



CHEMICAL MANUFACTURERS ASSOCIATION

June 6, 1994

Dear Vinyl Chloride Research Coordinators:

The following items are enclosed:

- 1) agenda for the June 13, 1994 conference call;
- 2) the May 19, 1994 Record of Meeting;
- 3) Dr. Richard Reitz's vinyl chloride risk assessment presentation;
- 4) historical perspective on the inter-industry vinyl chloride study;
- 5) benefits of updating the inter-industry study of vinyl chloride workers; and,
- 6) revised scope of work for the update of the 1986 epidemiology study.

Item numbers 3 and 4 were sent to you earlier; however, they are enclosed again for reference in your discussions with your management. When deciding whether to commit your company to update the vinyl chloride epidemiology study, please use \$300,000 as the estimated budget. This budget includes: epidemiology study cost; Dow Chemical's cost for designing and monitoring the study; data transfer cost from ENSR to another contractor if necessary; other consultant costs; contingency; and, CMA administration. The CMA administrative services will address: the epidemiology update; short-term exposure effects study; EPA's anticipated TSCA Section 4 testing; other ATSDR activities; EPA's risk assessment activities; and, response to the American Chemical Society on the TIME Magazine article.

Your company's pro-rata share will be based on your 1993 nameplate capacity for vinyl chloride. One-half of the actual commitment must be received by CMA prior to the execution of a contract and the other half would be due six months after the contract execution date. We will review the company responses to update the vinyl chloride epidemiology study on our June 13 conference call.

Prior to the conference call, Dr. Jonathan Ramlow should send me the estimated cost to provide designing and monitoring services for the update of the epidemiology study.

All other company representatives should call me with their decisions relating to participation in the update prior to the June 13 conference call.

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VCRC
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David Penney should send me a draft response to the American Chemical Society on the TIME Magazine article.

If you have any questions, please call me at (202) 887-1192. I am looking forward to talking to you on June 13.

Sincerely,



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

Enclosures

SL 107249

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Panel

Vinyl Chloride Research Coordinators

Tentative Agenda

DATE: June 13, 1994

TIME: 10:00 a.m., EDT

- 1.0 Approval of May 19, 1994 Record of Meeting
- 2.0 Review of Company Decisions to Update the Epidemiology Study
- 3.0 Review of the Revised Scope of Work to Update the Vinyl Chloride Epidemiology Study
- 4.0 Discussion of Dow's Cost Estimate to Design and Monitor the Update of the Epidemiology Study
- 5.0 Status Report on Short-term Exposure Effects Study
- 6.0 Status Report on EPA's Risk Assessment of Vinyl Chloride
- 7.0 Status Report on Dow Chemical's Review of Vinyl Chloride Teratology and Reproductive Effects Studies
- 8.0 Status Report on Response to TIME Magazine's Article on Vinyl Chloride Exposure and Development of Lymphoma
- 9.0 Set Date for Next Conference Call or Meeting

Has Shah

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

Subject to Approval

ANTITRUST CHECKLIST FOR CMA MEETINGS

This antitrust checklist is for use by CMA staff and member representatives in the conduct of CMA-sponsored meetings. Prohibited discussion topics apply equally to social gatherings incidental to CMA-sponsored meetings. The Checklist is not exhaustive and does not address antitrust issues relating to activities other than CMA meetings. Participants in CMA meetings also should be thoroughly familiar with: (1) "Antitrust Guide for CMA Committee Members;" and, (2) "General Principles Applicable to the Structure and Operations of Committees." Both of these documents may be found in the CMA Directory.

DO

Ensure strict performance in areas of:

OVERSIGHT/SUPERVISION:

- Have a CMA staff representative at each CMA-sponsored meeting (unless an exception has been authorized by the appropriate CMA vice-president);
- consult with an attorney of the CMA Office of General Counsel on all antitrust questions relating to CMA-sponsored meetings;
- limit meeting discussions to agenda topics (unless additional topics have been approved by the appropriate CMA staff representative), and
- provide each member company representative and CMA staff representative attending a CMA-sponsored meeting with a copy of this checklist, and have a copy available for reference at all CMA-sponsored meetings.

