CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Health Committee

Record of Meeting

with

Applied Epidemiology Inc.

Date: December 5, 1994
Time: 8:30 a.m.
Place: Lord Jeffrey Inn
Amherst, MA

List of Attendees:

Carol Bigelow	Applied Epidemiology Inc.
Linda Dell	Applied Epidemiology Inc.
Kenneth Mundt	Applied Epidemiology Inc.
Rainer Noess	Applied Epidemiology Inc.
Jonathan Ramlow	Dow Chemical
Has Shah	CMA

1.0 The objective of the meeting was to discuss the September 1, 1994 technical and administrative proposals from Applied Epidemiology Inc., and to receive a demonstration of the ProQuest software program used by AEI for epidemiology study information management.

2.0 Has Shah will identify key people from the Vinyl Chloride Panel member companies to expedite information gathering by the contractor for the epidemiology study update. Kenneth Mundt identified the following industry people who have or are working with him on vinyl chloride issues:

Bob Gilligan	OxyChem
Joe Ledvina	Vista Chemical
Tom Grumbles	Vista Chemical
David Penney	Vista Chemical
Jane Teta	Union Carbide

3.0 Jonathan Ramlow discussed the possibility of industry supporting a nested case control brain cancer study of vinyl chloride workers at the University of Louisville under the supervision of Dr. Carlo Tamburro. If the study is sponsored by the industry, Applied Epidemiology Inc., or any other selected contractor, the contractor may need to work with Dr. Tamburro to cost-

effectively complete both projects. Dr. Shah will send the relevant literature published by Dr. Tamburro to Dr. Mundt.

4.0 The following issues/action items were identified for follow-ups:

- Dr. Shah will discuss with ENSR the process for transferring the vinyl chloride epidemiology data to another contractor.

- Dr. Ramlow will follow-up with the National Death Index to see if the death certificate confidentiality agreements signed by Otto Wong with specific states or the National Death Index can be waived when transferring data from ENSR to another contractor selected by CMA for the update of the epidemiology study. If the response is affirmative, Dr. Ramlow will draft a form letter to obtain confidentiality waivers from the Group C states.

- Dr. Mundt will develop a procedure to be followed by participating companies to establish vital status of the vinyl chloride cohort that was alive as of 1982.

- Dr. Mundt will investigate the availability and cost of storage space for records and raw data from the epidemiology study for a period of ten years following the completion of the study.

5.0 Rainer Noess demonstrated the ProQuest software program for epidemiology study information management.

6.0 The meeting concluded at approximately 1:15 p.m.

Has Shah

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

Subject to Approval

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Health Committee

Record of Conference Call

Date: November 22, 1994

Time: 11:30 a.m.

List of Participants:

James Barter	PPG Industries
Ed Beeler	The GEON Company
Ron Gilbert	Westlake Polymers
Mark Gruenwald	Borden Chemicals and Plastics
Frank Hawk	Borden Chemicals and Plastics
James Knaak	Occidental Chemical
Dan Kracov	Patton Boggs LLP
Patrick Logue	Georgia Gulf Corp.
Caffey Norman	Patton Boggs LLP
David Penney	Vista Chemical
Jonathan Ramlow	Dow Chemical
Has Shah	CMA

1.0 The Committee discussed the ATSDR/EPA request for an Enforceable Consent Agreement research program to fill vinyl chloride data needs identified by EPA in the September 30, 1994 *Federal Register*. Caffey Norman reviewed the ATSDR/EPA policy statement of November 18, 1994, that indicated that any testing proposal under the ATSDR voluntary testing research program or under EPA's Enforceable Consent Agreement must address all testing needs identified in the solicitation notice of September 30, 1994, or EPA intends to proceed with a test rule to meet these needs. For vinyl chloride these include:

- a two-generation reproduction study;
- a teratogenicity study in two species; and,
- a neurotoxicity study.

Any voluntary program that addresses the above data needs must be approved by the ATSDR/EPA in a Memorandum of Understanding. Such an MOU must be executed by the Panel and ATSDR/EPA by May 31, 1995.

