CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Health Committee
Meeting With the University of Louisville
Tentative Agenda

DATE: April 18, 1997
TIME: 8:30 a.m. - 2:30 p.m.
PLACE: Health Sciences Center
University of Louisville
Louisville, KY

8:30-9:00	1.0	Review Agenda Items and Objectives
9:00-9:30	2.0	Status of Work in Progress at the University of Louisville
9:30-9:45	3.0	Update on Cohort Mortality Study at the Applied Epidemiology, Inc.
9:45-10:15	4.0	Discussion of Greenberg/Tamburro Methodology for Analysis of BF Goodrich Cohort Data, Including Statistical Power
10:45-11:00		Break
11:00-12:00	5.0	Discussion of Classical Case Control Analysis of BF Goodrich Cohort Data
12:00-12:30	6.0	Consensus on Methods of Analysis and Publication of Final Study Results
12:30-1:30		Lunch
1:30-2:30	7.0	Development of Final Protocol

- 7.1 Review GEP's to Assure that the Final Protocol Meets All Applicable Guidelines
- 7.2 Develop a Strategy for Addressing Peer Reviewers Comments in the Protocol
- 7.3 Establish a Time Line for Preparation, Reviews, and Approval of Final Protocol
- 7.4 Discuss Peer Reviewers' Sign-off of the Final Protocol

THE APPLICATION OF PHARMACOKINETIC AND DOSE-RESPONSE MODELING IN THE DEVELOPMENT OF MRLs

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Benchmark Dose Analysis

Methodology

- Benchmark Dose (BMD) = dose (or exposure) predicted to result in a specified increase in risk: the benchmark risk (BR)

- Calculated using a statistical dose-response model applied to either experimental toxicological or epidemiological data

- Statistical lower bound on the Benchmark Dose (BMDL) has been proposed as a replacement for the NOAEL

Benchmark Dose Analysis

Advantages over NOAEL/LOAEL

- Does not require arbitrary categorization of the data
- Makes better use of dose-response information
- Statistical lower bound appropriately reflects the sample size of the study and the variability of the data

Minimum Data Requirements for Benchmark Dose Modeling

I. Quantal Data (incidence/prevalence of a response):

A. Ungrouped Data (individual animal/subject data):

1. Dose or exposure concentration for each subject.
2. Response status (normal or abnormal) for each subject.

B. Grouped Data:

(results summarized by dose group or exposure category)

1. Number of animals/subjects in each dose group.
2. Number of animals/subjects in each dose group with abnormal response.
3. Dose or exposure concentration for each dose group.

Minimum Data Requirements for Benchmark Dose Modeling

II. Continuous Data (quantitative measures of response):

A. Ungrouped Data:

1. Dose or exposure concentration for each animal/subject.
2. Quantitative response for each animal/subject.

B. Grouped Data:

1. Number of animals/subjects in each dose group.
2. Mean response in each dose group.
3. Standard deviation (or standard error) of response in each dose group.
4. Dose or exposure concentration for each dose group.

Impact of Benchmark Dose Modeling on Intermediate Inhalation MRL for TCE

LOAEL:	50 ppm
LOAEL/10:	5 ppm
$BMDL_{0.1}$ using all dose groups:	56 ppm
$BMDL_{0.1}$ omitting highest dose:	31 ppm
-- with PBPK dose metrics:	21 ppm

Impact of Benchmark Dose Modeling on Intermediate Oral MRL for TCE

LOAEL:	0.18 mg/kg/d
LOAEL/10:	0.018 mg/kg/d
$BMDL_{0.1}$ using all dose groups:	**65 mg/kg/d**
$BMDL_{0.1}$ omitting highest dose:	0.24 mg/kg/d

MRLs for Methylene Chloride Using PBPK Approach in Comparison with Current MRLs

MRL	Current Approach	PBPK Approach	Ratio PBPK / Current
Inhalation			
Acute	0.4 ppm	0.8–4 ppm	2 - 10
Interme diate	0.03 ppm [a]	0.25 ppm [b]	8
Oral			
Chronic	0.06 mg/kg/d [a]	0.13 mg/kg/d [b]	2

