CHEMICAL MANUFACTURERS ASSOCIATION
Vinyl Chloride Panel
Health Committee
Tentative Agenda

DATE: October 6, 1994
TIME: 10:00 a.m. - 4:30 p.m.
PLACE: General A
CMA Offices
2501 M Street, NW
Washington, D.C.

1.0 Develop Strategy for Meeting with EPA to Discuss Vinyl Chloride Risk Assessment

2.0 Meet with EPA to Discuss Vinyl Chloride Risk Assessment

DATE: October 7, 1994
TIME: 8:30 a.m. - 3:00 p.m.
PLACE: Board A
CMA Offices

1.0 Approval of September 9, 1994 Record of Conference Call

2.0 Discussion of Vinyl Chloride Epidemiology Study Update Proposals from Contractors

- 2.1 Evaluation of Each Proposal
- 2.2 Selection of Contractor(s) for Further Consideration
- 2.3 Identification of Issues Needing Additional Information
- 2.4 Determination of Need for Site Visit

3.0 Discussion of Short-term Vinyl Chloride Exposure Effects Studies with James Swenberg of the University of North Carolina at Chapel Hill

4.0 Discussion of Meeting with EPA on Vinyl Chloride Risk Assessment

5.0 Discussion of Dow Chemical's Literature Review of Vinyl Chloride Teratology and Reproductive Effects Studies

6.0 Discussion of Course of Action with EPA on VC and EDC Testing Programs Under TSCA Section 4

7.0 Distribution of Financial Statement

8.0 Approval of Line Item Budgets for Health Committee Activities

9.0 Set Date for Next Conference Call or Meeting

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

Subject to Approval

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Health Committee

and

EPA

Record of Meeting

Date:	October 6, 1994
Time:	2:00 p.m. - 4:00 p.m.
Place:	U.S. EPA 401 M Street, SW Washington, D.C.

List of Attendees:

James Barter	PPG Industries
David Bayliss	EPA
Ed Beeler	GEON
Chou Chen	EPA
Arthur Chin	EPA
Harvey Clewell (Via CC)	ICF/Kaiser
Jim Cogliano	EPA
Mike Gargas	ChemRisk/McLaren/Hart
Mark Gruenwald	Borden
Charli Hiremath	EPA
Karen Hogan	EPA
Jim Holder	EPA
James Knaak	Occidental Chemical
John Balbus Kornfeld	EPA
Patrick Logue	Georgia Gulf
Elizabeth Margosches	EPA
Hugh McKinnon	EPA
David Penney	Vista Chemical
Bill Pepelko	EPA
Jonathan Ramlow	Dow Chemical
David Reese	EPA
Richard Reitz	ChemRisk
Sheila Rosenthal	EPA
James Swenberg	University of North Carolina
Linda Tuxen	EPA
Larry Valcovic	EPA
Alan Youkeles	EPA
Has Shah	CMA

1.0 Richard Reitz described the physiologically-based pharmacokinetic model for risk assessment of vinyl chloride. EPA representatives indicated interest in receiving the manuscript when the PB-PK model is published in a peer-reviewed journal. Has Shah will send a draft manuscript to James Cogliano when it is received from Dr. Reitz.

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 $T_{½}$ 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

