

DRAFT

CHEMICAL MANUFACTURERS ASSOCIATION
Vinyl Chloride Health Committee
Tentative Conference Call Agenda

DATE: July 30, 1997
TIME: 10:30 a.m. - 12 noon, EDT

- 1.0 ✓ Approval of the April 23, 1997 Record of Meeting and Administrative Items
- 2.0 ✓ Update on the Vinyl Chloride Cohort Study with Applied Epidemiology Inc.
- 3.0 ✓ Update on the University of Louisville Brain Cancer Study
- 4.0 ✓ Financial Update and Development of 1998 Budget
- 5.0 ✓ Update on the Developmental, Reproductive and Mechanistic Research Studies
 - 5.1 Huntingdon Life Sciences Developmental and Reproductive Studies
 - 5.2 University of North Carolina - J. Swenberg Satellite Study
- 6.0 ✓ Update on EPA's IRIS Pilot Project
- 7.0 ✓ Update on EVCM Presentation at SPI
- 8.0 ✓ Update on the International Life Sciences Institute Genotoxicity Project
- 9.0 Schedule Next Meeting or Conference Call

Subject to Approval

Wendy K. Sherman
Manager
Vinyl Chloride Health Committee

SL 109876

Molecular Dosimetry of Vinyl Chloride

James A. Swenberg, D.V.M., Ph.D.

Research Report and Budget Request

July 28, 1997

Research Report

Year 1 (1996-1997 Budget)

The laboratory portion of this project began this spring by sending teams of 3-4 of our laboratory personnel to New Jersey to collect tissues and liver cell types from rats that were exposed to 0, 10, 100, or 1100 ppm vinyl chloride (VC) for 1-20 days. Procedures were rather difficult during the first set of necropsies, but went much better for subsequent procedures after we sent an additional person and shipped up our own centrifuge. We were able to harvest good yields of cells and tissues for the experiment as a whole. It was unfortunate that the [$^{13}\text{C}_2$]-VC experiment was the first to come off, as this was the least smooth running of all. Even so, adequate numbers of cells were able to be harvested to meet our objectives.

We are currently isolating DNA from the 4-week hepatocytes, as these are the most plentiful cells. A new immunoaffinity chromatograph-GC/MS method is replacing our previous low pressure strong cation exchange-GC/MS method for the analysis of ethenoguanine. After this shakedown, we will begin working with the [$^{13}\text{C}_2$]-VC liver cells. Parallel to this effort will be the analysis of urines for excretion of ethenoadenine using immunoaffinity chromatography and LC-MS. Likewise, we will begin examining the major DNA repair pathway for VC DNA adducts including methyl purine glycosylase (MPG) and AP-endonuclease (AP).

Year 2 (1997-1998 Budget)

During Year 2 we will continue to work up the many samples collected in New Jersey. Priority will be given to establishing exposure response relationships, identifying cell-specific differences in DNA repair, determining effects of exposure on endogenously formed DNA adducts, and doing initial studies related to incorporating these data into a PB/PK risk assessment model. We are also developing new methods for the $^1\text{N},2$ -ethenoguanine adduct, which has never been characterized *in vivo*.

Year 3 (1998-1999)

We expect to complete this research during the third year. At this time, we will have analyzed all of the relevant tissues and cells for DNA adducts, will establish the role of defects in DNA repair and the effect of induction of DNA repair on exogenous and endogenous DNA adducts, and incorporate these data into a biologically-based risk assessment model.

Research Budget

My understanding of the funding available for this project is that between \$50,000-75,000 will be available per year for three years. The cost of this research project will greatly exceed this, with personnel costing ~\$140,000 this year. However, since VC has been and continues to be one of the chemicals that we are investigating under our NIEHS Superfund Basic Research Program Project. I can offset part of the cost, providing that the CMA agrees to share acknowledgement with NIEHS. Should we need additional [$^{13}\text{C}_1$]-VC exposures, they can be done at UNC, since the EOIC has agreed to fund new research that includes funds to set up a small nose-only exposure system for similar studies on ethylene oxide. Thus, we can maximize our future research dollars to fund critical studies. We need to move forward as fast as possible, as the EPA has already developed a new risk assessment on VC that suggests increased risk compared to their previous estimates. The new assessment incorporates metabolism data, but not information on DNA adducts or DNA repair. Finally, we incurred major expenses during the four trips to New Jersey that were not included in Year 1's budget. These are listed under sample collection in the budget.

