

January 11, 1979

To: Vinyl Chloride Audit Task Group (ATG)

E. G. Bell, Jr. - PPG Industries, Inc.
T. J. Benya - Ethyl Corporation
W. M. Bussey - 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. Manschel
Acting Project Manager
Vinyl Chloride Research

LCH:pmc
Enclosures

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Bass v. Conoco, Inc., No. 90-4827
14th Judicial District Court
Calcasieu Parish, Louisiana

4250

CMA 004516

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

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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.

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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 prompted by inadequacies in other studies performed by EBT.

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 ~~3~~ (Appendix 3) itself into three teams/ 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.

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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.

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PROTOCOL

MANUFACTURING CHEMISTS' ASSOCIATION, INC.

CHRONIC VAPOR INHALATION TOXICITY STUDY WITH
VINYL CHLORIDEI. 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).

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TABLE I
Chronic Vapor Inhalation Toxicity Study
Organization of Groups

<u>Test Material</u>	<u>Group</u>	<u>Number of Animals</u>					
		<u>Mice</u>		<u>Rats</u>		<u>Hamsters</u>	
		<u>Males</u>	<u>Females</u>	<u>Males</u>	<u>Females</u>	<u>Males</u>	<u>Females</u>
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

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CMA 004523

II. Chamber Parameters

Each group of animals will be exposed in a specially constructed plexiglas inhalation chamber having a capacity of approximately 6.0 M³, allowing animal loading of less than 2% when the animals reach maturity. Flow rate through the chamber will be at least 0.60 M³/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.

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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

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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
Tracheo
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 (4-6 μ), stained with hema-
toxylin and eosin, and evaluated by light microscopy. If

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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

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14th Judicial District Court
Calcasieu Parish, Louisiana

MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N.W. WASHINGTON, D.C. 20009 (202) 483-6126

JAMES R. CARNES
VICE PRESIDENT
SECRETARY-TREASURER

May 14, 1973

Dr. J. C. Calandra, President
Industrial BIO-TEST Laboratories, Inc.
1310 Frontage Road
Northbrook, Illinois 60062

CONFIDENTIAL
Subject to Protective Order in
Ross v. Biochem. Inc., No. 90-48
14th Judicial District Court
Calcasieu Parish, Louisiana

Dear Dr. Calandra:

By this letter, the agreement dated February 1, 1973, between Industrial BIO-TEST Laboratories, Inc. (BIO-TEST) and the Manufacturing Chemists' Association (MCA) for BIO-TEST to conduct a "Chronic vapor inhalation study with vinyl chloride" is extended to include an additional exposure group as described in the following paragraph.

This experimental group is to consist of 100 rats of the same sex, to be exposed to vinyl chloride vapors at a concentration of 5,000 ppm v/v. Food, water, and bedding are to be present in the cages in which the animals are exposed during the entire exposure period. Otherwise, experimental procedures, including exposure conditions, their documentation and control, and the handling, observation and necropsies of animals shall conform to those described in the Protocol incorporated by reference in the subject agreement, and hereby so incorporated in this agreement extension.

The cost for this additional exposure group will be \$15,000, payable in three equal installments, the first and second payable on the first day of the 7th and 16th months, respectively, of the study period covered by the basic agreement, and the third upon receipt of the final report from BIO-TEST.

CMA 004528

Dr. J. C. Colandra
May 14, 1973
Page Two

Please indicate your acceptance by signing the enclosed copy of this letter in the space provided and returning to us.

Sincerely,

J. L. Colandra

Accepted for:

Industrial BIO-TEST
Laboratories, Inc.

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Ross v. Conoco, Inc., No. 90-4832
14th Judicial District Court
Calcasieu Parish, Louisiana

Signed *J. L. Colandra*

Title President

Date May 22, 1973

CMA 004529

Sept. 7, 1973

MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N W WASHINGTON, D C 20009 (202) 483-6126

ALBERT C. CLARK
VICE PRESIDENT
TECHNICAL DIRECTOR

August 31, 1973

RECEIVED
Subject: Order in
Ross v. General Electric Co. No. 80-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

Dr. J. C. Calandra, President
Industrial BIO-TEST Laboratories, Inc.
1810 Frontage Road
Northbrook, Illinois 60062

Dear Dr. Calandra:

By this letter, the agreement dated February 1, 1973 between Industrial BIO-TEST Laboratories, Inc. (BIO-TEST) and the Manufacturing Chemists' Association (MCA), and the agreement extension thereto dated May 14, 1973, are amended by the revision of the concentrations of vinyl chloride monomer vapors to which experimental animals are to be exposed under the terms of the referenced agreements. The exposure levels, as revised by this amendment, are to be as specified in Table I (Revised) attached hereto. For purposes of brevity, the animal test group to which the May 14 extension relates has been designated "TE-IV."

The revised exposure levels shall apply to the animal exposures beginning September 4, 1973, at which time all exposure tests will be restarted with new animals. All other elements of the test protocol will continue to be governed by the referenced prior agreements.

There will be no change in cost to MCA by the implementation of the terms of this amendment.

CMA 004530

Dr. J. C. Calandra
August 31, 1973
Page Two

Please indicate your acceptance of this amendment
by signing the enclosed copy of this letter in the space
provided, and returning to me.

Sincerely,

acc

Accepted for:

Industrial BIO-TEST
Laboratories, Inc.

Signed

R. Q. Roman

Title Assistant to the President

Date September 7, 1973

Subject to Proceedings Order in
Ross v. Conoco, Inc., No. 90-4687
14th Judicial District Court
Calcasieu Parish, Louisiana

TABLE I (Revised August 31, 1973)

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 - 200 ppm	100	100	100	100	100	100
	TE-III* High level - 2,500 ppm	100	100	100	100	100	100
	TE-IV** High level - 2,500 ppm	---	---	100#		---	

* No food, water, or bedding in cages during exposure

** Food, water, and bedding to remain in cages during exposure

All rats of same sex, either sex permitted

JAN 30 1975



THE DOW CHEMICAL COMPANY

BENNETT BUILDING

2030 DOW CENTER

MIDLAND, MICHIGAN 48640

January 27, 1975

Mr. Milton Freifeld
Manufacturing Chemists' Assoc.
1825 Connecticut Ave, N.W.
Washington, D.C. 20009

RECEIVED
Subpoena Order in
Case No. 30-4337
U.S. District Court
Calcasieu Parish, Louisiana

Dear Mr. Freifeld:

The attached table was compiled from information received over the telephone January 20, 1975. Dr. Keplinger of Industrial Bio Test wanted to know if the committee wished to sacrifice the surviving control mice and the 13 female rats exposed to 200 ppm. After talking to as many of you as I could get ahold of, I found that the majority preferred to keep the rats as long as possible and to maintain the mice at least for 18 months.

