Molecular Dosimetry of Vinyl Chloride

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

Research Report and Budget Request

July 28, 1997

BFG40943

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.

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

BFG40945

THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

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From: James Swenberg
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Date: September 22, 1997
Subject: Calendar of "events"
Pages (including cover): 3

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Swenberg Laboratories 1997-1998

Sept. 97:	εG methods development continues DNA from 4 wk whole livers
Oct. 97:	1st analyses rat whole liver 4 week, all doses start εA analyses in urines - [illegible]
Nov. 97:	^{13}C whole liver DNA in εG method DNA from 4 wk heps and NPCs urine analyses
Dec. 97:	urine analyses ^{13}C whole liver DNA in εG method 4 wk heps and NPCs DNA in εG method
Jan. 98:	Urine analyses Abasic site measurement 4 wk whole liver ^{13}C heps and NPC DNA
Feb. 98:	Urine analyses Abasic site measurement 4 wk whole liver ^{13}C heps and NPC DNA in εG method 32P postlabeling analyses of εA and εC 4 wk whole liver
Mar. 98:	Urine analyses Abasic site measurement 4 wk whole liver ^{13}C heps and NPC DNA in εG method 32P postlabeling analyses of εA and εC 4 wk whole liver 1,N^2-εG analyses start
Apr. 98:	Abasic site measurement 4 wk whole liver ^{13}C heps and NPC DNA in εG method 32P postlabeling analyses of εA and εC continue 1,N^2-εG analyses
May 98:	Abasic site measurement 4 wk whole liver 32P postlabeling analyses of εA and εC 1,N^2-εG analyses
June 98:	MPG & AP endonuclease assays begin Abasic site measurement 4 wk whole liver 32P postlabeling analyses of εA and εC 1,N^2-εG analyses

July 98:	MPG & AP endonuclease assays begin Abasic site measurement 4 wk whole liver 32P postlabeling analyses of εA and εC 1,N^2-εG analyses
Aug. 98:	MPG & AP endonuclease assays begin Abasic site measurement 4 wk whole liver 32P postlabeling analyses of εA and εC 1,N^2-εG analyses
Year 2:98-99	Begin with brain
Year 3:99-00	Lung, Kidney, risk assessment analyses begin

STUDY PLAN
(Revised April 22, 1997)

COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY TESTING OF VINYL CHLORIDE

I. Test Requirements Contained in Study Plan

Inhalation Two-Generation Reproduction Study of Vinyl Chloride in Rats

Inhalation Developmental Toxicity Study of Vinyl Chloride in CD Rats

II. Administrative Official and Project Manager:

Wendy K. Sherman
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

Phone: 703/741-5639
Fax: 703/741-6091

III. Testing Facility:

Huntingdon Life Sciences, Inc.
P.O. Box 2360
Mettlers Road
East Millstone, NJ 08875

Study Director: Raymond E. Schroeder M.S.

Phone: 908/873-2550 (ext 2910)

IV. Professional Qualifications

Curriculum Vitae (C.V.) providing the training and experience of each professional involved in this study were provided as an attachment to the original study plan. Copies of those C.V.s are available upon request from Ms. Sherman.

V. Identity of Test Substance

An analysis of the material which is being used in the studies was conducted and the results are available from Huntingdon Life Sciences, Inc.

VI. Study Protocol

The protocol for the combined inhalation two-generation reproduction and developmental toxicity testing was included as an attachment to the original study plan. A copy of the protocol is available upon request from Ms. Sherman.

VII. Test Schedule

Developmental Toxicity Study:

In-life phase starts:	October, 1996
In-life phase completed:	April, 1997
Progress report:	April, 1997
Progress report	October 1997
Final report:	December, 1997

Draft from Huntingdon due within couple of weeks from 10/06.

Reproduction Study:

In-life phase starts:	October, 1996
In-life phase completed:	September, 1997
Progress report:	April, 1997
Progress report:	October, 1997
Progress report:	April, 1998
Final report:	July, 1998

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

JUL 28 1997

Ms. Wendy K. Sherman
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, Virginia 22209

Dear Ms. Sherman:

The Agency for Toxic Substances and Disease Registry (ATSDR) commends the efforts of the Chemical Manufacturers Association (CMA) to assist our agency in addressing key gaps in toxicological information through voluntary research. The purpose of this letter is to reaffirm the importance of your efforts.

ATSDR is the lead agency within the Public Health Service responsible for implementing the health-related provisions of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). As such, one of ATSDR's goals is to evaluate relationships between hazardous substances in the environment, exposure, and adverse human health outcomes.

In 1991, ATSDR initiated its Substance-Specific Applied Research Program (SSARP) by determining 117 priority data needs for its 38 highest ranking hazardous substances found at Superfund hazardous waste sites. Identifying and addressing these research needs are crucial to ATSDR in determining the types and levels of hazardous substance exposures that may present significant risks of adverse human health effects.

ATSDR is pleased that the CMA vinyl chloride study, "Combined inhalation two-generation reproduction and developmental toxicity study in CD rats," has been initiated and that CMA has updated the agency on the study's progress. Vinyl chloride currently ranks number 4 on ATSDR's priority list of hazardous substances, and it has been found in at least 493 National Priorities List (NPL) sites.

Research on this substance is not only important to citizens who live near hazardous waste sites, but also will have implications for workers and others who may be exposed to vinyl chloride during remediation of waste sites.

We appreciate the opportunity to work with CMA to assure the success of this very important cooperative research effort.

Sincerely yours,

Barry L. Johnson

Barry L. Johnson, Ph.D.
Assistant Surgeon General
Assistant Administrator