RECORDKEEPING:

- Have an agenda and minutes which accurately reflect the matters which occur;
- provide agendas and minutes to the CMA Office of General Counsel for review and approval in advance of distribution; and,
- fully describe the purposes and authorities of all task groups, work groups, ad hoc or other standing committee subgroups in the minutes of the appropriate parent committee.

VIGILANCE:

- Protest against any discussion or meeting activities which appear to violate this checklist; disassociate yourself from any such discussion or activities and leave any meeting in which they continue.

DON'T

Do not, in fact or appearance, discuss or exchange information on:

PRICES, INCLUDING:

- Individual company prices, price changes, price differentials, markups, discounts, allowances, credit terms, etc.;
- Individual company data on costs, production, capacity, inventories, sales, etc.; and,
- Industry pricing policies, price levels, price changes, differentials, etc.

PRODUCTION, INCLUDING:

- Plans of individual companies concerning the design, production, distribution or marketing of particular products, including proposed territories or customers; and,
- changes in industry production, capacity or inventories.

TRANSPORTATION RATES:

- Rates or rate policies for individual shipments, including basing point systems, zone prices, freight equalization, etc.

MARKET PROCEDURES, INCLUDING:

- Company bids on contracts for particular products; company procedures for responding to bid invitations; and,
- matters relating to actual or potential individual suppliers or customers that might have the effect of excluding them from any market or influencing the business conduct of firms toward them.

CONSENT DECREE SUBSTANCE:

- Any matter relating to trisodium phosphate (a restriction required by a 1962 consent decree to which CMA is a party).

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**

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 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

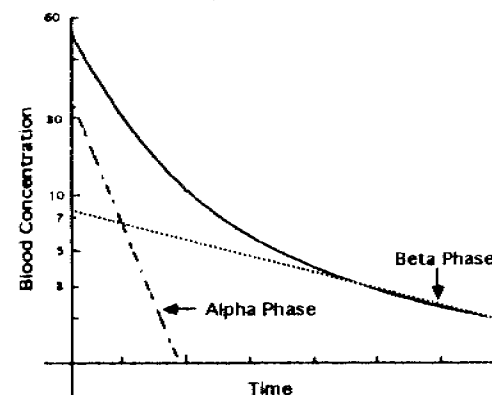
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Classical Pharmacokinetics: "Stripping the Curve"

Curve Stripping (Exponentials)

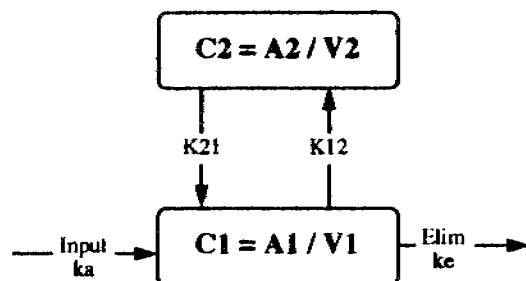
$$C(t) = A_1 + e^{-\lambda_1 t}$$



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Classical Pharmacokinetics: Compartmental Models



Differential Equations:

$$\begin{aligned} dA_0/dt &= -k_a \cdot \text{Dose} \\ dA_1/dt &= k_a \cdot \text{Dose} - K_{12} \cdot C_1 + K_{21} \cdot C_2 - k_e \cdot C_1 \\ dA_2/dt &= +K_{21} \cdot C_1 - K_{12} \cdot C_2 \\ dE_{lim}/dt &= -k_e \cdot C_1 \end{aligned}$$

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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