I informed Keplinger of this decision and he will keep these animals until notified otherwise. Therefore, about March 1 I will be contacting you again on the disposition of the surviving control mice. Since Maltoni has kept his animals for their entire life and since you may be considering more studies at a later date, there appears to be reason to keep these animals for longer than the original protocol called for.

Note that it was necessary to sacrifice several moribund hamsters, mice and rats on January 20. All exposed mice are now gone as well as all the top dose of rats and virtually all the top dose hamsters.

There is no apparent explanation for the reversal in mortality of the groups of female hamsters. It's just one of those things.

Sincerely yours,

Theodore R. Torkelson

Theodore R. Torkelson
Corporate Medical Department

kjf

CMA 004533

encl.

cc: Distribution List Attached.



cc: Vinyl Chloride Research Coordinators:

Dr. Zeb G. Bell, Jr.
PPG Industries, Inc.
One Gateway Center
Pittsburgh, PA 15222

Dr. Walter D. Harris
UNIROYAL, Inc.
Oxford Management & Research Center
Middlebury, Conn. 06749

M. N. Johnson, M.D.
The B.F. Goodrich Company
Medical Center
500 South Main St.
Akron, Ohio 44318

Mr. H. L. Kusnetz
Shell Oil Company
P.O. Box 2463
Houston, TX 77001

Dr. W. Mayo Smith
Air Products & Chemicals
P.O. Box 538
Allentown, PA 18104

Dr. William Rinehart
Ethyl Corporation
Medical Department
451 Florida Avenue
Baton Rouge, LA 70801

Mr. R. N. Wheeler
Union Carbide Corp.
Chemicals & Plastics Div.
P.O. Box 8004
S. Charleston, W. VA 25303

M. L. Keplinger
Industrial BioTest Laboratories, Inc.
1810 Frontage Road
Northbrook, ILL 60062

J. Goode
Industrial BioTest Laboratories, Inc.
1810 Frontage Road
Northbrook, ILL 60062

Order in
No. 90-4837
District Court
Calcasieu Parish, Louisiana

CMA 004534

SURVIVING ANIMALS AT INT AS OF JAN. 20, 1975

Inhaled Concentration Of Vinyl Chloride	Hamsters		Mice		Rats		Female with Food
	Male	Female	Male	Female	Male	Female	
2500 ppm	16	0(3)	0	0	0(4)	0	0(7)
200 ppm	26	41	0	0	5 ^h	13 ^h	--
60 ppm	42	17	0(7)	0(2)	69	55	--
Control	50	22	18 ^h	54 ^h	75	77	--

() Indicates moribund or sick animals sacrificed this date.

^h To be kept indefinitely.

^h To be kept at least until March 10.

RECEIVED
 JAN 21 1975
 FEDERAL BUREAU OF INVESTIGATION
 U.S. DEPARTMENT OF JUSTICE
 WASHINGTON, D.C. 20535

Industrial BIO-TEST Laboratories, Inc.

DECATUR RESEARCH
1800 EAST PERSHING ROAD
DECATUR, ILLINOIS 62526

MENTAL SCIENCES

SCIENCES
SCIENCES

August 2, 1973

AREA CODE 217
TELEPHONE 877-9254

Dr. H. Slatin
Manufacturing Chemists Association
1826 Connecticut Avenue, N. W.
Washington, D. C. 20009

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Estate of George J. No. 00-4387
14th Judicial District Court
Calcasieu Parish, Louisiana

Dear Dr. Slatin:

Due to problems which have occurred in the early stages of the vinyl chloride inhalation project, IBT 663-03222, we respectfully request that we be allowed to restart the study.

In our opinion, two major problems make this request necessary:

- (a) The design on the animal feeding system is not working satisfactorily. This caused considerable weight loss in the hamsters and they have been terminated. The rats and mice have not had normal weight gains and the feeder system must be redesigned.
- (b) Some of the changes deemed necessary by the MCA committee on their last visit to the laboratory, have been made but others are delayed due to shipping dates on equipment.

In our opinion, to continue such an important project with animals which have been stressed and in which sampling and air handling equipment would be changed in the near future, would compromise the data and leave Bio-Test open to eventual criticism.

We feel that all equipment changes can be made by September 1, 1973, at which time the study would be restarted with new groups of animals.

CMA 004536

I am sure that a favorable decision on this matter will allow Bio-Test to conduct a study which will be better received by the scientific community.

Sincerely,

John W. Goode

John W. Goode, Ph.D.
Manager
Decatur Research Laboratories

JG/dm

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Calcasieu Parish, Louisiana

MCA

MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N.W. WASHINGTON, D C 20009 (202) 483-6126

WILLIAM C. CLARK
VICE PRESIDENT
GENERAL DIRECTOR

August 3, 1973

John W. Goode, Ph.D., Manager
Decatur Research Laboratories
Industrial Bio-Test Laboratories, Inc.
800 East Pershing Road
Decatur, Illinois 62526

~~CONFIDENTIAL~~
Subject: ...
3093 ...
1-20 ...
Calculated for ... Louisiana

Dear Dr. Goode:

Thank you for the courtesies extended to Mr. Harry Slatin and the representatives of our member companies, Dr. T. R. McKelson, Dr. Z. G. Bell, Dr. W. D. Harris, and Mr. H. L. Metz in their visit to your laboratories August 2, 1973.

We were all sorry to hear, as you told them and your letter of August 2, 1973, indicates, that the current start on the vinyl chloride inhalation project, IBT-663-03222, is such that you recommend a restart of the study on September 1, 1973. We understand from discussions at the time of the visit that the total cost of this study to MCA will remain as originally agreed.

MCA and its member representatives concur with you that a restart of the study is desirable and advise you to proceed.

It is appreciated that the changes you have made in your physical setup, as well as those you contemplate will help the study appreciably.

If there are any other problems, please advise us.

