



CHEMICAL MANUFACTURERS ASSOCIATION

April 22, 1997

William Cibulas, Ph.D.
Chief, Research Implementation Branch
Division of Toxicology
Agency for Toxic Substances & Disease Registry
1600 Clifton Road, NE
Mailstop E29
Atlanta, GA 30333

Re: Vinyl Chloride MOU

Dear Dr. Cibulas:

Enclosed are interim progress reports on the two-generation reproductive and developmental toxicity studies of vinyl chloride in CD rats that the CMA Vinyl Chloride Health Committee Panel is sponsoring pursuant to our Memorandum of Understanding (MOU) with the Agency for Toxic Substances and Disease Registry (ATSDR). As you have discussed with our counsel, Caffey Norman, also enclosed is a revised study plan indicating that these reports will be submitted together in April 1997. The modified study plan also reflects that I am replacing Dr. Robert Venezia as Project Manager. We will assume that the modified study plan is acceptable unless we hear otherwise from you.

On October 25, 1996, we informed you that the combined reproductive and developmental study would be initiated within a few days. You will see from the progress reports that dosing of the animals did not actually begin until January 7, 1997 for the reproductive study and March 19, 1997 for the developmental study. The delay was attributed to the resolution of a number of technical issues including additional time for setting up the chamber generation system and monitoring for leaks, Good Laboratory Practices characterization of the test material, calibration of gas chromatographs for periodic monitoring of the exposure concentrations and for comparison with infrared spectrophotometer results, and extension of the mating period for six days to achieve additional matings.

Please call me at 703/741-5639 if you have any questions or need additional information.

Sincerely,

Wendy K. Sherman
Manager, Vinyl Chloride Panel

Enclosures (3)

cc: W. Caffey Norman, Esq.

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

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

Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats

Progress Report Reproduction Phase

In this study, parental (P1,P2) generation animals (30/sex/group) are being treated via whole-body inhalation to vinyl chloride at exposure levels of 0, 10, 100 and 1100 ppm. The study is currently in the gestation/lactation periods of the P1 parental generation to produce the F1 litters. These animals have completed a 10 week pre-mating treatment period (exposures were 6 hrs/day, 5 days/week - January 7 - March 18, 1997) and a 20 day mating period (exposure 6 hrs/day, 7 days/week - March 18 - April 6, 1997). Once mated, females were treated 6 hrs/day from Days 0-20 of gestation and females delivering litters will be treated from Days 4-25 of lactation). Following is a timetable for key events through the remainder of the study.

Event	Proposed Date
P2 pre-mating treatment period (6 hrs/day, 5 days/week):	
Initiate	May 20, 1997
Complete	July 29, 1997
Mating period P2 - F2 litters (6 hrs/day, 7 days/week):	
Initiate	July 29, 1997
Complete	August 12, 1997
Gestation/Lactation of F2 litters	
Initiate	July 30, 1997
Complete	September 23, 1997
Sacrifice Schedule:	
P1 Males	April 28 & 29, 1997
P1 Females	May 19 & 20, 1997
P2 Males	September 15 & 16, 1997
P2 Females	September 24 & 25, 1997
Submission of the audited draft report	Week of March 23, 1998

Study Comments:

The start of the study was delayed by approximately two months from the contract date (anticipated start October 28, 1996). Animals for the study (P1) arrived December 23, 1996. This delay was attributed to the following: additional time required to set up the chamber generation system (test material in a one ton cylinder arrived September 19, 1997) and monitor for leaks; GLP characterization of the lot of test material received; and calibration of the gas chromatograph for the periodic monitoring of the exposures concentrations for comparison with the infrared spectrophotometer (MIRAN) results. Mating period was extended by six days to achieve more matings.

Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats

Progress Report Developmental Phase

In this study, mated rats (24/group) were treated with vinyl chloride via whole-body exposure (6 hrs/day) over the Day 6-19 gestation period (day of mating evidence = Day 0 of gestation). Body weight, food consumption and clinical findings were recorded periodically throughout gestation. Animals were sacrificed on Day 20 of gestation and corpora lutea/uterine implantation data recorded. Fetuses were weighed, sexed and given a gross external examination. One-half of the fetuses in each litter were evaluated for visceral malformations/variations (microdissection procedure) and the remaining fetuses are being stained with Alizarin Red S for skeletal examination. Females were given a gross postmortem examination and liver, kidney and gravid uterine weights recorded. Gross lesions, kidneys and liver tissue were taken and preserved.

Exposures and the Day 20 gestation maternal sacrifices have been completed for the developmental phase. Dates for these events are as follows:

Mating initiated:	March 12, 1997
Treatment period (Days 6-19 of gestation, 6 hrs/day):	March 19 - April 10, 1997
Maternal Day 20 gestation sacrifices:	April 2 - 11, 1997
Submission of the audited draft final report:	Week of August 25, 1997

Study comments:

Animals in the developmental phase were exposed along with the animals in the reproduction phase of the study. The fetal evaluations are on-going.

Submitted by: Raymond E. Schroeder Date: 18 April 1997
Raymond E. Schroeder, M.S., DABT
Title: Study Director
For: Huntingdon Life Science Inc.