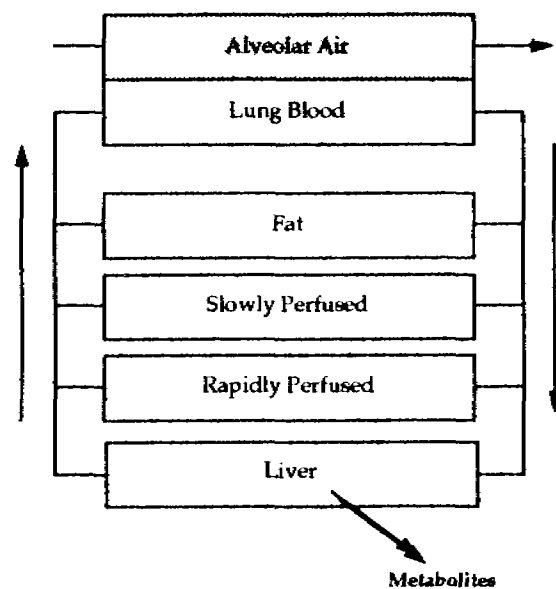
Allow Extrapolations

- 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

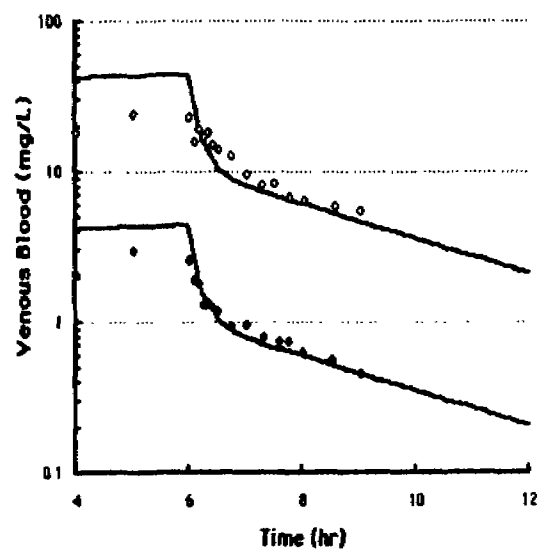
- Will use examples from studies of Reitz et al., at Dow Chemical Co., with 1,1,1-trichloroethane (Methylchloroform, MC)
- Data used to illustrate potential applications for VC PB-PK Model.

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MC Rat Inhalation (Blood Levels)

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

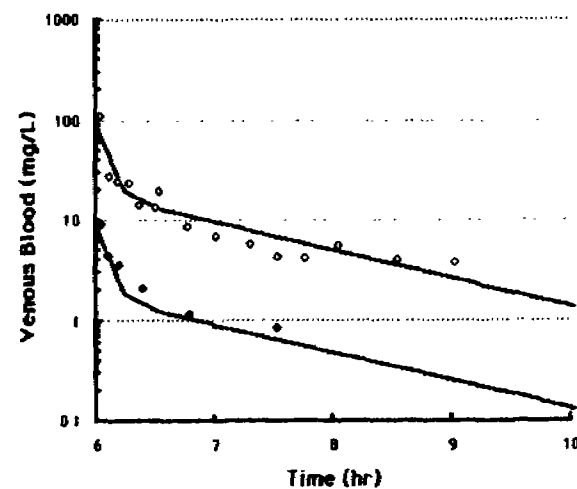


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MC Mouse Inhalation (Blood Levels)

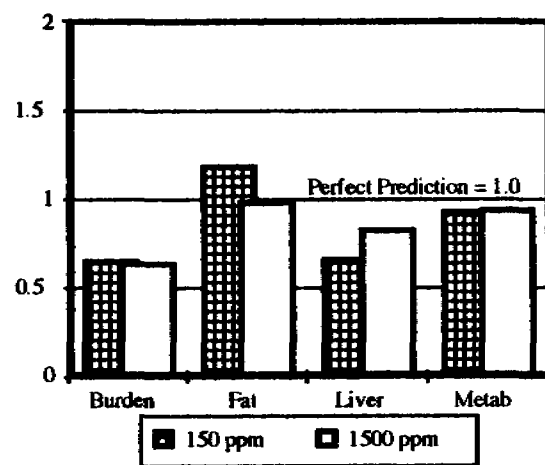
Methylchloroform, (MC) used as an example of the technique.



