- Useful if compared to human sensitivity of adduct formation
- Bio monitoring - could dif—
  could be used as a biomarker
- Not useful as is.

Molecular Dosimetry of Vinyl Chloride

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

Research Report and Budget Request

July 28, 1997

- How do we do it? - need human comparison

R&S154509

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 [$^{13}C_2$]-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 [$^{13}C_2$]-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}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.

R&S154510

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}C_2$]-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

R&S154511

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/11/97

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 April 25 with subsequent reports due every 6 months thereafter until studies are completed and final reports 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 animal exposure 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 will visit Huntingdon in mid-April to monitor progress of 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 CMA at intervals specified in the agreement.
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 04/11/97

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. Gino Scarano of ILSI provided a progress report on the project. Gino Scarano will notify CMA of the date of the meeting of the sponsors when it has been set. 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 Monitor ILSI activities on this project. DEADLINES
EPA INTEGRATED RISK INFORMATION SYSTEM PILOT PROJECT EPA has selected vinyl chloride for its IRIS pilot project. 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	ACTION ITEMS Monitor EPA activities on this project. DEADLINES

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/11/97

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 will meet 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. **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 is drafting a letter to ATSDR correct the data and suggest an alternative to the presentation of the storage data in Chapter 4 of the Tox Profile. IMPORTANCE	**ACTION ITEMS** Follow up with ATSDR on Committee comments. **DEADLINES**

R&S154515

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/11/97

ATSDR *MEDICAL MANAGEMENT GUIDELINES* FOR VINYL CHLORIDE Committee provided comments on 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 The concern from ACGIH is based on an article by Simonato, et al. in the Scand J. Work	ACTION ITEMS The Committee will examine the Simonato paper and make contact with William Waddell to propose presenting information to ACGIH.

R&S 154516

VINYL CHLORIDE HEALTH COMMITTEE ACTIVITIES 04/11/97

& 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**