Sincerely,

William C. Clark

CMA 004538

June 15, 1973

Zeb Bell
Walter Harris
Russ Maycock
Maurey Johnson
Bill Rinehart
R. N. Wheeler

Office in
90-4867
Court
Louisiana

cc: John Goode
Ken Johnson
Howard Kusnetz
Moreno Keplinger

VISIT TO INDUSTRIAL BIO-TEST LABORATORIES, DECATUR, ILLINOIS

On June 7, 1973, Ken Johnson (MCA), Howard Kuznetz (Shell), and myself, visited the Decatur Research Laboratories of Industrial Bio-Test Laboratories, Inc. The purpose of the visit was to observe the equipment and facilities and to discuss the program to be sponsored by MCA. We were accompanied in our visit by Ken Schadeberg, John Goode and Moreno Keplinger of Industrial Bio-Test.

Following a brief introduction, we were shown the inhalation facilities in a large room on the lowest floor of a relatively new building in Decatur. We had expected the exposure to be underway, but to our disappointment found out that, although many of the animals were on hand, the experiments were not ready to begin. We were assured exposures would be underway in 10-14 days, but after viewing the incompletd facilities, we expressed concern for this possibility. One month appeared more reasonable before exposure could start. As described, the inhalation facility is new and this will be the maiden voyage for much of the equipment. Therefore, we had many questions about the adequacy of the equipment and whether it will be shaken down before the experiment gets underway. A number of comments were made, including the following:

Because of the shape of the chambers, the large number of animals per chamber, and the fact that the cages were attached to the walls and separated by trays, there was possibility of channeling of air through the chamber. It was suggested that

an air distribution plenum, and/or a circulating fan, and certainly a plenum vent system be considered to assure distribution of air throughout the chamber. It was pointed out that it would be necessary to verify the adequacy of the air distribution by a suitable analytical method.

There were floor drains in the bottom of each chamber and there was concern that these drains' holes might become unplugged and that contaminated air could back up into the chambers from a common floor drain. It was suggested that a more positive seal such as a screw cap be considered. It was also suggested that draft gauges with alarms be included to assure closure of the chambers and operation of the pumps so that the animals do not die of asphyxia.

Because it was considered necessary to do very frequent sampling during the first part of the experiment and routine monitoring later (twice/day per chamber), it was recommended that a multi-point continuous analyzer be considered in order to reduce the cost. This analyzer could also be used to verify the distribution of air throughout the chambers. An electron capture detector on a gas chromatograph was suggested.

The orifice meters used to control the air flow into the chambers were connected by rather long, flexible hoses. It was suggested that these be shortened to decrease the likelihood of leaks. Air was supplied through a common duct, which had its inlet inside the room. It was therefore considered possible that during wash-down procedures there could be feedback into other chambers and that cross contamination should be carefully guarded against.

The matter of daily records was discussed. It was recommended that a daily log of meter readings, exposure times, flow meter readings be kept, and that calibrations of equipment become part of the experimental record. In this regard, if flow meters (rotometers) are used, they should be glass and not plastic.

There appeared to be unusually small hoses from the chambers to the common exhaust. These were obviously connected in a temporary manner with tape, but it was assumed that this was merely to check out the operation of the chambers and that they would have more permanent attachments. Exhaust from all chambers went into a common duct, which was recognized as another possible source of cross contamination.

Because of the possibility of injury and death of the experimental animals or explosion if the concentration increased to the flammable range due to failure of an air pump, it was suggested that an alarm system be included in the setup to assure movement of air through the chambers.

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14th Judicial District Court
Caddo Parish, Louisiana

June 15, 1973

In regard to records, it was pointed out that it would be necessary to account for the fate of every animal and that they should be coded in such a way as to prevent mix-ups, which could occur in the somewhat crowded conditions.

Pathological examination will be done by technicians who will make gross observations, photograph any unusual growths, and save tissues from all animals, including abnormal growths. It was stressed that all abnormal growths must be examined microscopically since this is the ultimate purpose of the study.

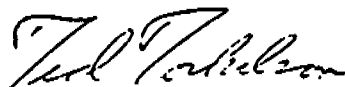
Everything appeared to be in order on shipment and delivery of samples and there was understanding what would be done to assure a supply on hand at all times.

One major concern was the possible number of company contacts who might approach Industrial Bio-Test for information. It was felt undesirable to allow 20 companies to be asking for information. It was determined that no information would be given by Bio-Test to anyone except Ken Johnson unless Bio-Test was specifically authorized to do so by Ken Johnson. This was considered necessary so that well-intentioned but unauthorized people from the various supporting companies would not be putting Industrial Bio-Test in the embarrassing situation of having to refuse to give information to their clients.

In summary, we are seriously concerned about the newness of the equipment and the fact that it has not been demonstrated in previous experiments to provide good air distribution. We are seriously concerned about the possibility of cross-contamination between chambers because of common inlets, outlets, and floor drains. We are concerned about the adequacy of the analysis and about the keeping of records.

Because of the excellent reputation of Industrial Bio-Test, we feel they will correct many of these problems, but it is our recommendation that the committee work very closely with them so that the experimental results are not jeopardized by technical errors. Bio-Test's personnel were impressed with the importance of the situation, and we think we have their complete understanding.

Sincerely yours,



T. R. Torkelson
Registration Section
Ag-Organics Department

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14th Judicial District Court
Calcasieu Parish, Louisiana

la

CMA 004541



INTER-OFFICE CORRESPONDENCE

To: R. E. Widing

Date: August 6, 1975

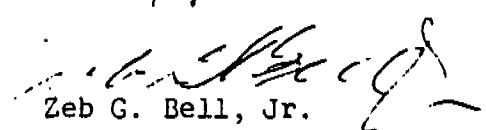
From: Zeb G. Bell, Jr.

Location: 19 East

Subject: Industrial Biotest
Laboratory Visit,
Decatur, Illinois

As a member of the MCA-VCM Technical Coordinators Task Group, the undersigned visited the Industrial Biotest Laboratory facility in Decatur, Illinois, where the MCA innalation study on VCM is being performed. There were some problems in the test chamber design reported by Dr. T. Torkelson (Dow) on his last visit there. This visit revealed that these conditions have been or are being rectified. We (MCA) have been advised through the attached letter that some early problems have developed resulting in their recommendation that the study be re-started. This constitutes a further delay in getting this program "off the ground", however, it is a very wise move since the experiment may have had to be terminated at a later date because of these factors anyway.

