J. Barr

MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N.W., WASHINGTON, D.C. 20009

TELEPHONE (202) 328-4200
TELEX: 89617 (MCA WSH)

January 11, 1979

To: Vinyl Chloride Audit Task Group (ATG)

Z. G. Bell, Jr. - PPG Industries, Inc.
T. J. Benya - Ethyl Corporation
W. M. Busey - Experimental Pathology Laboratories, Inc.
G. K. Hatfield - Diamond Shamrock Corporation
R. K. Hinderer - The BFGoodrich Company, Chemical Division
C. D. Kary - Shell Oil Company
T. R. Torkelson - The Dow Chemical Company

Subject: ATG Report

Members:

Enclosed are copies of the following documents:

1. Appendix index
2. Retyped draft of ATG report
3. Appendixes

If another meeting of the ATG is held, it will be at the call of the Chairman.

Sincerely,

Lucille C. Henschel
Acting Project Manager
Vinyl Chloride Research

LCH:pmt
Enclosures

THE WRITER'S DIRECT DIAL NUMBER IS (202) 328- 4250

Appendix 1

Report by Dr. William M. Busey, Experimental Pathology Laboratories, Inc.

Appendix 2

Protocols

- February 1, 1973
- May 22, 1973
- September 7, 1973
- January 30, 1975
- August 2, 1973
- August 3, 1973

Appendix 3

Site Visits

- June 15, 1973 letter
- August 6, 1973 letter
- August 10, 1973 letter
- April 17, 1974 letter (necessity of this questioned)
- February 19-24 Record of Meeting

DRAFT

Final Report of Audit Task Group on LIFETIME INHALATION STUDY ON VINYL CHLORIDE at Industrial BIO-TEST Laboratories, Inc.

Introduction

In 1972, 31 vinyl chloride (VC) producers and users through the coordination of the MCA, contracted with the Industrial BIO-TEST Laboratories (IBT) to conduct a long-term carcinogenic study in rats, mice and hamsters. Because of the absence of a final report and subsequent questions on other studies by IBT, an Audit Task Group (ATG) was established by the Technical Panel on VC Research on January 12, 1978. The group, including technical representatives of the companies and William M. Busey, D.V.M., Ph.D. of the Experimental Pathology Laboratories, Inc. (EPL), who was retained as an independent consultant, have conducted a partial audit of the histopathologic records. The findings and recommendations from this audit are presented in this report, including Dr. William M. Busey's Vinyl Chloride Pathology Report, January 9, 1979. (Appendix 1)

History

Based on available information, a protocol for a lifetime study was designed which included exposure of male and female rats, mice and hamsters to either 0, 50, 200 or 2500 ppm. (See Appendix 2) The contract for this study was let in February 1973 and exposures started on September 15, 1973. Reports of site visits conducted during the study are in Appendix 3.

Interim reports were periodically received by MCA and have been transmitted to the Technical Panel. Since no final report was received, an ATG was formed by the Technical Panel to determine the feasibility of obtaining a valid document. This was further accepted by inadequacies in other studies performed by IBT.

Procedure

The ATG recognized several questions that would have to be answered properly if this study was to be considered of adequate technical quality to be useful. However, after inspection of the available IBT records, it seemed more appropriate to the ATG to first conduct a partial audit to assess the quantity and quality of the autopsy and histopathological data. Depending upon whether adequate tissues, blocks and slides were available or not, it would be possible to determine the usefulness of extending the audit to animal records, exposure records, source of animals, and other equally important questions. If it was found that adequate autopsy material was not available, nothing would be gained by several months effort to conduct a complete audit. Therefore, this partial audit of pathology records was conducted.

With the cooperation of remaining IBT personnel at the Decatur location, the ATG and its consultant, Dr. William M. Busey, divided itself into three teams (Appendix 3). The activities of the first team were described in Dr. Busey's report of January 9, 1979. The other two teams examined the autopsy records to determine the disposition of

the experimental animals and the number that had been sacrificed and saved for histological examination. The totals are included in Tables I, II and III of the January 9, 1979 report. In addition, the ATG examined a small sample of the wet tissues to determine if the number of organs required by the protocol had been taken at autopsy. The findings suggested that the number of organs was deficient and IBT was requested to do a complete inventory of tissues, blocks and slides. This was subsequently done and the totals of available tissues are presented in Tables V, VI, and VII of the January 9, 1979 report.

The ATG estimates that the full group has spent more than 800 hours in completing this partial audit, in addition to several weeks by MCA staff and IBT personnel.

Conclusions and Recommendations

The ATG concludes that the conduct of the study by IBT is scientifically unacceptable and makes the following recommendations:

1. That Dr. William Busey's report be accepted by the Technical Panel as the final report of this study.
2. That as recommended by Dr. Busey "no further pathology work be done on this study".
3. That IBT be instructed that no further work be done on this study and that all materials and records of this study be retained by IBT indefinitely according to conformity with the Good Laboratory Practice Regulations, as published in the Federal Register, December 22, 1978.

