CHEMICAL MANUFACTURERS ASSOCIATION

January 6, 1995

Dear Vinyl Chloride Health Committee Members:

A copy of the cover letter sent to James Cogliano of EPA along with Richard Reitz's draft vinyl chloride risk assessment manuscript is enclosed. Please review this letter and the manuscript prior to the next meeting. We will discuss the manuscript and our course of action with EPA at the meeting on January 30.

I also have enclosed records of meeting or conference call for the following dates: October 6 pre-meeting; October 6 EPA meeting; October 7; October 24; October 31; November 7; November 22; and, December 5.

If you have any questions, please call me at (202) 887-1192. I look forward to seeing you on January 30.

Sincerely,

Has Shah

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

Enclosures

JAN 9 1995

SL 107868

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CHEMICAL MANUFACTURERS ASSOCIATION
Vinyl Chloride Health Committee
Record of Meeting

Date:	October 6, 1994
Time:	10:30 a.m. - 1:30 p.m.
Place:	General A CMA Offices Washington, D.C.

List of Attendees:

James Barter	PPG Industries
Ed Beeler	GEON
Mike Gargas	ChemRisk/McLaren Hart
Mark Gruenwald	Borden
James Knaak	Occidental Chemical
Patrick Logue	Georgia Gulf
David Penney	Vista Chemical
Jonathan Ramlow	Dow Chemical
Dick Reitz	ChemRisk
James Swenberg	University of North Carolina
Has Shah	CMA

1.0 The Committee discussed the risk assessment of vinyl chloride using physiologically-based pharmacokinetic model (PB-PK). The model was developed by Richard Reitz. Dr. Reitz will present this model to EPA scientists at the meeting this afternoon. The model predicts the true risk more accurately because it is based on actual pharmacokinetic data. For vinyl chloride, the unit risk based on the PB-PK principles is 150-fold lower than that predicted by non PB-PK models (Heast Table, May 1993, EPA). The PB-PK model is described in the attachment.

2.0 James Swenberg described his research proposal to determine $T_{\frac{1}{2}}$ of the ethenoguanine DNA adduct in rats using [$^{13}C_2$] vinyl chloride, and quantifying the amount of the methyl purine DNA glycosylase and P450 2 E1 in tissues of humans of different ages. The Committee will consider Dr. Swenberg's proposal in relation to other research projects and decide if funds are available for his proposal.

3.0 The meeting adjourned at approximately 11:45 a.m.

Has Shah

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

Subject to Approval

SL 107869

Estimating Human Risk from Exposure to VC

Quantification with PB-PK Modeling

Richard H. Reitz
Michael L. Gargas

McLaren/Hart, ChemRisk Division

for
Environmental Protection Agency
October 6, 1994

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

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

Advantages of PB-PK Models:

Compound Specific Information

- Vapor Pressure
- Solubilities (Partitioning) in Tissues

Species Specific Information

- Physiology
- Metabolism

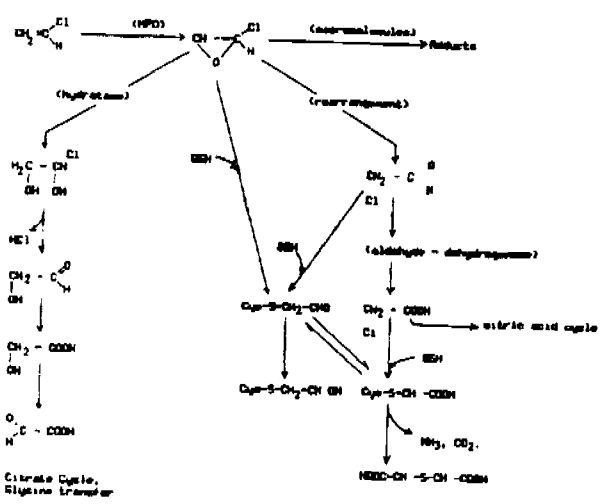
Route Specific Information

- Oral Route, 1st Pass Through Liver

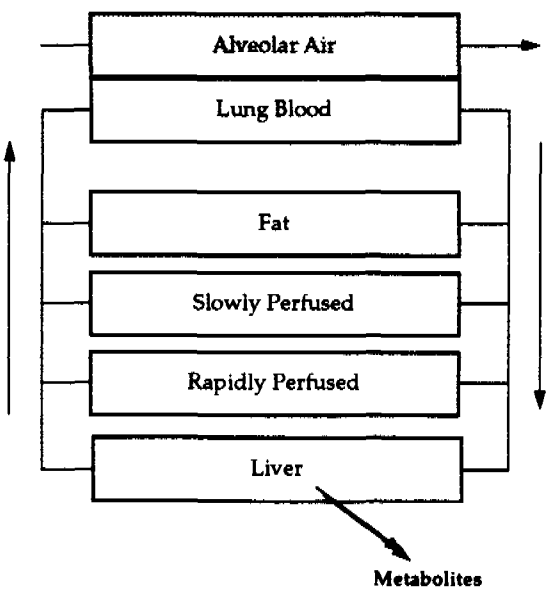
Allow Extrapolations

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

FIGURE 4
Major Pathways in Metabolism of VC
(adapted from L. Fishbein, "Industrial Carcinogens", Elsevier, 1979)



A PB-PK Model for VC



Based on Ramsey & Andersen, 1984.