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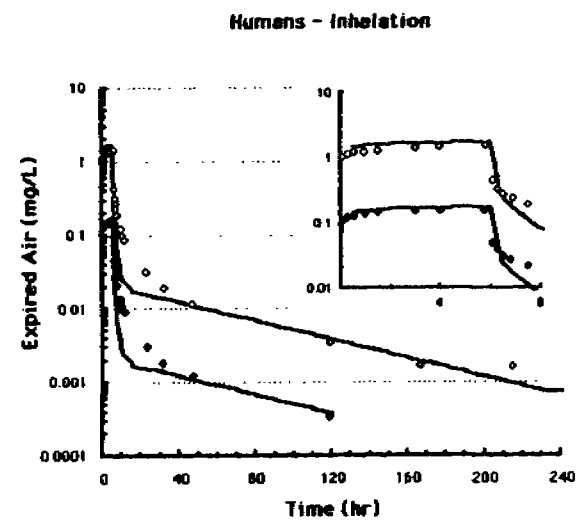
MC Mouse Inhalation (Other Endpoints)



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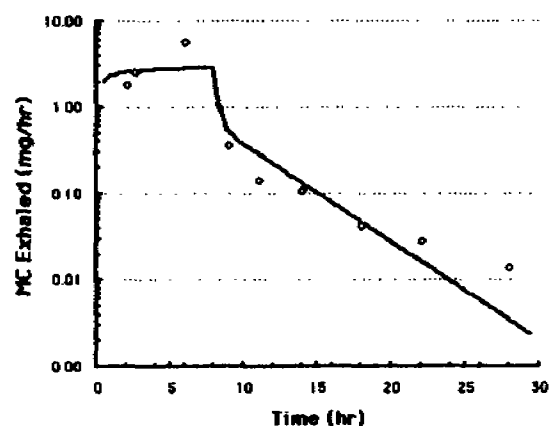
MC Human Inhalation (Exhaled Air)



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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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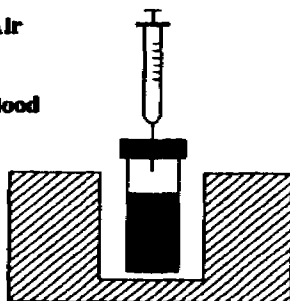
VC Partition Coefficients Vial Equilibration

Measure:

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

Calculate:

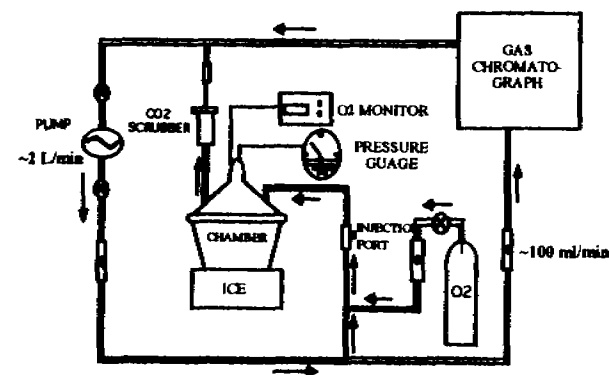
- Tissue/Blood



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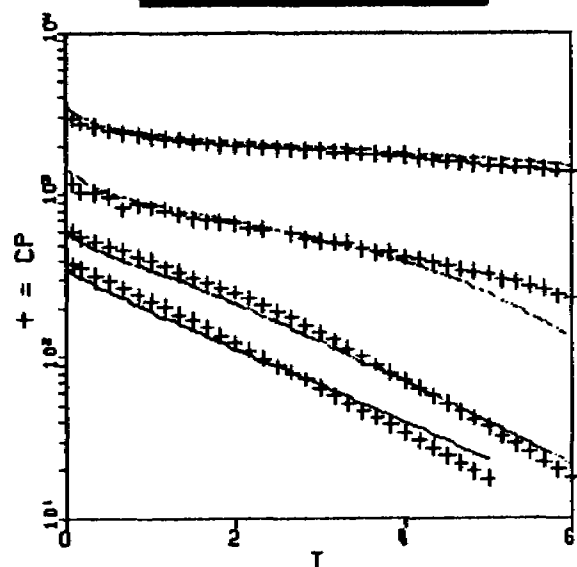
VC Metabolic Rate Constants Gas Uptake Apparatus



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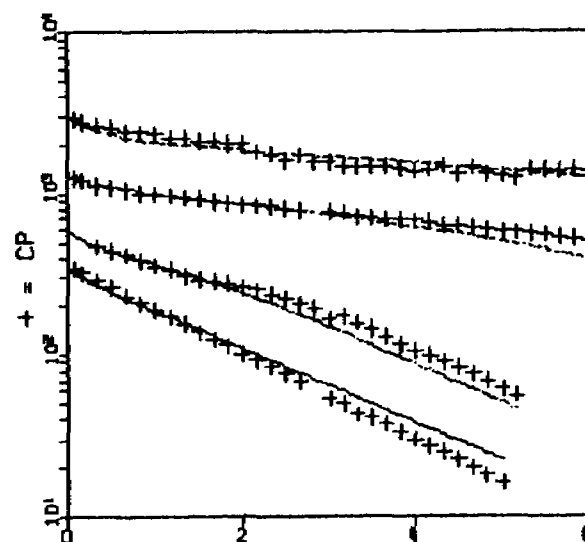
Gas Uptake Data (Male Rats)



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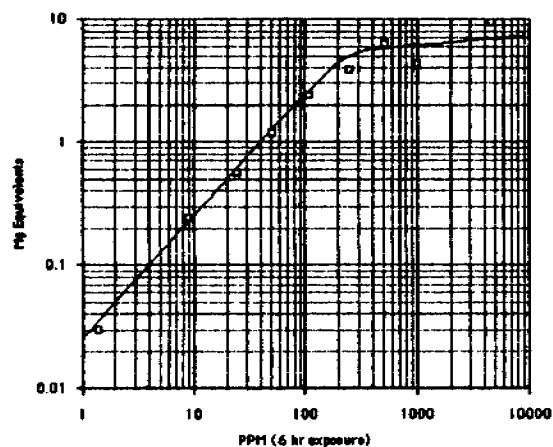
Gas Uptake Data (Female Rats)



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



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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