Industrial Biotest Laboratory has acted in good faith in complying with our recommendations, but they have had some unfortunate uncontrollable circumstances develop that prompted them to suggest a re-start. I see that we have no other choice than to concur.


Zeb G. Bell, Jr.

ZGB:rmp

Attachment

cc: J. A. Clapperton
L. B. Grant, M.D.
J. L. MacMillan
H. Slatin (MCA)
T. R. Torkelson (Dow)

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MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N.W. WASHINGTON, D.C. 20009 (202) 483-6126

August 10, 1973

Memorandum

TO: A. C. Clark
FROM: H. L. Slatin

~~CONFIDENTIAL~~
Subject: ~~CONFIDENTIAL~~ in
10th Street Court
Calcasieu Parish, Louisiana

SUBJECT: Visit August 2, 1973
Industrial BIO-TEST Laboratories, Inc.
Decatur, Illinois

At the meeting of the Technical Task Group on Vinyl Chloride Research, July 11, 1973, considerable concern was expressed over certain aspects of the animal studies being performed by Industrial BIO-TEST Laboratories (IBL). To assure that discrepancies in the facilities and program noted during the visit to IBL by Drs. Torkelson and Johnson have been corrected, it was agreed to schedule a follow-up visit after the tests had been started.

This will summarize discussions and observations during the conference on August 2, 1973, which I attended for Dr. K. D. Johnson.

In attendance:

For

MCA

IBL

Dr. T. R. Torkelson
Dr. Z. G. Bell, Jr.
Dr. W. D. Harris
Mr. H. L. Kusnetz
Mr. H. L. Slatin

Dr. J. W. Goode
Mr. Ken Schadeberg
Mr. Dennis Lindberg

The difficulty Industrial BIO-TEST was having with the animals was discussed. The animals were received during a period of an air strike of Ozark, the only scheduled airline into Decatur. It was necessary to truck the animals from Northbrook, Illinois using temporary cages and an irregular schedule. It was felt this was an unusual stress to the animals, particularly the hamsters.

CMA 004543

The protocol required that food be taken away from the animals while they are exposed to inhalation of the mixture of vinyl chloride. In order to do this, special food racks were provided by IBL, which did not allow the animals, particularly the smaller ones, to eat the food. Consequently, they lost weight and some died.

Industrial BIO-TEST felt it would be better to scrap these experiments and start anew. September 1, 1973 was suggested as the new starting date. By this date, IBL could effect the following additional improvements: construct a new air exhaust system; install a new gas chromatography unit to automatically and regularly monitor the vinyl chloride concentration in each of the different inhalation chambers; and provide a new feeding device which would allow the animals to get at the food.

The starting delay means that we will not have test data for one year available until September 1974. The one year (12 month) data could be presented at the annual fall meeting of the Industrial Hygiene Foundation as the first part of the 24-month test period.

Dr. Torkelson felt that the key part of the experiment is the one wherein the food would be in the chamber at all times. This part had not been initiated to date, but will be an integral part of the experiment as it is restarted.

It was indicated that restarting the study would involve no additional cost to the MCA sponsoring group. All in attendance favored the restart.

It was also requested that Industrial BIO-TEST obtain from Charles River, at the start of the experiment, information on all of the animals as to their background and the number of multiparous litters from which they came.

In any case, if everything was not ready by September 1, 1973, but the animals were, the experiment would start anyway.

Dr. Goode noted that the high dose of 5,000 ppm v/v was a feasible testing dose. He also stated there are 18 different points from which the chambers are sampled. The Baffle plates and funnels do not affect the homogeneity

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of the VCM/air mixtures. It took about 35 minutes for the chambers to reach equilibrium, which remained steady thereafter. The chambers have a complete air change every ten minutes. The current animals will be used to check out the feeding part of the experiment.

Industrial BIO-TEST agreed to make suitable arrangements for a possible leak and/or rupture of one or more containers of vinyl chloride. Changes will also be made to the air exhaust system so that the air intake will be at a point up and away from the air exhaust.

Subsequent to the meeting, committee members M. N. Johnson, M. D., Dr. W. E. Rinehart, and Mr. R. N. Wheeler were contacted by phone and all concurred with the decision to restart the testing procedure September 1.



H. L. Slatin

HLS:mb

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MCA

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Subject to be discussed in
Room 700, 1000-1837
1000-1837, 1000-1837
1000-1837, 1000-1837

April 17, 1974

To: TECHNICAL TASK GROUP ON VINYL CHLORIDE RESEARCH

Subject: Report on Conference with Industrial BIO-
TEST Laboratories, April 15, 1974

Gentlemen:

As a result of the telephoned information received by MCA from Industrial BIO-TEST personnel last week, a conference at the Northbrook, Illinois offices of IBT was set up at which an oral status report on the chronic inhalation studies with vinyl chloride was presented to MCA, industry and federal agency representatives.

Those in attendance, and their affiliations, are shown below:

Z. G. Bell, Jr.	PPG Industries, Inc.
A. S. Cummin	Borden, Inc.
E. J. Fairchild	NIOSH
J. W. Goode	Industrial BIO-TEST Laboratories
D. E. Gordon	Industrial BIO-TEST Laboratories
W. D. Harris	UNIROYAL, Inc.
M. N. Johnson, M.D.	The B. F. Goodrich Company
Flynt Kennedy	Continental Oil Company
M. L. Keplinger	Industrial BIO-TEST Laboratories
R. J. Kociba	The Dow Chemical Company
H. L. Kusnetz	Shell Oil Company
D. V. Lassiter	OSHA
W. E. Rinehart	Ethyl Corporation
W. M. Smith	Air Products & Chemicals, Inc.
J. F. Stara	U. S. Environmental Protection Agency
T. R. Torkelson	The Dow Chemical Company
R. N. Wheeler	Union Carbide Corporation
B. M. G. Zwicker	B. F. Goodrich Chemical Company
R. F. Blewitt	MCA
A. C. Clark	MCA
K. D. Johnson	MCA

CMA 004546

Dr. Goode first presented the mortality data and gross observations, and then Dr. Gordon described the pathology observed in the mice. The data, as presented, are shown in the attached tables. There are apparent discrepancies between the total mortality data and the detailed listing of recent deaths. These will be resolved. No test-related pathology has yet been noted in any animals other than mice.