The Committee agreed to pursue a voluntary testing program with ATSDR that includes a two-generation reproduction study. For the teratogenicity study, the Committee agreed to discuss with ATSDR the adequacy of existing data to fill its

data needs. For neurotoxicity studies, the Committee agreed to discuss with EPA the rationale for the neurotoxicity data needs.

Mr. Norman will draft a letter to ATSDR/EPA indicating the Committee's intent to enter into negotiations that would lead to a Memorandum of Understanding by May 31, 1995.

2.0 Jonathan Ramlow briefly reviewed his conversation with Carlo Tamburo of the University of Louisville regarding the brain cancer case control study of vinyl chloride workers. Dr. Shah will invite Dr. Tamburo to the next Committee meeting to discuss his proposal.

3.0 Dr. Shah reported that a revised cost proposal from Applied Epidemiology Inc. has been received. The revised cost for the epidemiology study update is approximately $335,000. Drs. Ramlow and Shah plan to meet with key staff from Applied Epidemiology Inc. in the beginning of December to discuss the AEI proposal and to receive a demonstration of its ProQuest software program for epidemiology study information management.

4.0 The conference call was concluded at approximately 12:30 p.m.

Has Shah

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

Subject to Approval

CHEMICAL MANUFACTURERS ASSOCIATION
Vinyl Chloride Health Committee
Record of Conference Call

Date: November 7, 1994
Time: 9:30 a.m.

List of Participants:

Jim Barter	PPG Industries
Frank Hawk	Borden Chemicals and Plastics
Jim Knaak	Occidental Chemical
Caffey Norman	Patton Boggs LLP
Jonathan Ramlow	Dow Chemical
Has Shah	CMA

1.0 The Committee reviewed the November 4 options paper prepared by Caffey Norman for addressing ATSDR/EPA test rule. The Committee agreed to work with ATSDR to address the data needs it initially identified. The Committee agreed with ATSDR's data need for a two-generation reproductive effects study. For the teratogenicity study, the Committee felt that the available data are adequate to meet the ATSDR needs. Jim Barter will prepare a draft position paper on the adequacy of the teratogenicity data to meet the ATSDR data needs. Mr. Norman will check with ATSDR officials to see if they would consider negotiating a voluntary testing program for vinyl chloride with industry.

For the neurotoxicity data needs, Mr. Norman will follow-up with EPA's TSCA and Clean Air offices to clarify the Agency's rationale for the neurotoxicity study.

2.0 Jonathan Ramlow briefly discussed the brain cancer case control study of vinyl chloride workers proposed by Carlo Tamburo of the University of Louisville. Dr. Ramlow concluded that additional information from Dr. Tamburo is necessary to evaluate his proposal. Has Shah will invite Dr. Tamburo to the next Committee meeting to fully discuss his proposal.

Has Shah

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

Subject To Approval

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Health Committee

Record of Conference Call

Date: October 31, 1994

Time: 9:30 a.m.

List of Participants:

Mark Gruenwald	Borden Chemicals and Plastics
Frank Hawk	Borden Chemicals and Plastics
James Knaak	Occidental Chemical
Jonathan Ramlow	Dow Chemical
David Pun	Formosa Plastics
Caffey Norman	Patton Boggs LLP
Has Shah	CMA

1.0 The Committee discussed the ATSDR/EPA research data needs for vinyl chloride. Caffey Norman will prepare an options paper for the Committee's review on the next conference call.

2.0 The next conference call is scheduled for November 7, 1994 at 9:30 a.m., EST.

Has Shah

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

Subject to Approval

CHEMICAL MANUFACTURERS ASSOCIATION
Vinyl Chloride Health Committee
Record of Conference Call

Date: October 24, 1994
Time: 9:30 a.m.

List of Participants:

James Barter	PPG Industries
Ed Beeler	The GEON Company
Ron Gilbert	Westlake Polymers
Mark Gruenwald	Borden Chemicals and Plastics
James Knaak	Occidental Chemical
Joe Ledvina	Vista Chemical
Patrick Logue	Georgia Gulf Corporation
David Pun	Formosa Plastics
Jonathan Ramlow	Dow Chemical
Has Shah	CMA

1.0 Has Shah reviewed his conversation with Bryan Riedel of EPA regarding the ATSDR/EPA research data needs for vinyl chloride. According to Mr. Riedel, the neurotoxicity testing was recommended by the Clean Air Office. Mr. Riedel has expressed a willingness to meet with industry representatives to discuss technical issues before submitting a testing proposal to EPA.