WPAFB Model for VC

December 1990: Crump Div Clement Inter.

Collaborators:

- **J. Fisher**
- **H. Clewell, III**
- **M. Andersen**
- **M. Gargas**

Also Based on Ramsey/Andersen Model

Two Metabolic Pathways for VC

- **Saturable (MFO)**
- **Low Affinity (Non-Saturable)**

Enhancements (SimuSolv):

- **Sensitivity Analyses, Optimization**
- **Single Metabolic Pathway**
- **New In Vivo Rat Data (Watanabe)**
- **Human In Vivo Studies (Baretta)**
- **EXTRAPOLATION TO HUMANS**

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)

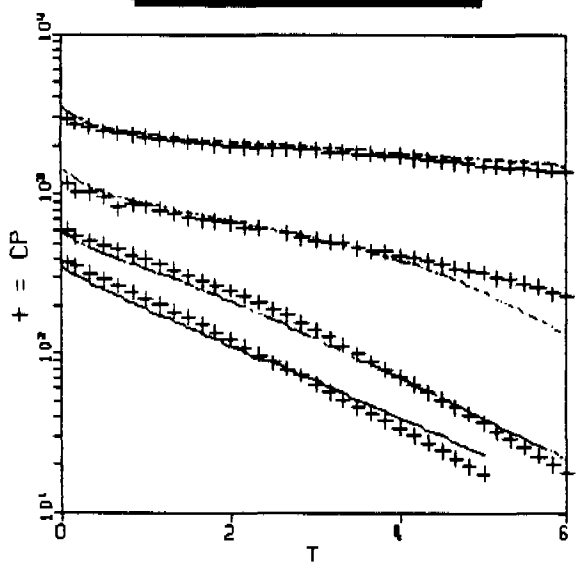
(2) Validate Model

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

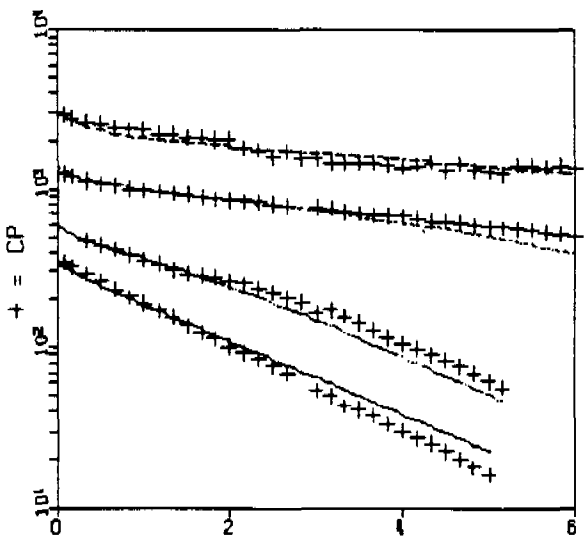
(3) Extrapolate Risks

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

Gas Uptake Data
(Male Rats)



Gas Uptake Data
(Female Rats)



In Vivo Metabolism
(Watanabe)

High Specific Activity ^{14}C-Vinyl Chloride

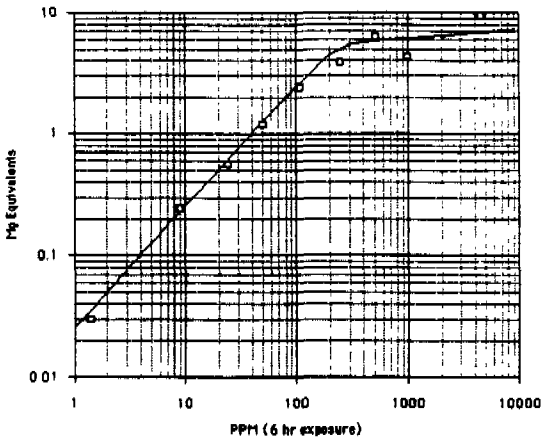
Six Hour Inhalation Exposure

- **Several Different Concentrations**
- **Above and Below Metabolic Saturation**

Radioactivity Quantitates Metabolite Production

- **DIRECT measurement of metabolism (Gas Uptake Indirect Measure)**
- **One or Two Metabolic Pathways**