Dr. Fairchild, of NIOSH, reported that Dr. David Rall, of HEW, had appointed a committee to coordinate departmental toxicology and related programs, and that under this committee there has been named a subcommittee to develop a "white paper" on guidelines for research to determine "socially acceptable" levels of risk. A report from this subcommittee, which will cover both philosophical and statistical considerations, is expected in the next few weeks.

Dr. Stara expressed the view that the vinyl chloride problem presented industry with a unique opportunity to seek to demonstrate a "no effect level" of a human carcinogen with a sensitive animal model of well-documented validity.

Dr. Lassiter expressed a guarded judgment that the mouse data reported by IBT would not lead OSHA to modify the emergency temporary standard, but that it might well cause OSHA to accelerate the rule-making process for the development of a permanent standard.

Dr. Lassiter also reported briefly on the retrospective morbidity and mortality studies being conducted by NIOSH/CDC at nine or ten locations (six companies) around the country. No epidemiological data were presented.

In an afternoon session of the Research Coordinators, it was agreed that the exposure of the mice in the present project should be terminated at nine months, but that exposures of both rats and hamsters should proceed for the initially-planned twelve months.

It was further moved, seconded and carried that the chairman appoint a group to begin investigating the cost and availability of facilities of new experiments to be conducted at lower levels of exposure, with larger groups of animals. He was asked specifically to seek to encourage the National Center for Toxicological Research, at Pine

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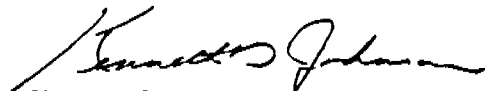
CMA 004547

Bluff, Arkansas, to offer to undertake such a program. Details of the test protocol are to be left open until after the Rall committee makes its report available.

The Research Coordinators asked MCA to call a meeting of the Technical Task Group on Vinyl Chloride Research as soon as the report of Tabershaw-Cooper Associates on their epidemiological study reaches them.

A copy of the MCA news release reporting the Industrial BIO-TEST mouse data has been sent to you in this morning's mail.

Sincerely,



Kenneth D. Johnson, Ph.D.
Secretary
Technical Task Group on
Vinyl Chloride Research

KDJ:mb

Tables Attached

cc : Mr. A. W. Barnes
D. P. Duffield, M.D.
Dr. Tiziano Garlanda
Vinyl Chloride Management Contacts

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TABLE 2

Mouse Mortality Data

DATE	GROUP							
	<u>Controls</u>		<u>TI</u>		<u>TII</u>		<u>TIII</u>	
	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>
February 10, 1974	2	8	6	26	2	4	7	8
April 12, 1974	5	11	9	31	13	7	13	18

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Industrial BIO-TEST Laboratories, Inc

1810 FRONTAGE ROAD

EASTBROOK, ILLINOIS 60062

TABLE II

Summary of Tumors in Vinyl Chloride Exposed Mice
IBT Number 663-03222-MCA

<u>Group, Animal No., Sex</u>	<u>Histopathologic Findings</u>			<u>Date of Death</u>
	<u>Lung</u>	<u>Liver</u>	<u>Skin</u>	
T-I				
1023 Male	AA (s)*	HS (s)**	***	
1110 Female	AA (s), Metastatic Skin Tumor		EC (para-aural)	3-20-74
1119 Female		HS (s)		3-24-74
1200 Female	Metastatic Skin Tumor		EC & MC+ (Femoral region)	3-30-74
T-II				
1347 Female	Metastatic Skin Tumor		EC (Abdomen)	3-5-74
1309 Female		HS (s)		3-18-74
1382 Male	AA (s)	HS		3-25-74
1382 Female		HS (s)		4-2-74
1350 Female	AA (s)	HS (s)		4-5-74
1299 Female	AA (s)		EC & MC (Inguinal Region)	4-9-74
T-III				
1538 Female	AA (s)	HS (s)		3-6-74
1532 Female	AA (s)		LSO	3-7-74
1562 Female	AA (s)	HS (s)		3-8-74
1598 Female	AA (s)	HS (s)		
1405 Male	AA (s)	HS (s)		2-25-
1494 Male	AA (s)	HS (s)		3-22-
1574 Female	AA (s)	HS (s)		3-22-
1531 Female		HS (s)	EC & MC (Femoral region)	3-23-
1588 Female		HS (s)		3-25-
1593 Female	AA (s)	HS (s)		3-30-
1505 Female	AA (s)	HS (s)		4-3-
1565 Female	AA (s)	HS (s)		4-3-
1409 Male	AA (s)	HS (s)		4-5-
1543 Female	AA (s)	HS (s)		4-5-
1544 Female	AA (s)	HS		4-5-
1546 Female	AA (s)	HS (s)	MC (Axillary region)	4-5-
1535 Female	AA (s)	HS (s)		4-7-
1432 Male	AA (s)			4-8-
1477 Female	AA (s) Metastatic Skin Tumor?	HS (s)	EC (Para-Aural) MC (Abdomen) EC (Pelvic region)	

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TABLE III

*Industrial BIO-TEST Laboratories, Inc.*1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062Summary of Mortality & Tumor Data Among Vinyl Chloride Mice
IBT Number 663-03222 (MCA)

Group	No. Mortalities with Neoplasms	Location of Tumors		
		Lung	Liver	Skin Metastasis →
T-I	4 (1 Male, 3 Females)	2(50%)	2(50%)	2(50%) 2
T-II	6 (1 Male, 5 Females)	3(50%)	4(66.7%)	2(33%) 1
T-III	19 (4 Males, 15 Females)	17(89.5%)	17(89.5 %)	3(15.8%)

Key to Symbols

- Alveologenic Adenoma of Lung (AA)
- Hemangiosarcoma of Liver (HS)
- Epidermoid Carcinoma of Skin (EC)
- Mammmary Carcinoma of Skin (MC)
- ⊙ Lymphosarcoma of Thymus
- (a) Multiple tumors of indicated type

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Manufacturing Chemists Association