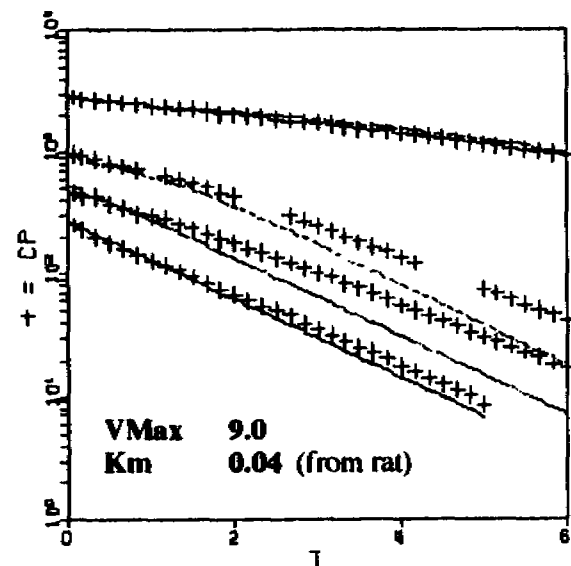
Normalize to Rat In Vivo

	Mouse	Human
MeCl_2	2.57	0.21
CHCl_3	2.71	-
Average	2.64	0.21

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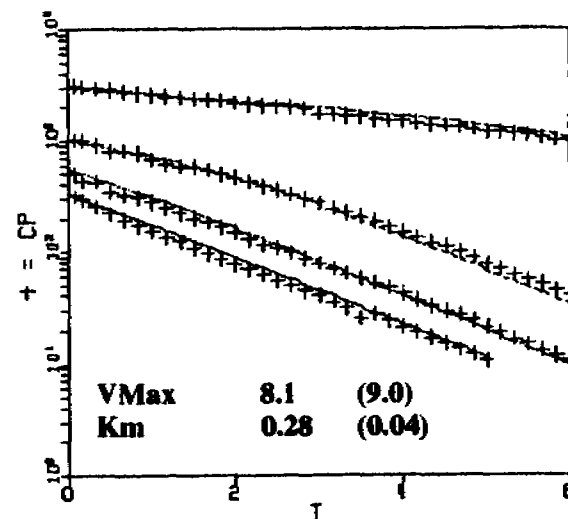
Testing Estimated Mouse Metabolic Constants



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Optimized Mouse Data

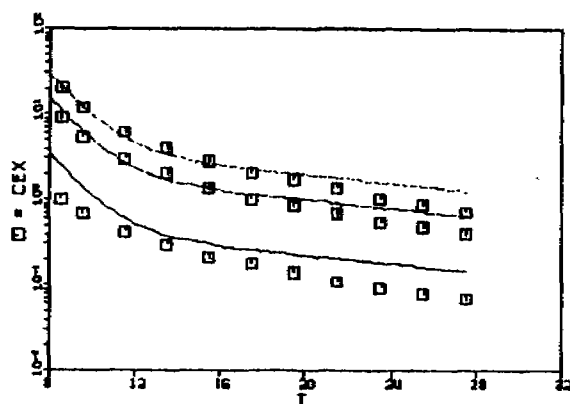


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Validation of Human Model

(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)

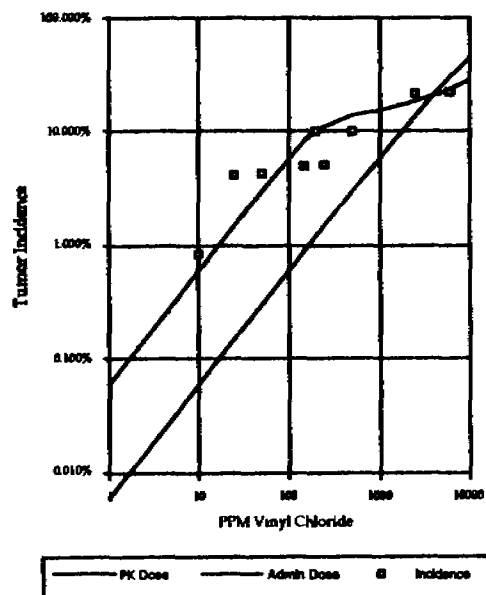
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Predicted Tumor Incidence in Rats

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.**

DOT

Please make
copies and
distribute. Please
return yellow (buff)
originals to me

Thanks

JAB

H. Shah 6/6/94 letter

CHEMICAL MANUFACTURERS ASSOCIATION
Vinyl Chloride Panel
Research Coordinators
Record of Meeting

DATE: May 19, 1994
TIME: 10:00 a.m. - 2:00 p.m.