2.0 The Committee agreed to retain a counsel to represent its interests with ATSDR and EPA. The Committee recommended retaining Caffey Norman of Patton Boggs LLP because of his knowledge of similar issues with the Halogenated Solvents Industry Alliance. Dr. Shah will convey the Committee's recommendation to CMA's General Counsel for approval.

3.0 The Committee agreed to award the epidemiology study update contract to Kenneth Mundt of Applied Epidemiology Inc. Jonathan Ramlow will discuss technical issues identified by the Committee with Dr. Mundt and identify areas of cost savings. Dr. Shah then will follow-up with Dr. Mundt to obtain a revised cost proposal from Applied Epidemiology Inc.

4.0 The Committee agreed to the October 12, 1994 budget developed by Dr. Shah, which included $350,000 for the epidemiology study update, $20,000 for data transfer cost from ENSR to Applied Epidemiology Inc., and $30,000 for consultant services of Jonathan Ramlow of Dow Chemical.

5.0 The conference call concluded at approximately 11:30 a.m.

Has Shah

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

Subject to Approval

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Health Committee

Record of Meeting

Date:	October 7, 1994
Time:	8:30 a.m. - 1:00 p.m.
Place:	M Street CMA Offices Washington, D.C.

List of Attendees:

James Barter	PPG Industries
Ed Beeler	GEON
Mark Gruenwald	Borden
James Knaak	Occidental Chemical
Patrick Logue	Georgia Gulf
David Penney	Vista Chemical
David Pun	Formosa Plastics
Jonathan Ramlow	Dow Chemical
Has Shah	CMA

1.0 The Committee approved the September 9, 1994 Record of Conference Call as written.

2.0 The Committee discussed the three proposals that CMA received to update the CMA-sponsored 1942-1982 vinyl chloride epidemiology study. The New York University Medical Center proposal was rejected because of the unacceptable duration (4 years) of the study and the high cost (approximately $1.5 million). The Committee considered the remaining two proposals (Applied Epidemiology, Inc., and Applied Health Sciences) as technically acceptable. Based on overall technical merit of the proposal, the Committee preferred AEI. However, the AEI proposal contained certain tasks (consultants and a third Expert Advisory Panel member) that the Committee did not view as essential to the study. The Committee felt that the project should be completed in 24 months rather than 29 months as proposed by AEI. Jonathan Ramlow will follow-up with Kenneth Mundt of AEI to discuss these tasks and the time-line. A revised administrative proposal will be requested from AEI if AEI agrees with the changes.

Dr. Ramlow and Has Shah will visit AEI to meet with the project staff and receive a demonstration of the ProQuest software program used by AEI for epidemiology study information management.

3.0 Dr. Shah will request an outline of a research proposal from James Swenberg of the University of North Carolina at Chapel Hill.

4.0 The Committee agreed on the need to work with EPA to modify the vinyl chloride unit risk assessment in the Heast Table.

The Committee discussed holding an international workshop on vinyl chloride risk assessment. The targeted audience would include: EPA, OSHA, ATSDR, academia; industry, research organizations, and international organizations involved in scientific reviews. The Committee agreed that a workshop would provide a good forum for scientific exchange, but additional discussion is necessary to determine the timing of a workshop for maximizing the benefits of the workshop.

5.0 Dr. Ramlow briefly discussed the available teratogenicity and reproductive effects data on vinyl chloride and suggested that discussion with ATSDR and EPA is necessary to clearly understand the ATSDR's need for additional data. Dr. Shah will follow-up with EPA to see if a meeting of industry and EPA/ATSDR scientists can be arranged to discuss these data needs.

6.0 The Committee decided that any advocacy for testing of ethylene dichloride under the anticipated Hazardous Air Pollutant Rule will be performed under the umbrella of the Halogenated Solvents Industry Alliance.