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

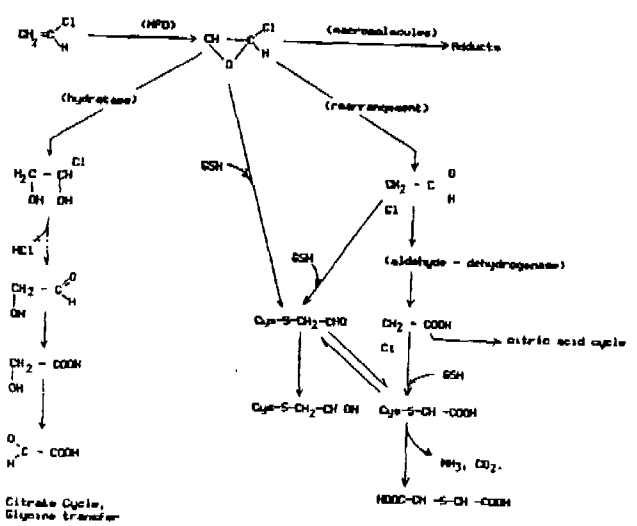
Route Specific Information

- Oral Route, 1st Pass Through Liver

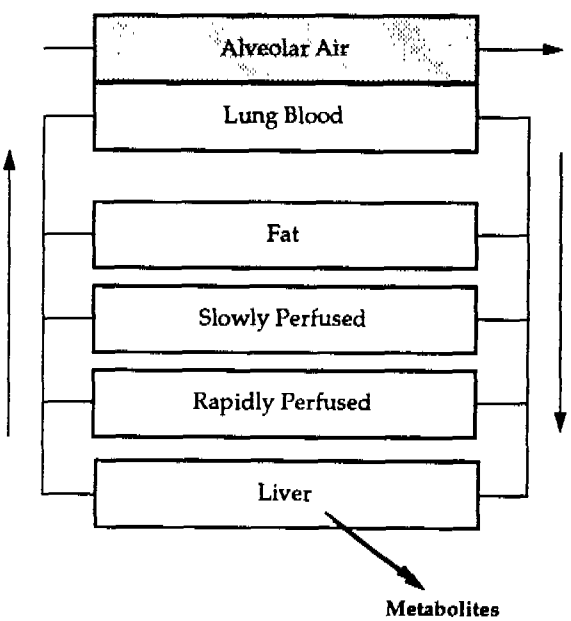
Allow Extrapolations

- 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.

In Vivo Metabolism
(Watanabe)

High Specific Activity ^{14}C-Vinyl Chloride

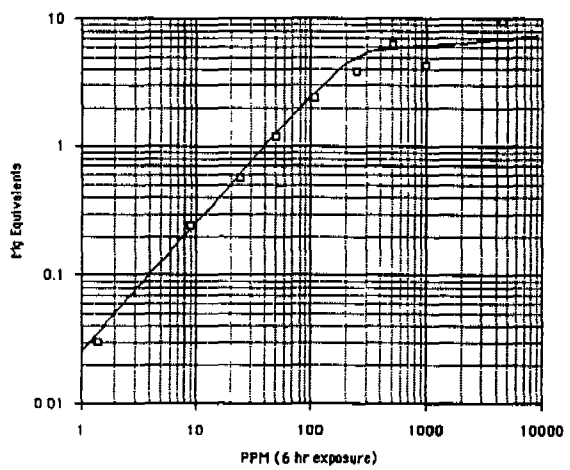
Six Hour Inhalation Exposure

- **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

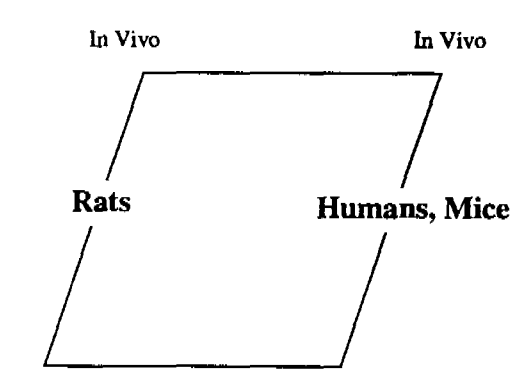
- **Methylene Chloride ($MeCl_2$) (Rats, Mice, Humans)**
- **Chloroform ($CHCl_3$) (Rats, Mice)**

Calculate VMax / gram Liver

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

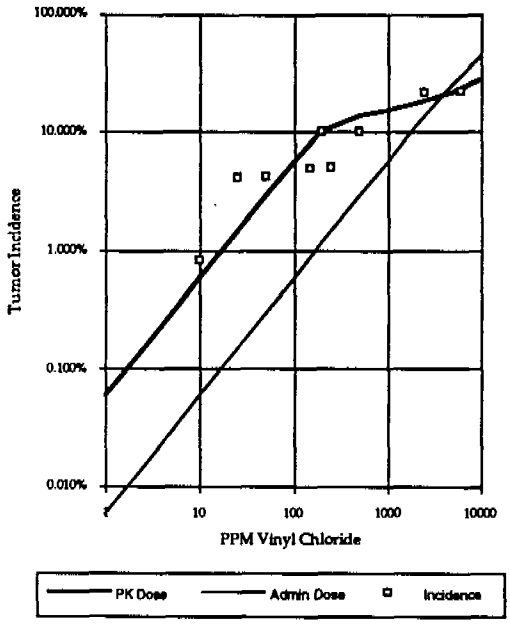
	Mouse	Human
$MeCl_2$	2.57	0.21
$CHCl_3$	2.71	-
Average	2.64	0.21

Parallelogram Approach



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}