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

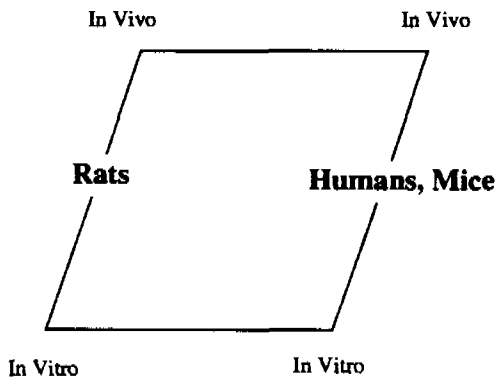
- **Methylene Chloride ($MeCl_2$) (Rats, Mice, Humans)**
- **Chloroform ($CHCl_3$) (Rats, Mice)**

Calculate VMax / gram Liver

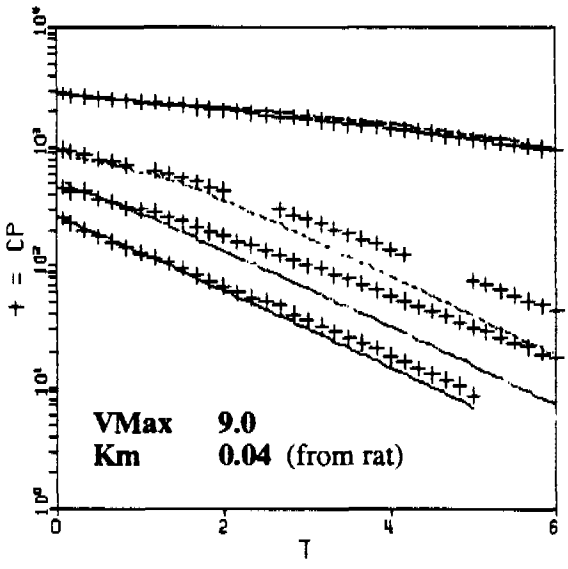
Normalize to Rat <u>In Vivo</u>

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

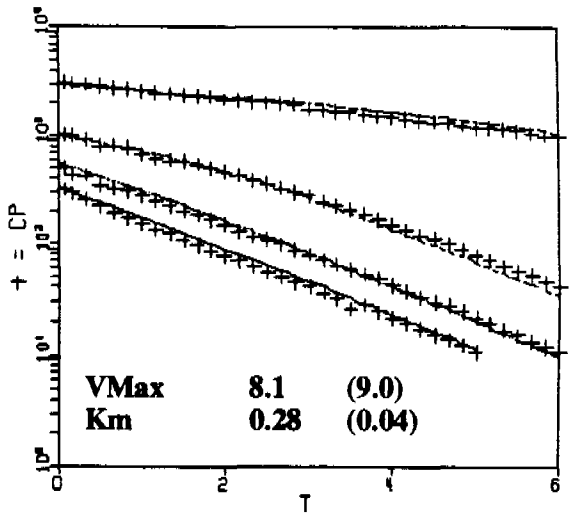
Parallelogram Approach



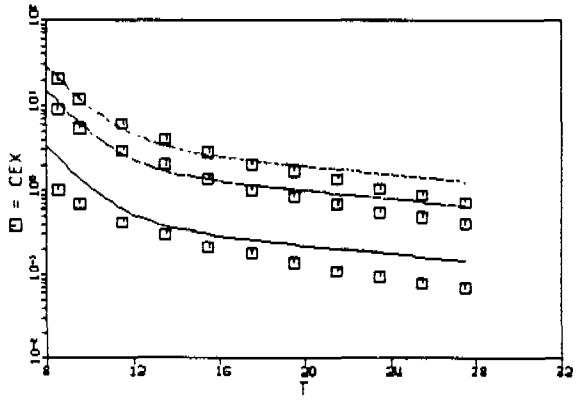
Testing Estimated Mouse Metabolic Constants



Optimized Mouse Data



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

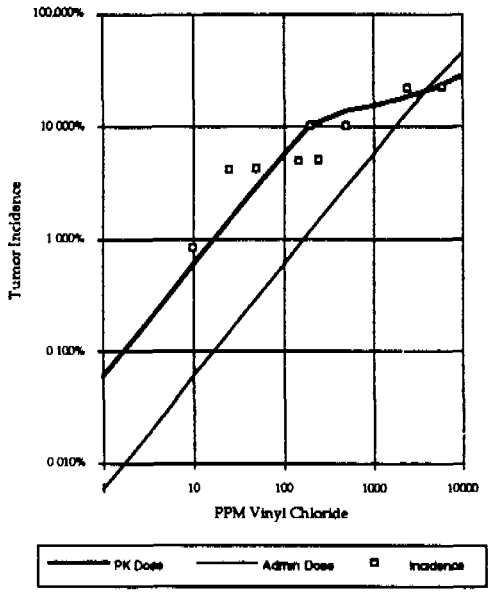
- **Average Amount VC Metabolites per day per Liter of Liver Tissue**

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 1μg/m³, 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	20,000	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 <u>In Vivo</u> 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.**