1997-1998 Budget request

Sample collection		\$20,695
Travel expenses	\$8172	
Shipping	752	
Supplies	11771	
Research budget		\$66,500
Personnel	35000	
Supplies	24000	
LC-MS/MS time (\$25/hr)	2500	
Travel	3000	
Equipment maintenance agreements	2000	
TOTAL BUDGET REQUEST		\$87,195

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES

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MEMORANDUM OF UNDERSTANDING (MOU) WITH THE AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) The MOU has been signed. In April 1997, 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 The next set of progress reports for the developmental and reproductive studies are due to ATSDR in October 1997. The final developmental report is due to ATSDR in December 1997.
REPRODUCTIVE & DEVELOPMENTAL TOXICITY STUDIES AT HUNTINGDON LIFE SCIENCES (HLS) Skeletal evaluations are taking place now for the developmental study. In the reproductive study, matings of the F(1) generation start July 29th. J. Knaak plans a visit to Huntingdon in late August. IMPORTANCE This research is in lieu of a potential TSCA Section 4 testing requirement.	ACTION ITEMS Continue monitoring progress of study. DEADLINES The draft developmental report is due to CMA on August 24th. Huntingdon may ask for an extension. According to the revised study plan of April 22, 1997, the next set of progress reports for the developmental and reproductive studies are due to ATSDR in October 1997. The final developmental report is due to ATSDR in December 1997.
MOLECULAR CARCINOGENESIS SATELLITE STUDIES AT HLS/ UNIVERSITY OF NORTH CAROLINA-JAMES SWENBERG The agreement with HLS for in-life portion of the satellite study has been executed. According to the terms of the gift letter, J. Swenberg received the second \$25,000 payment in mid-July 1997. The money is for the post-exposure treatment of animals and adducts analyses. 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 Clarify budget request from J. Swenberg. DEADLINES

SL 109880

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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: benzene, vinyl chloride and butadiene. According to G. Scarano of ILSI, the case study on VC is expected this fall. The meeting of Committee members and sponsors may be rescheduled from this fall to winter 1997. 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. EPA's Vinyl Chloride Peer Review Panel meet on June 3rd and 4th. After peer review comments are incorporated, the report is expected to go through EPA's consensus review process by the end of August. According to A. Mills, EPA hopes to have the reviews of all the pilot chemicals completed by late September/October. The pilot study is scheduled to conclude this summer, with a decision on the success of the program expected by the fall of 1997. According to Mike Gargas, Harvey Clewell is the EPA contractor examining vinyl chloride.	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

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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 W. Sherman will forward comments from K. Mundt and panel members to Dr. Carlo Tamburo on his revised protocol. DEADLINES Study progress reports are due at CMA on dates indicated in the agreement.
VINYL CHLORIDE COHORT STUDY UPDATE / APPLIED EPIDEMIOLOGY INC. Progress report no. 7 (July 8th) was received from K. Mundt. 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. A letter was sent in April 1997 to ATSDR correcting the data and suggesting an alternative to the presentation of the storage data in Chapter 4 of the Toxicological Profile. IMPORTANCE	ACTION ITEMS Follow up with ATSDR on Committee comments. DEADLINES
ATSDR MEDICAL MANAGEMENT GUIDELINES FOR VINYL CHLORIDE Committee provided comments on the guidelines. As of July 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

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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

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AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS (ACGIH) / INITIATIVE TO LOWER THE THRESHOLD LIMIT VALUE (TLV) FOR VINYL CHLORIDE 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	ACTION ITEMS The Committee will examine the Simonato paper and make contact with William Waddell to propose presenting information to ACGIH. 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

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