4. That IBT be instructed that this project is considered closed and that no further funds will be available from MCA.
5. If the report of the ATG is accepted by the Technical Panel that it be transmitted to the appropriate government agencies.

February 1, 19

PROTOCOL

MANUFACTURING CHEMISTS' ASSOCIATION, INC.

CHRONIC VAPOR INHALATION TOXICITY STUDY WITH VINYL CHLORIDE

I. Outline of Investigation

A.	Type and Length*:	12-month vapor inhalation in White Mice 12-month vapor inhalation in Albino Rats 12-month vapor inhalation in Hamsters
B.	Number of Animals:	800 Mice 800 Rats 800 Hamsters
C.	Exposure Schedule:	Seven Hours per Day Five Days per Week
D.	Test Materials:	Vinyl Chloride (Ethylene derived)
E.	Organization:	See Table I
F.	Dose Levels:	See Table I

*After exposure, animals will be maintained for observation and sacrifice at end of two-year period (18 months for mice).

TABLE I

Chronic Vapor Inhalation Toxicity Study

Organization of Groups

Test Material		Group	Number of Animals					
			Mice		Rats		Hamsters	
			Males	Females	Males	Females	Males	Females
None		Control	100	100	100	100	100	100
Vinyl Chloride (Ethylene derived)	TE-I	Low level - 50 ppm	100	100	100	100	100	100
	TE-II	Intermediate level - 500 ppm	100	100	100	100	100	100
	TE-III	High level - 5000 ppm	100	100	100	100	100	100

II. Chamber Parameters

Each group of animals will be exposed in a specially constructed plexiglas inhalation chamber having a capacity of approximately 6.0 M^3, allowing animal loading of less than 2% when the animals reach maturity. Flow rate through the chamber will be at least 0.60 M^3/min. providing a theoretical air change every ten minutes. The chamber supply air will be filtered and maintained at 40% to 60% relative humidity and 70° to 75°F.

III. Animal Parameters

A. Clinical Observations

All animals will be observed daily for lesions and behavioral changes attributable to the test material. The time of appearance and location of all tumors that occur among both control and test animals will be recorded. Mortality records will be kept on all groups of animals. All animals which die during the study will be necropsied and their tissues processed in accordance with the methods given in the Anatomic Pathology Section. Care will be exercised to minimize loss of tissues through cannibalism or autolysis. Animals in a moribund state will be sacrificed *in extremis* when death is imminent.

B. Body Weights

Individual body weights will be recorded once before exposure and after 1, 2, 3, and 4 weeks of testing. Thereafter, mean group body weights will be determined monthly up to the 12-month point of the study.

C. Clinical Pathology

Hemoglobin, hematocrit, total erythrocyte and total leukocyte counts will be performed at 18 and 24 months on 30 (15 male and 15 female) rats of the control and each test group. Differential leukocyte counts will be performed on all animals having high total leukocyte counts.

D. Anatomic Pathology

1. Methods of Sacrifice

Upon completion of the study, all survivors will be sacrificed by exsanguination following carbon dioxide anesthesia.

2. Gross Pathology

Complete necropsies will be performed on all animals which die or are sacrificed and all macroscopic lesions will be recorded. The lungs will be inflated with formalin fixative.

3. Histopathology

Representative specimens of the following organs

and tissues will be taken from all animals at time of sacrifice and fixed in 10.0% neutral buffered formalin:

Adrenal Glands
All Gross Lesions
Bone (femur, tarsal and metatarsal, including long bones of all four limbs)
Bone Marrow (sternal)
Brain
Both Ears (external auditory canal with ceruminal (Zymbal's) glands)
Esophagus
Eye
Gonads (testes and ovaries)
Kidneys
Large Intestine (caecum and colon)
Liver
Lungs
Lymph Nodes (tracheobronchial, cervical and mesenteric)
Optic Nerve
Pancreas
Parathyroid Gland
Pituitary Gland
Prostate
Salivary Gland
Seminal Vesicles
Skin
Small Intestine (duodenum, jejunum and ileum)
Spleen
Stomach
Thymus
Thyroid Gland
Trachea
Urinary Bladder
Uterus

The above tissues, from animals of the control, TE-II, and TE-III will be processed by conventional methods, embedded in paraplast, sectioned (4-6μ), stained with hematoxylin and eosin, and evaluated by light microscopy. If

drug-related lesions are detected in tissues from the high or intermediate dose (TE-II or TE-III) animals, affected tissues from the TE-I group animals will be processed and examined in the same manner as the above.

Only major organs (liver, kidney, spleen, heart, lungs) and neoplasms from animals which die and are found in an advanced state of autolysis will be processed for histopathologic evaluation.

IV. Reports

Quarterly summaries of mortalities, clinical observations, clinicopathologic and anatomopathologic findings will be prepared. Upon completion of the study, a complete report will be prepared and issued.

February 1, 1973