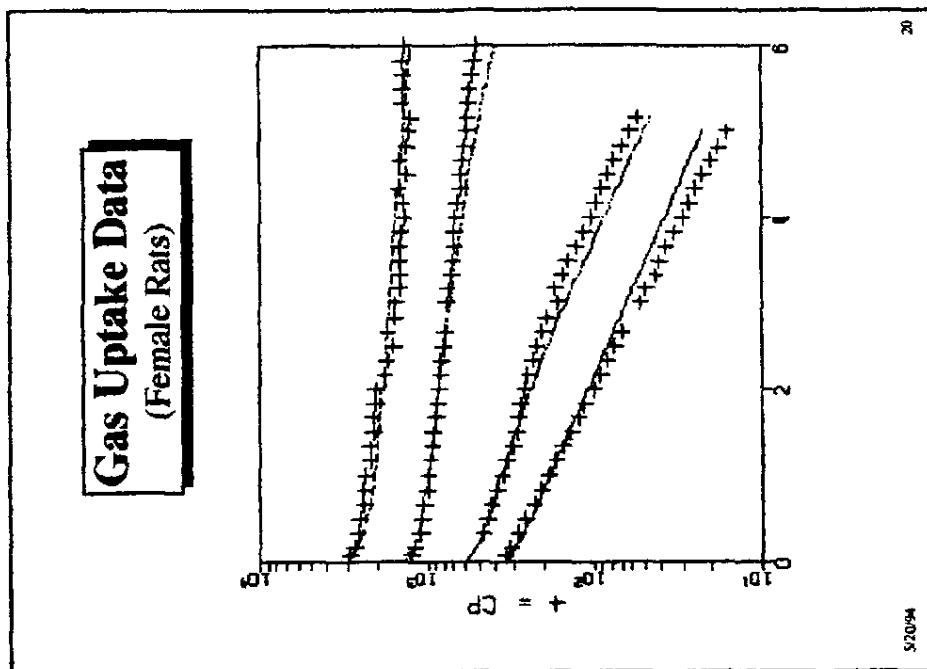
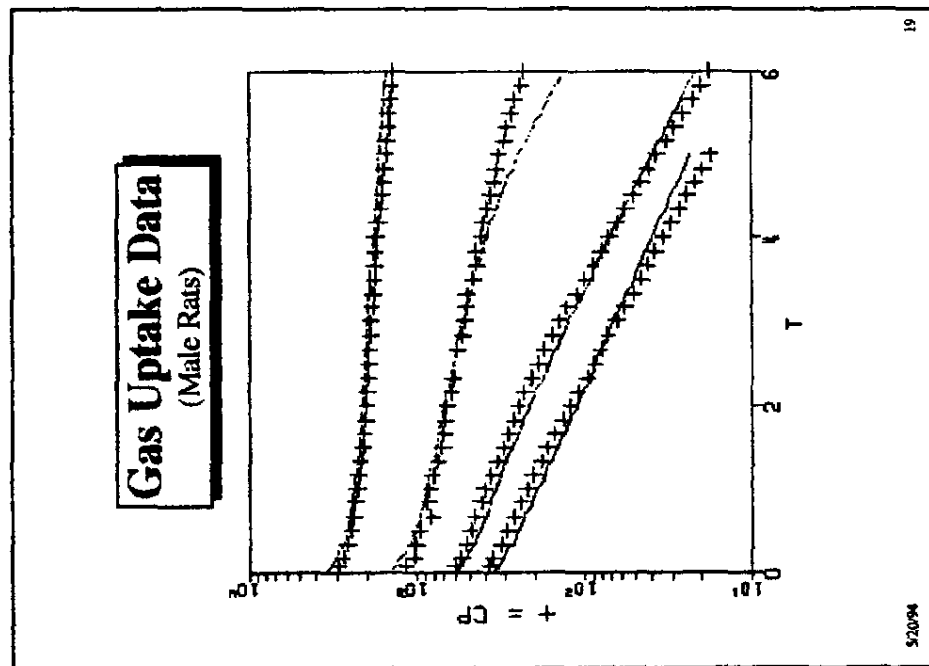
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VC Metabolic Rate Constants Gas Uptake Apparatus



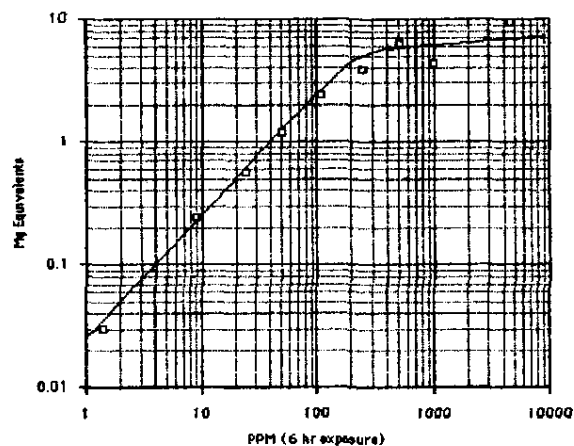
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Validation of Rat Model

(Watanabe et al., 1976)



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Estimating Mouse Metabolic Rate Constants