MRLs for Trichloroethylene Using PBPK Approach in Comparison with Current MRLs

MRL	Current Approach	PBPK Approach	Ratio PBPK / Current
Inhalation			
Acute	2 ppm	2–8 ppm	1 – 4
Interme diate	0.1 (0.04)[c] ppm [b]	0.1–0.2 ppm [b]	1 – 2 (2.5 - 5)[c]
Oral			
Acute	0.5 mg/kg/d [a]	0.02–0.04 mg/kg/d [b]	0.04 – 0.08
Interme diate	0.002 mg/kg/d [a]	0.0002–0.0004 mg/kg/d [b]	0.1 – 0.2

Review of Chemicals for Suitability of PBPK or BMD Modeling in MRLs

Chemical	PBPK	BMD
Aldrin	--	**1/2**
Dieldrin	**A/H**	**1/3**
Arsenic	A/H	0/1
Cadmium	**A/H**	**1/2**
Carbon Tetrachloride	**A/H**	0/4
Chlordane	--	**3/4**
Chloroform	**A/H**	**2/6**
DDT	--	0/2
Mercury	**A/H**	**3/5**
Tetrachloroethylene	**A/H**	0/3
Total	7/9	11/32

Conclusions

Use of PBPK Modeling in MRL Process

Most important impact: Cross-species scaling (and route-to-route)

Challenge: Selection of dose metric ("mode of action")

Pharmacokinetic principles can be applied without full PBPK model

Need multiple "mode-of-action" defaults for cross-species extrapolation (cf. EPA RfC Dosimetry Guidelines)

Cross-Species Dosimetry for Inhalation

- Traditional: mg/kg/day

  metric: C x V x T x F / BW

- New RfC Dosimetry Guidelines:

  Category 1: reactive materials (e.g., formaldehyde)

  metric: C x V x T x F / SA

  Category 2: water-soluble materials (e.g., propanol)

  metric: C x V x T x F / BW

  Category 3: water-insoluble materials (e.g., styrene)

  metric: C x T

Human Equivalent Concentrations Based on Pharmacokinetic Dose Metrics for Three Volatile Chemicals[1]

Inhalation Exposure

- Toxicity Due to Parent Chemical Exposure (MC, TCE, VC):

  -- PBPK HEC within a factor of 2 of default

- Toxicity Due to Reactive Metabolite (MC, VC):

  -- PBPK HEC 2.5- to 25-fold *higher* than default

- Toxicity Due to Stable Metabolite (TCE):

  -- PBPK HEC 10- to 100-fold *lower* than default

[1] Based on PBPK model calculations for methylene chloride (MC), trichloroethylene (TCE), and vinyl chloride (VC)

Human Equivalent Concentrations Based on Pharmacokinetic Dose Metrics for Three Volatile Chemicals[1]

Oral Exposure:

- Toxicity Due to Parent Chemical Exposure (MC, TCE, VC):

  -- PBPK human dose 3- to 30-fold *lower* than RfD default

- Toxicity Due to Reactive Metabolite (MC, VC):

  -- PBPK human dose 2- to 10-fold *higher* than RfD default

- Toxicity Due to Stable Metabolite (TCE):

  -- PBPK human dose 5- to 20-fold *lower* than RfD default

[1] Based on PBPK model calculations for methylene chloride (MC), trichloroethylene (TCE), and vinyl chloride (VC)

Conclusions

Use of BMD Modeling in MRL Process

- Most important impact: Replacement of LOAEL/10
- Challenge: "Goodness of fit" evaluation
- Need better reporting of data in toxicology literature

Conclusions

Use of PBPK and BMD Modeling in the MRL Process

- Both techniques synergistically improve accuracy of quantitative dose-response calculations

- Impact of greater accuracy in quantitative analysis is typically small compared to impact of qualitative factors:

  -- Selection of critical study

  -- Choice of Uncertainty/Modifying Factors

Interaction of PBPK/BMD with Uncertainty Factors

- Interindividual variability / Sensitive subpopulations (10)

  Typically unaffected by PBPK or BMD modeling

- Subchronic to chronic / Acute to subchronic (10)

  Typically unaffected by PBPK or BMD modeling

- LOAEL vs NOAEL (10)

  EPA: $BMDL_{0.1}$ = NOAEL

- Animal to human (10)

  EPA: 10 = 3 (PK) x 3 (PD)

  UF reduced to 3 for <u>either</u> default (parent) dosimetry

  <u>or</u> use of PBPK model

Priorities for the Application of PBPK and BMD Modeling for MRLs

1 MRLs based on a LOAEL where the benchmark dose (BMD) method could be used to estimate a NOAEL

2 Oral MRLs where the toxicity is due to a stable metabolite and the current MRL may underestimate the human hazard

3 MRLs where the toxicity is due to a reactive intermediate and the current MRL may overestimate the human hazard

Recommended MRL Cases

1. Manganese:

BMD analysis of 1 MRL.

The chronic inhalation MRL is based on a LOAEL in an epidemiological study, and the critical study includes adequate data to perform BMD analysis to determine a NOAEL.

Recommended MRL Cases

2. Dieldrin:

BMD analysis of 1 MRL and PBPK analysis of 3 MRLs.

The acute oral MRL is based on a LOAEL, and the critical study includes adequate data to perform a BMD analysis to determine a NOAEL. Moreover, all 3 MRLs for dieldrin represent oral toxicity by a stable compound and the default animal-to-human extrapolation may underestimate the relative human hazard.

Recommended MRL Cases

3. Mercury:

BMD analysis of 2 MRLs and PBPK analysis of 1 MRL.

Both the metallic and organic mercury acute inhalation MRLs are based on LOAELs, and the critical studies include adequate data to perform BMD analysis to determine NOAELs.

Recommended MRL Cases

4. Cadmium:

BMD analysis of 2 MRLs.

Both the oral and inhalation chronic MRLs for cadmium are based on human epidemiological studies which are suitable for BMD analysis to evaluate the NOAELs.

Recommended MRL Cases

5. Tetrachloroethylene (PERC): PBPK analysis of 1 MRL.

A PBPK model for PERC could be applied to evaluate the animal-to-human dosimetry for the acute oral MRL, which represents oral toxicity by a stable compound and for which the default animal-to-human extrapolation may underestimate the relative human hazard.

Recommended MRL Cases

6. Chloroform: PBPK analysis of 1 MRL.

A PBPK model for chloroform could be used to correct the animal-to-human dosimetry for the acute inhalation MRL. (It is currently calculated incorrectly.)

Recommended MRL Cases

7. Carbon tetrachloride: PBPK analysis of 4 MRLs.

A PBPK model for carbon tetrachloride could be applied to evaluate the animal-to-human dosimetry for the acute and intermediate inhalation MRLs, which represent inhalation toxicity by a reactive metabolite and for which the default animal-to-human extrapolation may overestimate the relative human hazard. The model could also be used to evaluate the oral MRLs, although they are not likely to be effected significantly.