7.0 Dr. Shah reported that Carlo Tamburro of the University of Louisville has postulated a threshold for vinyl chloride induced hepatic angiosarcoma based on data available to him. Dr. Ramlow will follow-up with Dr. Tamburro on the type of data available to him for such a hypothesis and recommend to the Committee whether additional work should be supported to validate the hypothesis.

8.0 Dr. Shah distributed the financial statement and proposed a budget for the remainder of 1994 and 1995. The proposed budget with its rationale will be sent to the Committee members for approval by their management.

9.0 The meeting adjourned at approximately 1:00 p.m.

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.

2.0 The Committee members discussed with EPA scientists the vinyl chloride unit risk assessment in the Heast Table 3: Carcinogenicity. The unit risk assessment in the Table appears very high in view of the unit risk calculated based on the PB-PK model. Dr. Shah will follow-up with Dr. Cogliano on the process for modifying the Heast Table, if the Agency agrees to use the PB-PK model for the vinyl chloride unit risk assessment.

3.0 The meeting adjourned at approximately 4:00 p.m.

Has Shah

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

Subject to Approval

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

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

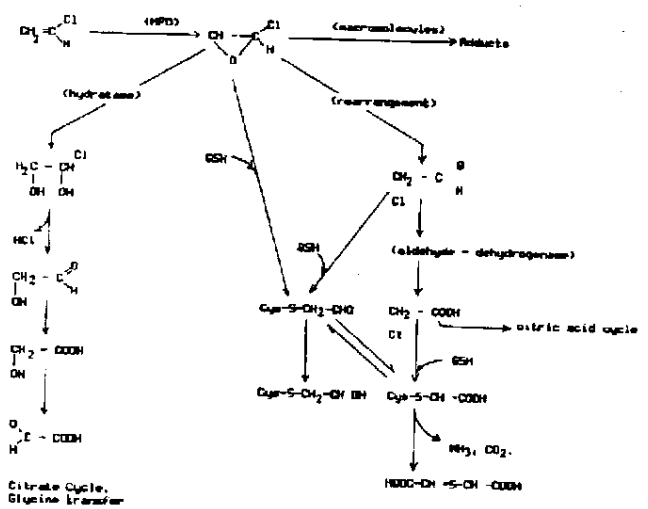
Route Specific Information

- Oral Route, 1st Pass Through Liver

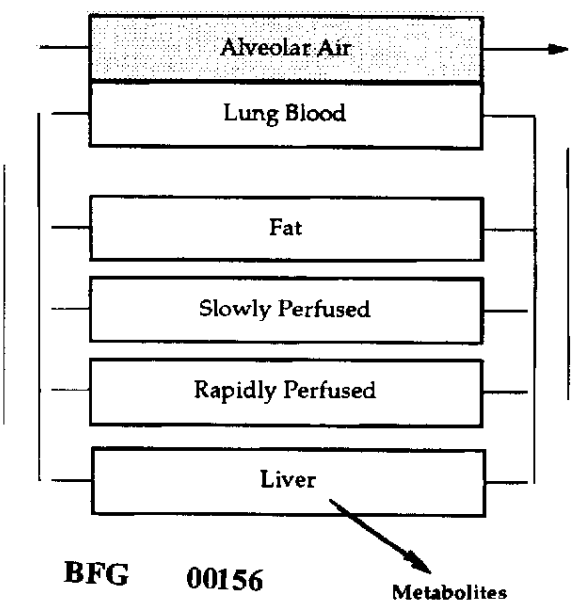
Allow Extrapolations

- 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



BFG 00156

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)