Record of Meetings

TASK GROUP FOR AUDIT OF VINYL CHLORIDE CHRONIC INHALATION STUDY

Industrial BIO-TEST Laboratories, Inc.
Sheraton Inn

Decatur, Illinois
Decatur, Illinois

February 19-24, 1978

Dr. Bell presided and convened the meetings with the following in attendance at the respective meetings described below:

Industrial BIO-TEST Laboratories Meeting

MEMBERS PRESENT

Z. G. Bell, Chairman
T. J. Benya
G. K. Hatfield
R. K. Hinderer

C. D. Kary
T. R. Torkelson
J. T. Seawell

PPG Industries, Inc.
Ethyl Corporation
Diamond Shamrock Corporation
The BFGoodrich Company,
Chemical Division
Shell Oil Company
The Dow Chemical Company
MCA Staff

GUESTS PRESENT

W. M. Busey

P. Churukian
J. W. Goode
W. J. Koretke
D. C. Lindberg
J. H. Mennear
R. Rhudy
R. J. Roman
D. J. Sullivan
I. Te Vault
M. Vlaovic

Experimental Pathology Laboratories,
Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
Industrial BIO-TEST Laboratories, Inc.
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Meetings of the Task Group for Audit of Vinyl Chloride (VC)
Chronic Inhalation Study at the Sheraton Inn

Dr. Zeb G. Bell, Chairman, and Mr. J. T. Seawell, Project Manager, began work on the development of basic and contingent audit design plans on Sunday, February 19, 1978. Dr. Bell, Dr. C. D. Kary, and Mr. Seawell conducted a general assessment review of all material available for the audit in the administrative offices and laboratories of Industrial BIO-TEST Laboratories, Inc. (IBT), Decatur, during the morning of February 20, 1978.

Dr. Bell opened the initial meeting of the entire Task Group at 1:35 p.m., February 20, 1978 at the Sheraton Inn with only Members Present (see Members Present roster listed above). Additional meetings of the Audit Task Group were held as follows:

February 20, 1978	7:10 p.m. - 10:30 p.m.
February 21, 1978	6:20 p.m. - 9:30 p.m.
February 22, 1978	9:45 p.m. - 12:15 a.m.

All other meetings were held at IBT with IBT management, project supervisors, specialists in necropsy and histopathology, and laboratory technicians present (see Guests Present listed above).

1.0 Background Information

Audit plans were designed with due recognition of and consideration given to the following factors which dictated conditions under which the audit was conducted:

- 1) Initial exposures of test animals began on September 10, 1973.
- 2) The test protocol involved three different animal species, i.e.:

Mice: CDI Swiss Charles River
Rats: COBS Charles River
Hamsters: COBS Golden Syrian
- 3) There were three different exposure levels for the mice and hamsters and four exposure groups of rats. The exposure levels were as follows:

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Controls

Group TE I - 50 ppm
Group TE II - 200 ppm
Group TE III - 2500 ppm
Group TE IV* - 2500 ppm

*Rats only, special cage
conditions for this test
group.

- 4) There were 2,500 test animals.
- 5) Inhalation exposures were initiated and terminated as follows:

<u>Species</u>	<u>Initiated</u>	<u>Terminated</u>
Mice	September 10, 1973	June 10, 1974
Rats*	September 10, 1973	September 10, 1974
Hamsters	September 10, 1973	September 10, 1974

- 6) The last interim report on this research project issued on September 23, 1975. No additional data or reports subsequent to this date were available to the Task Group.
- 7) On Monday morning, February 20, 1978 it was learned that final shipments of VC test documents, organ and tissue evidence from IBT, Northbrook to IBT, Decatur were completed on Friday, February 17, 1978. There were available to the Audit Task Group, only gross inventories of the shipment components.
- 8) No summaries or detailed inventories were available on the:
 - a. Status of necropsy sheets or reports
 - b. Status of histopathology readings
 - c. Wet tissues inventoried or catalogued

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- d. Tissue blocks inventoried by designated animal numbers
- e. Histologic slides available and inventoried by animal numbers

2.0 Audit Designs and Contingency Plan Developed by Task Group Chairman and Project Manager

2.1 Introductory Comments

It is to be emphasized that the intrinsic magnitude of test data and research evidence from 2,500 test animals (in the form of wet tissues, tissue blocks, and histopathologic slides) dictated that audit plans be comprehensive and well designed prior to the initiation of work by any of the audit teams. This being accomplished, then the teams could proceed rapidly and effectively within their respective audit parameters, complete their work within the limited time frame allowed, and have a limited time in which to summarize their findings.

Since no data pertinent to items 7) and 8) (see above) were available prior to the audit design work conducted on February 19, 1978, the Chairman and the Project Manager developed two basic plans by which the in-depth audit could be conducted. The third audit design developed on February 19, 1978 was a contingency plan which was based on an estimate of conditions prior to and immediately following shipment on February 17, 1978 of documents and research evidence from IBT, Northbrook to IBT, Decatur.

2.2 Audit Plan I

This plan was designed to incorporate criteria established by the Food and Drug Administration in their proposed Good Laboratory Practices (GLP) document. Among the more important GLP criteria which guided the audit designs were the following:

- . Was the research being conducted in strict conformity with the protocol and were all pertinent echelons of the research facility briefed on protocol specifications?

- . Analysis of the test agent and exposure chamber concentrations and investigations of possibilities of stratified flow in the test chambers.
- . Test animals - test facilities' procedures for quarantined, randomization, identification, and environment. Possible deviations from these procedures -

Execution of Study:

- . Frequency of observations of animals for possible abnormalities.
- . Clinical laboratory test conducted.
- . Recording of clinical observations in bound laboratory notebooks with appropriate signatures and initials of investigators.
- . Nature of test conducted on animals found dead.

Necropsies (Gross Pathology):

- . Were necropsies performed on all animals?
- . Examination of animals found dead and subject to postmortem autolysis.
- . Supervision of examination by Board Certified Pathologist.
- . Organs described and weighed.
- . Descriptive data on all lesions observed.
- . What wet tissues and tissue blocks were preserved and were these clearly identified or labeled and recorded?
- . Where are wet tissues and histopathologic slides stored and under what storage conditions?

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Histopathology:

- . Who examined what tissues and when were they examined in relation to completion of gross pathology?
- . Records of all tumors or other unusual findings noted on gross examination.
- . Were these findings studied microscopically?