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/22/97

MEMORANDUM OF UNDERSTANDING (MOU) WITH THE AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) The MOU has been signed. A revised study plan was sent to ATSDR because of the delay in the initiation of the study. **IMPORTANCE** The MOU was developed to meet the research needs of ATSDR and the Environmental Protection Agency in lieu of a TSCA Section 4 testing requirement.	**ACTION ITEMS** **DEADLINES** Initial progress reports are due at ATSDR in April 1997 with subsequent reports due every 6 months thereafter until studies are completed and final reports are submitted.
REPRODUCTIVE & DEVELOPMENTAL TOXICITY STUDIES AT HUNTINGDON LIFE SCIENCES (HLS) The contract with Huntingdon has been signed. Analytical work on the test material is complete and the exposure portion of the study has begun. Preliminary results of the analytical work were delivered to CMA for inspection. Jim Knaak reviewed the material and approved it. Jim Knaak, David Penney, and Wendy Sherman visited Huntingdon on April 10, 1997 to monitor the progress of the studies. **IMPORTANCE** This research is in lieu of a potential TSCA Section 4 testing requirement.	**ACTION ITEMS** Continue monitoring progress of study. **DEADLINES** Progress reports are due to ATSDR at intervals specified in the revised study plan of April 22, 1997.
MOLECULAR CARCINOGENESIS SATELLITE STUDIES AT HLS/ UNIVERSITY OF NORTH CAROLINA-JAMES SWENBERG Ray Schroeder (HLS) and James Swenberg (UNC) revised the protocols for the satellite studies. Fewer animals will be needed to conduct the studies and studies will not be subject to GLP standards. This significantly reduces the cost of the satellite studies. **IMPORTANCE** This series of studies on the formation and repair of DNA adducts induced by vinyl chloride should provide a better understanding of the mechanisms of vinyl chloride carcinogenesis.	**ACTION ITEMS** Execute agreement with HLS for in-life portion of satellite study. Prepare a gift letter for $50K to University of North Carolina for the post-exposure treatment of animals and the adducts analyses. **DEADLINES**

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/22/97

SYNTHESIS OF 13C2 VINYL CHLORIDE / CAMBRIDGE ISOTOPE LABORATORIES The product was delivered to Huntingdon. According to Gary Hoffman (HLS) the analytical specifications of the material are acceptable. **IMPORTANCE** By utilizing 13C2-vinyl chloride, the formation and repair of vinyl chloride-induced DNA adducts can be studied relative to those adducts formed endogenously. This aspect of the satellite studies could provide important information for risk assessment dealing with low exposures, such as might be associated with accidental releases that reach the fenceline.	**ACTION ITEMS** **DEADLINES**
INTERNATIONAL LIFE SCIENCES INSTITUTE (ILSI) The VCHC contributed $10,000 to ILSI for .a project on the use of non-tumor data in cancer risk assessment. Case studies are being performed for three chemicals: bezene, vinyl chloride and butadiene. Gino Scarano of ILSI provided a progress report on the project. A meeting of committee members and sponsors is expected sometime this fall. Gino Scarano will notify CMA of the date of the meeting. **IMPORTANCE** The current scientific and regulatory climate is such that the use of endpoints other than tumors to quantitatively estimate cancer risk is on the horizon. This project was initiated to address the question of whether and how genotoxicity and other data could be used as part of a cancer risk assessment.	**ACTION ITEMS** Continue to monitor ILSI activities on this project through Gino Scarano. **DEADLINES**
EPA INTEGRATED RISK INFORMATION SYSTEM PILOT PROJECT EPA has selected vinyl chloride as one of eleven plus chemicals for its IRIS pilot project. The goal of the pilot is to improve the efficiency in gathering and reviewing data and the quality of the information available through IRIS. A peer review of vinyl chloride is scheduled for the week of May 12th. The pilot study is scheduled to conclude this summer, with a decision on the success of the program expected by the fall of 1997.	**ACTION ITEMS** Monitor EPA activities on this project through Amy Mills (202/260-0569), the project manager and William Pepelko (202/260-5904), the chemical manager for the vinyl chloride risk assessment. **DEADLINES**