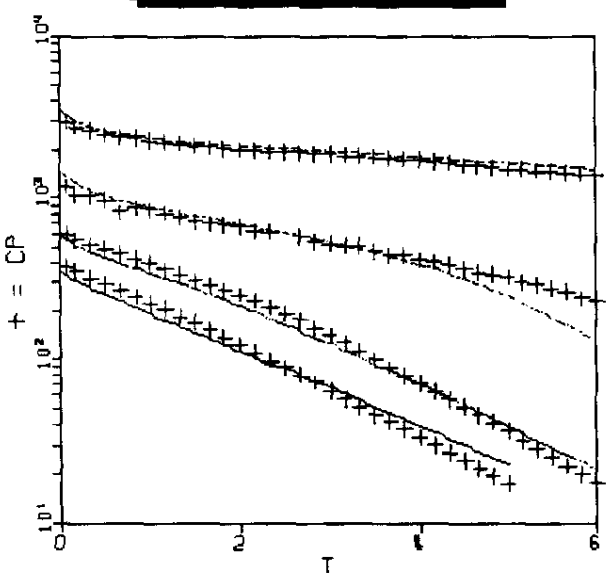
(2) Validate Model

- **Independent Rat, Mouse and Human <u>In Vivo</u> Studies**

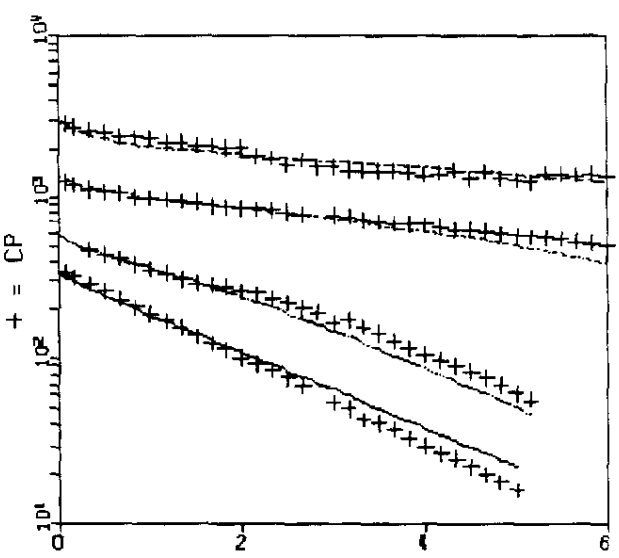
(3) Extrapolate Risks

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

Gas Uptake Data
(Male Rats)



Gas Uptake Data
(Female Rats)



BFG 00157

In Vivo Metabolism
(Watanabe)

High Specific Activity ^{14}C-Vinyl Chloride

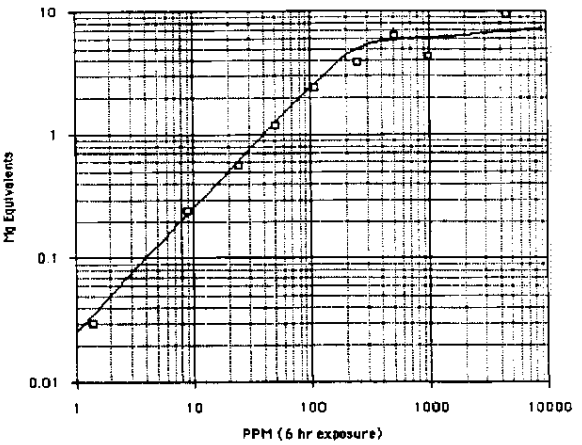
Six Hour Inhalation Exposure

- **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

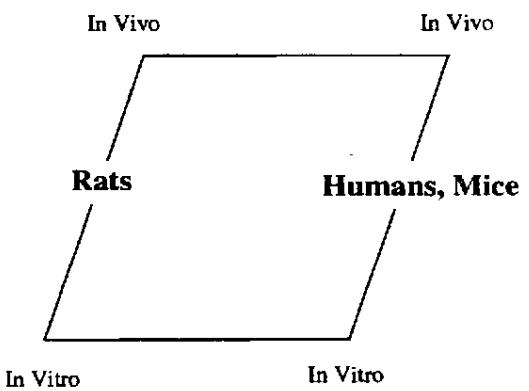
- **Methylene Chloride ($MeCl_2$) (Rats, Mice, Humans)**
- **Chloroform ($CHCl_3$) (Rats, Mice)**