Data, Records, and Reports:

- . The overall laboratory plan for the collection of data.
- . Were all animals involved in the study accurately accounted for?
- . If any errors were observed, what could be their potential impact on the scientific integrity of the study?

Audit Teams and Parameters to be Covered by Each Team

Plan I provided for in-depth analyses of case histories of selected animals within given exposure groups. The audit teams were structured as follows:

Team 1 - Pathology

Audit Parameters

- . Tissue preparation
- . Slide - preparation
- . Slides - storage and retrievability
- . Uncut material or wet tissues - examination of storage of preserved and prepared tissue

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- . Pathology - examination of prepared slides
- . Number of tissues being prepared
- . Organs selected for histopathologic study

Team 2 - General Laboratory Audit

Audit Parameters

- . Body weights
- . Organ weights
- . Analytical chemical data
- . Clinical chemical data
- . Hematological data - blood parameters
- . Clinical observations
- . Air flow in exposure chambers
- . Records of concentrations of test chemical in exposure chambers
- . Cross checks of necropsy sheets with behavioral sheets

Team 3 - Audit and Review of Mortality Data and Reported Lesions

Audit Parameters

All recorded and/or reported mortality data.

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2.3 Audit Plan II

Team 1 - Good Laboratory Practices

Audit Parameters

Animal Data

. Data on Shipment

Source

Shipping date and date of receipt at
test facility

Number shipped - by sex

How many shipped per case

Batch numbers

- . Historic background data - sires, dams
- . Ages at mating
- . Numbers in each litter
- . Individual or gross weights at time of shipment

Animal Preparatory and Test Data

- . Identification of individual animals -
procedure used and tie-in with
identification of tissues (both wet
tissues and tissue blocks)

- . Randomization - procedure used

- . Quarantine - conditions

- . Replacements

Source

Documentation

Previous Environment

- . Initial exposure(s)

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- . Individual weights) _ _ weight change data
Organ weight) _ _ relevant to both

Exposure Chamber Data

- . Concentrations of test chemical
- . Computer printouts
- . Detailed records of down-times and reasons for, duration of
- . Checks for stratified flow in chamber(s)
- . Number of full exposure days
- . Criteria used to determine a full exposure day

Team 2 - Research Procedures up to and Including Necropsy

Audit Parameters

- . Laboratory Notebooks -

Type

System of recording entries

Tie-in with computer entries and printouts

- . Types of observations recorded

- . Mortality incidences

- . Mortality curves

- . Records of postmortem autolysis

- . Clinical observations

- . Mortality Curves Versus Calendar Incidences

Comparative summations of:

Animals found dead versus day of week

Animals sacrificed versus day of week

Records of all tissues saved

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. Necropsy Sheets

What tissues were actually saved - check
for individual animals or conduct random
checks within given exposure groups

Tissues saved versus protocol requirements

Recorded tissue masses -
Time to first tumor observations

Behavioral reactions

Detailed examinations and analyses of
histopathology sheets

Team 3 - Histopathology

Audit Parameters

- . Residual tissues
- . Wet tissue preparation
- . Wet tissue preservation
- . Preservative used for eyes
- . Cataloguing of missing tissues
- . Inventory of "good" tissues and check of
source animal (animal number)

Complete this inventory as soon as
possible to enable Board Certified
Pathologist to conduct confirmatory
observations or readings

- . Number of tissues prepared
- . Type of examinations of pathologic slides
- . Organs selected for histopathologic study

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Possible Target Organs and Organs of Major Concern, e.g.,

Brain	Lungs
Heart	Mammary Gland
Kidneys	Spleen
Liver	Stomach

. Tissue Blocks

Preparation procedure
Preservation
Inventory records - by test animal number

2.4 Audit Plan III

This plan was designed on the basis of findings evolving from the general assessment and review of research documents and materials conducted on February 20, 1978.

The results of the general assessment survey conducted during the morning of February 20, 1978 showed clearly that Plan III would have to be used. Detailed audits based on the original necropsy/histopathology sheets for each control and test animal would have to be conducted and the tissues histopathologically read and/or retained for each test animal would have to be recorded on master audit sheets showing each of the possible 38 organs of each test animal from which tissues reportedly had either been taken, or for which histologic slides had been prepared, or from which wet tissues had been preserved.

The organization of this audit plan is as follows:

Team 1- Histopathology

Audit Team 1, Members

Dr. W. M. Busey
Dr. G. K. Hatfield
Drs. D. J. Sullivan and M. Vlaovic and members
of the IBT histopathology and necropsy staffs

Areas Audited and Work Performed by Audit Team 1

. Inventory of tissues examined microscopically

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- . Random checks of slide readings against recordings on histopathologic summary sheets
- . Verification of slide readings
- . Verification of selected tumor diagnosis
- . Tabulation of angiosarcomas
- . Summary prepared of all tumor diagnoses

Audit Team 2, Members

Dr. T. J. Benya
Dr. R. K. Hinderer
Dr. D. J. Sullivan, Mr. W. J. Koretke,
Ms. I. Te Vault and members of the IBT
staff

Areas Audited and Work Performed by Audit
Team 2, Test Animal - Mice

- . Review of all research entries under
"Gross Pathological Observations"
- . Review of all recorded data under
"Histological Observations"
- . Preparation of summaries of all gross
pathological observations and histological
observations recorded on a possible total
of 38 organs
- . Verification cross checks of "Days on Test"
as recorded on necropsy sheets versus
computer printouts
- . Summaries prepared under 44 classifications
of all tumor data recorded for 17 organs for
all animals in Control and Test Groups T-I,
T-II, and T-III

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Audit Team 3, Members

Dr. Z. G. Bell
Dr. C. D. Kary
Dr. D. J. Sullivan, Dr. M. Vlaovic,
Mr. W. J. Koretke, Ms. I. Te Vault,
and members of IBT staff

Areas Audited and Work Performed by Audit
Team 3, Test Animals - Hamsters

The areas audited and investigations conducted by Audit Team 3 are covered by the descriptive work titles shown under this comparable section under Audit Team 2.