List of Participants:

James Barter	PPG
Ed Beeler	GEON
Greg Bond	Dow Chemical
Frank Borrelli	Georgia Gulf
Mike Gargas (PT)	CHEMRISK - McLaren/Hart
Mark Gruenwald	Borden
Jim Knaak	Oxy
Dave Penney	Vista
David Pun	Formosa
Jonathan Ramlow	Dow Chemical
Richard Reitz (PT)	Consultant
Kim Reed	CMA
Has Shah	CMA

- 1.0 The Panel approved the February 14, 1994 Record of Meeting as written.
- 2.0 Jonathan Ramlow reviewed the draft scope of work for the update of the mortality among vinyl chloride workers. The scope of work asks contractors to provide an additional ten years of follow-up to the cohort previously studied by Environmental Health Associates (1986). The Panel also would like the update to incorporate state of the art modelling methods for data analyses and use the Eighth or Ninth Revision of the International Classification of Disease to code all death certificates. The 1986 study used the Seventh Revision. The new update also would compare the worker mortality with regional and national averages, as compared to only the national average in the 1986 study.

Due to the shifting of ownership of many plants, some plant data are no longer directly available to Panel members. Has Shah will contact non-Panel companies that produce or produced vinyl chloride to see if they will participate in the update. Panel members should contact their Vinyl Institute Executive Board members to have them encourage Westlake to participate in the update.

The Panel discussed the potential contractors for the update. Potential contractors include: Howard Rockette (University of Pittsburgh); Kenneth Mundt (Applied Epidemiology, Inc.); Roy Shore (New York University Medical Center); and, Don Whorton (ENSR).

Panel members favored a cost-sharing formula based on the nameplate capacity of VCM for 1993 with an off-set for Dow Chemical as compensation for providing extensive staff resources in designing and monitoring the study. Dr. Ramlow will provide an estimate of an off-set amount to Dr. Shah within the next several weeks.

Panel members will determine whether their companies will participate in the update based on the 1993 nameplate capacity cost-sharing formula by June 2 and contact Dr. Shah with their decisions. Immediately following company commitments, each Panel member should send nameplate capacity data (in pounds) to Dr. Shah so that a financial share can be determined based on the total estimated cost of the study.

Dr. Ramlow will revise the scope of work for the update and send it to Dr. Shah for distribution to the Panel. Once commitments are received from the member companies, Dr. Shah will solicit requests for proposals from the potential contractors.

- 3.0 Richard Reitz presented a pharmacokinetics model for estimating human risk from exposure to vinyl chloride. Copies of Dr. Reitz's model and methodology will be distributed to Panel members. Dr. Reitz suggested that Dr. Shah contact Bill Farlin of EPA to determine if the Agency plans to conduct a risk assessment for vinyl chloride. If the response is positive, Dr. Shah will suggest that Dr. Reitz speak to the Agency about his physiologically-based pharmacokinetic risk assessment model for vinyl chloride.
- 4.0 Jim Knaak discussed the decision-making process of when to close major highways due to the threat of a chemical release. The Panel discussed the types of information on which the members generally base such decisions. The Panel identified a potential need for short-term exposure data in making such decisions. Dr. Shah and Dr. Knaak will prepare a program for developing short-term exposure effects data. Frank Borrelli will keep the Vinyl Institute aware of any research programs that the Panel undertakes.
- 5.0 Dr. Shah reviewed the proposed ATSDR research data needs for vinyl chloride. Of the seven data needs discussed in the Federal Register notice, EPA plans to fill the teratogenicity and 2-generation reproduction effects data needs by TSCA Section 4 rulemaking. The other five will be addressed by ATSDR under different options in the future. Dr. Ramlow will review and summarize the reproductive and teratogenic studies completed by Dow and provide a summary to Dr. Shah for distribution to the Panel.
- 6.0 Dr. Shah informed the Panel that a law firm, Cohen Milstein, solicited vinyl chloride information on behalf of a client involved in litigation, and that he sent the law firm the EHA epidemiology study report.
- 7.0 Panel members discussed a TIME magazine article entitled, "Stopping Cancer in Its Tracks," which associates lymphomas with vinyl chloride exposures. The source of the article appears to be th

American Chemical Society. David Penney will draft a letter to send to the American Chemical Society responding to this article. The letter will accompany a statement from the Wong, et al., study stating that vinyl chloride does not appear to cause lymphoma. The letter will be distributed to the Panel for review prior to its release.