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/22/97

According to Mike Gargas, Harvey Clewell is the EPA contractor examining vinyl chloride. **IMPORTANCE** IRIS is an EPA database which contains consensus scientific positions on potential human health effects from environmental contaminants. The database has expanded and its use has increased over the last decade. It is the primary source of risk assessment and management information for many other agencies at the federal, state and local levels.	
BRAIN CANCER STUDY / UNIV OF LOUISVILLE The study is proceeding on schedule. **IMPORTANCE** The 20-year prospective assessment of B.F. Goodrich's Louisville cohort provides a unique opportunity to determine whether there is any association between brain cancer and vinyl chloride exposure.	**ACTION ITEMS** The Committee and University of Louisville representatives met on April 18th to explore alternative methods for analyzing data so the final study is seen as credible by both clinical and traditional epidemiological communities. Dr. Carlo Tamburo will revise the protocol to incorporate the comments received at the meeting and will send a revised draft protocol to Has Shah at CMA by May 18, 1997. **DEADLINES** Study progress reports are due at CMA on dates indicated in the agreement.
VINYL CHLORIDE COHORT STUDY UPDATE / APPLIED EPIDEMIOLOGY INC. Ken Mundt received the remaining death certificate information from ENSR. He asked for assistance from Committee members to track employment and vital status on some of the cohort members. **IMPORTANCE**	**ACTION ITEMS** **DEADLINES** Study progress reports are due at CMA on dates indicated in the study agreement.
ATSDR *TOXICOLOGICAL PROFILE FOR VINYL CHLORIDE* Committee provided comments on the health and environmental portions of the profile to ATSDR. Data on production volume, facilities and use in the profile, is inaccurate. Caffey Norman has drafted a letter to ATSDR correcting the data and suggesting an alternative to the presentation of the storage data in Chapter 4 of the Toxicological Profile.	**ACTION ITEMS** Follow up with ATSDR on Committee comments. **DEADLINES**

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/22/97

IMPORTANCE	
ATSDR *MEDICAL MANAGEMENT GUIDELINES* FOR VINYL CHLORIDE Committee provided comments on the guidelines. As of April 1997, there was no established timeline for finalizing the Guidelines. **IMPORTANCE**	**ACTION ITEMS** Follow-up with Jennifer Hiese (617/674-7358) on when the guidelines will be finalized. **DEADLINES**
EPA / PETITION TO RAISE THE "REPORTABLE QUANTITY" (RQ) OF VINYL CHLORIDE The Vinyl Institute will take the lead on determining whether a petition to raise the RQ is feasible. The VCHC will provide technical expertise if the VI decides that it is feasible. Caffey Norman will provide background on the criteria for determining the RQ. **IMPORTANCE**	**ACTION ITEMS** **DEADLINES**
EPA / AIR TOXICS PROGRAM EPA identified vinyl chloride and 36 other chemicals as "high priorities" for regulation under its Air Toxics Program. The Agency plans to develop a comprehensive integrated strategy for establishing an "air toxics management model." Caffey Norman provided background on EPA's activities with the Air Toxics Program, and CMA has asked to be a stakeholder. **IMPORTANCE**	**ACTION ITEMS** **DEADLINES**
ASSOCIATION OF PLASTICS MANUFACTURERS IN EUROPE (APME) / REGISTRY OF CASES OF ANGIOSARCOMA APME has developed a protocol for the maintenance of a register of cases of angiosarcoma related to PVC production. **IMPORTANCE**	**ACTION ITEMS** CMA will monitor the development of the registry. **DEADLINES**
AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS (ACGIH) / INITIATIVE TO LOWER THE THRESHOLD LIMIT VALUE (TLV) FOR VINYL CHLORIDE	**ACTION ITEMS** The Committee will examine the Simonato paper and make contact with William Waddell to propose presenting information to ACGIH.

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/22/97

The concern from ACGIH is based on an article by Simonato, et al. in the Scand J. Work & E.H. ACGIH met on October 5, 6, 7, 1996 in Philadelphia. Peter de la Cruz of Keller & Heckman (Vinyl Institute) responded to Dr. William Waddell of the Univ. of Louisville (ACGIH) for Frank Borelli. **IMPORTANCE**	**DEADLINES**
CALEPA / DEVELOPMENTAL AND REPRODUCTIVE TOXICANT (DART) IDENTIFICATION COMMITTEE PRIORITY LIST Vinyl chloride is a potential candidate for listing under Proposition 65. The VCHC submitted comments to CalEPA. **IMPORTANCE**	**ACTION ITEMS** The Committee will monitor this issue. **DEADLINES**