Calculate VMax / gram Liver

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

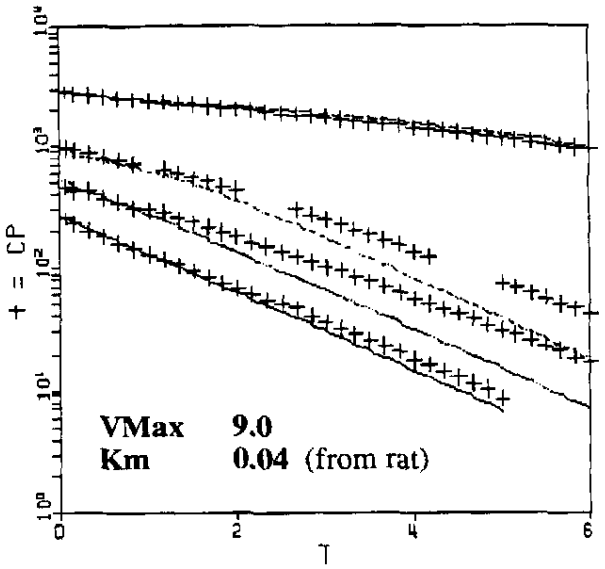
	Mouse	Human
$MeCl_2$	2.57	0.21
$CHCl_3$	2.71	-
Average	2.64	0.21

Parallelogram Approach

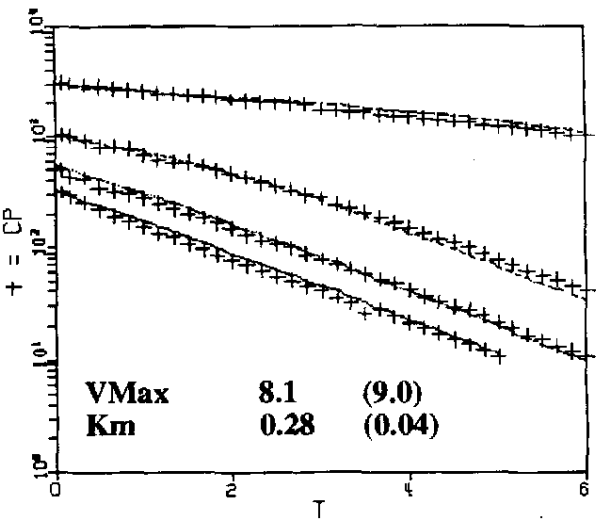


BFG 00158

Testing Estimated Mouse Metabolic Constants

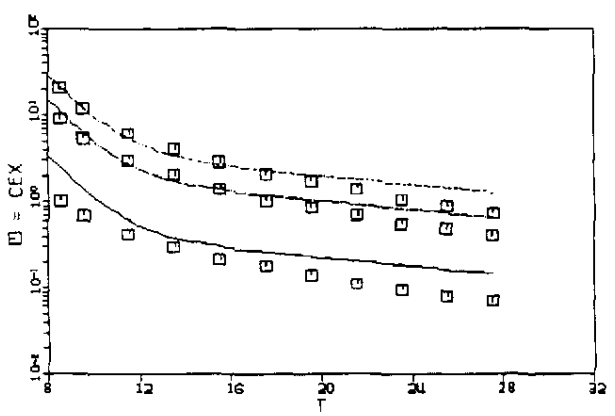


Optimized Mouse Data



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**

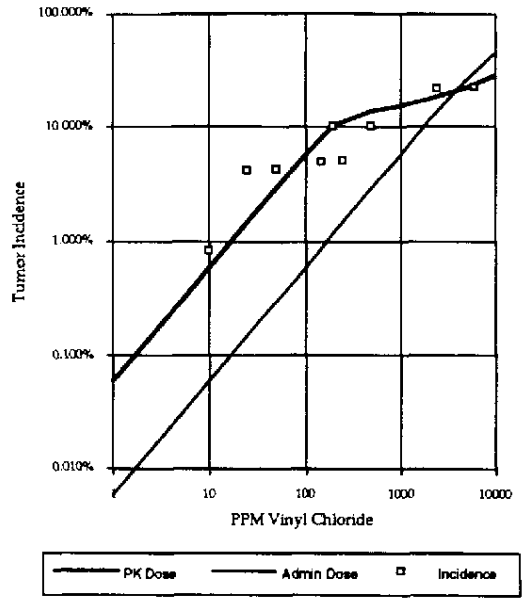
Howe & Crump's GLOBAL83 Multistage Model Dose Response (Maximum Likelihood Estimate)

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

BFG 00159

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}

BFG 00160

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 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.**