- 8.0 The Panel elected Dr. Ramlow as Chairman. Dr. Ramlow replaces Dr. Bond who will no longer be active on the Panel. The newly elected Chairman will serve until July 1, 1995. A Vice Chairman will be elected at a later date.
- 9.0 Dr. Shah distributed the financial statement to the Panel.
- 10.0 The next Panel conference call is scheduled for June 13, 1994 at 10:00 a.m., EDT.



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

Subject to Approval

HISTORICAL PERSPECTIVE ON INTER-INDUSTRY VINYL CHLORIDE STUDY

- | | |
|-----------|--|
| 1960-1963 | Report published documenting anesthetic effects in animals and humans and liver injury in animals from chronic exposure. |
| 1967 | Acroosteolysis reported in humans exposed to high levels of VCM. |
| 1971 | Carcinogenicity of VCM discovered in animals, including angiosarcoma of the liver. |
| 1973 | CMA sponsors Tabershaw-Cooper Associates to conduct an epidemiologic study of 8,384 vinyl chloride workers from 34 plants. |
| 1974 | First reports of angiosarcoma of the liver cases in VCM workers. |
| 1974 | Tabershaw-Cooper report preliminary results confirming high risk of angiosarcoma of the liver and suggesting excess cancers of respiratory system, brain and lymphoma. |

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HISTORICAL PERSPECTIVE ON INTER-INDUSTRY VINYL CHLORIDE STUDY

(cont.)

- | | |
|------|--|
| 1974 | OSHA holds hearings and revises PEL down to 1 ppm. |
| 1981 | Cooper expands original epidemiology study to include 10,173 workers from 37 plants--reports show angiosarcoma and brain cancer to be in excess through 1972. |
| 1986 | EHA updates inter-industry study with follow-up through 1982--reports angiosarcoma, brain cancer and emphysema to be in excess--no excess respiratory cancer or lymphoma/leukemia. |
| 1991 | EHA study is published. |
| 1993 | CMA letter to the editor and EHA response are published clarifying the brain cancer and emphysema findings. |
| 1994 | CMA Vinyl Chloride Research Coordinators meet to discuss updating study. |

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"The study carried out by Environmental Health Associates on behalf of the U.S. Chemical Manufacturers Association is the largest and most informative investigation thus far undertaken."

Sir Richard Doll
Scand J Work Environ Health 1988;
14:61-78

BENEFITS OF UPDATING INTER-INDUSTRY STUDY OF VINYL CHLORIDE WORKERS

- **Product Stewardship**
 - Demonstrates to workers, community residents, customers, and other audiences our collective commitment to characterize cancer risks associated with employment in VCM/PVC processes.
- **Scientific Knowledge**
 - Refines the estimate of the number of cases of human angiosarcoma of the liver (ASL) associated with operating VCM/PVC plants in the pre-1972 era in North America.
 - Provides basis for refining human cancer risk assessments which are used by government agencies for permitting facilities, etc.
 - Contributes ASL cases to the international registry.
 - Helps to resolve unanswered questions about alleged links to cancers of the brain, lung, and hematopoietic system as well as address non-cancer causes of death such as emphysema.
- **Litigation Defense**
 - VCM/PVC manufacturers continue to face toxic tort litigation alleging that numerous other types (non-ASL) of cancer are related to VCM/PVC employment. This type of research is useful in defending such litigation.

BENEFITS OF UPDATING INTER-INDUSTRY STUDY OF VINYL CHLORIDE WORKERS

(cont.)

- Chlorine Issue
 - VCM/PVC continue to be a part of the general debate on health and environmental impacts of chlorinated organics. This type of research serves a valuable role in helping to debate the issues on the basis of good science.