**Small, Halogenated Hydrocarbons
Metabolized by CyP450 2E1**

In Vivo VMax's from Experiments

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

Calculate VMax / gram Liver

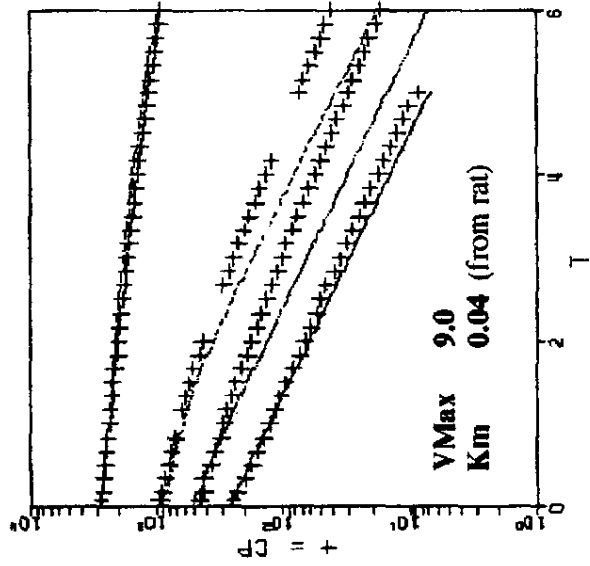
Normalize to Rat In Vivo

	Mouse	Human
MeCl_2	2.57	0.21
CHCl_3	2.71	-
Average	2.64	0.21

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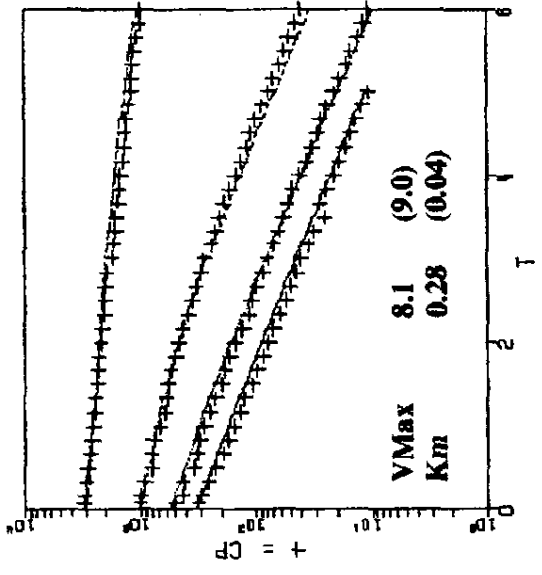
Testing Estimated Mouse Metabolic Constants



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Optimized Mouse Data

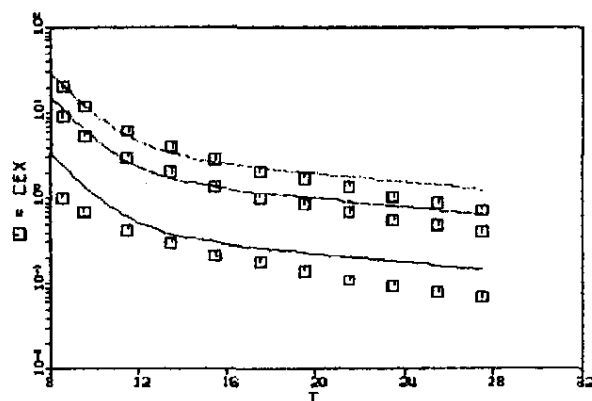


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Validation of Human Model

(Baretta et al., 1969)



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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)

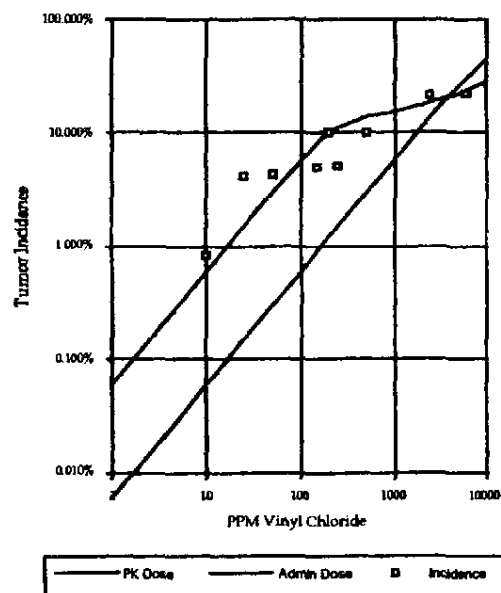
Comparison: Linear Model Fitted to
Top Two Doses (MTD, MTD/2)

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Predicted Tumor Incidence in Rats

Administered and PB-PK Dose Scales
Risk Specific Dose (10^{-4}) = 1.77×10^{-1}
(mg metabolite/liter/day)



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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}

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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 angiosarcomas in controls. Lee and Maltoni saw none.

B6C3F1 Ultrasensitive?

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

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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 $1\mu\text{g}/\text{m}^3$, 24 hr/day.

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

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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

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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	20,000	36.03	2,532	—
Twenty Years Exposure				
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	—

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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.**