Audit Team 4, Members

Dr. T. R. Torkelson
Mr. J. T. Seawell
Dr. D. J. Sullivan, Dr. M. Vlaovic,
Mr. W. J. Koretke, Ms. I. Te Vault,
and members of IBT staff

Areas Audited and Work Performed by Audit
Team 4, Test Animals - Rats

The areas audited and the investigations performed by Audit Team 4 are covered by the descriptive work titles shown under this comparable section under Audit Team 2. However, Audit Team 4 reviewed all research entries under "Gross Pathological Observations" and "Histological Observations" for Controls, Test Group I, II, III, and IV. The fourth test group for this species of test animal was included in this exposure series to enable comparison with animals subjected to comparable test conditions in the laboratories of Dr. Cesare Maltoni.

Test Group 4 audited gross and histopathological data for 900 test animals, 38 organs per animal, or a total of 34,200 organ

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data summaries. Teams 2 and 3 audited gross and histopathological data for 800 test animals, 38 organs per animal, or a total of 30,400 possible organ entries.

Audit Team 4, as did the other teams, gave special consideration to the following organ tissues of possible specific importance with respect to VC exposure:

Brain	Mammary Gland
Kidney	Spleen
Liver	Stomach
Lung	Zymbal Gland
Lymph Nodes	

3.0 Combined Meeting of the Members of the Task Group for the Audit of Vinyl Chloride Chronic Inhalation Study and the Executive Staff of IBT, Decatur, for the Purpose of Reviewing Findings and Presenting the Recommendations of the Audit Task Group

Dr. T. R. Torkelson presented a thoroughgoing history of the project to date to include work leading up to the acceptance of the protocol by the Technical Panel, a summary of conditions pertinent to the initial exposures, and a chronological recapitulation of dates on which research findings have been made available to the Research Coordinators, and ultimately the Technical Panel.

Dr. Z. G. Bell presented a review of the findings reported in the 23-month status report, and observations evolving from the studies made by the four audit teams of necropsy sheets and histopathologic findings reported to date.

The VC Audit Task Group recommended to the IBT Executive Staff that the following course of action be taken. It was emphasized that these recommendations are based on investigations and observations made at IBT, Decatur during the week of February 20, 1978.

The recommendations presented are as follows:

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3.1 Phase I - An Inventory of All Wet Tissues, Tissues in
Blocks, and Histologic Slides

The Task Group was unanimous in its recommendation that IBT complete the following at the earliest possible time:

1. A complete inventory is to be made of:
 - A. All wet tissues in preservative in plastic containers are to be inventoried by opening each container and specifically identifying all tissues present.
 - B. All tissues in blocks with specific identification of each tissue therein.
 - C. All histologic slides with a complete identification and listing of each tissue for each animal.
 - D. A histopathology sheet is to be used for recording all entries evolving from inventories under A., B., C. above.
 - E. Summary sheets similar to those developed by the Audit Task Group, i.e., 50 animals per sheet/38 organs per animal, are to be used when preparing data summaries.
2. Arrange in order all animals as to the days on test at death by:
 - A. Species
 - B. Group
 - C. Exposure level
 - D. Sex
 - E. Animal numbers

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All animals for which there are no wet tissues, tissue blocks or slides are to be excluded.

3. Data obtained in 1. and 2. (of section 3.1) above are to be sent to MCA for immediate distribution to the Vinyl Chloride Audit Task Group.
4. A meeting is to be arranged in the Chicago area within 4-6 weeks to be attended by the Chief Pathologist of IBT, any other IBT executive concerned with this study, and the members of the Vinyl Chloride Audit Task Group for the purpose of discussing the results of the inventory and reaching a decision concerning the next course of action.
5. If the inventory reveals that adequate data are available to enable the investigations of target organs and suspicious lesions recommended by the consulting pathologist, Dr. W. M. Busey, then IBT is to draft a report which will be forwarded to MCA.
6. The Audit Task Group will comment on the IBT draft report.

3.2 Phase 2 - Alternative Recommendations on IBT Action in the Event that Data Evolving from the Inventory are Insufficient for the Resolution of a Consensus on Effects

In the event that data evolving from the inventories cited above are not sufficient to resolve a consensus on effects, then tissues will be worked-up for specific target organs in low and high exposure levels. If this proves inadequate, then tissues for exposure groups T-I and T-II animals will be histologically examined and reported to the members of the Vinyl Chloride Audit Task Group.

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Item 2 - At this stage, the IBT pathologist and members of the Audit Task Group will proceed according to Phase 1, Step 4 (of section 3.1) described above.

3.3 Procedure to Govern Reading of Histologic Slides

Only one pathologist should be assigned tissue examinations. By no means should different pathologists histologically examine animal tissues from the same species. Further, IBT should use a consistent code of findings when summarizing histopathologic data.

4.0 Concluding Comment by Dr. John H. Mennear, Technical Director, IBT, Decatur

Dr. Mennear stated that he fully recognized the importance of this study and concluded by saying that he wanted to get it completed as promptly as possible.


J. T. Seawell
Project Manager
Vinyl Chloride Research

JTS:ec
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Manufacturing Chemists Association

Record of Meeting

AUDIT TASK GROUP (ATG) OF VINYL CHLORIDE TECHNICAL PANEL

Experimental Pathology
Laboratories, Inc.

Herndon, Virginia

January 8-9, 1979

Dr. Torkelson presided and convened the meeting with the following in attendance:

MEMBERS PRESENT

T. R. Torkelson, Acting Chairman
T. J. Benya
G. K. Hatfield
R. K. Hinderer

C. D. Kary

L. C. Henschel

The Dow Chemical Company
Ethyl Corporation
Diamond Shamrock Corporation
The BFGoodrich Company,
Chemical Division
Shell Oil Company

MCA Staff

PRESENT BY INVITATION

W. M. Busey

Experimental Pathology
Laboratories, Inc.

MEMBER ABSENT

Z. G. Bell

PPG Industries, Inc.

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Fort Worth, Texas

1. Dr. W. M. Busey's Pathology Report

The Audit Task Group (ATG) reviewed and accepted Dr. W. M. Busey's Vinyl Chloride Pathology Report.

2. ATG Report

A draft of the report of the ATG was written and a tentative list of appendixes was prepared. The following items were to be included:

- Dr. W. M. Busey's Pathology Report
- Protocols
- Reports on Site Visits

3. The ATG wishes to express their appreciation for Dr. W. M. Busey's generous hospitality during this meeting.

4. The meeting adjourned at 12:30 p.m.

Lucille C. Henschel

Lucille C. Henschel
Acting Project Manager
Vinyl Chloride Research

LCH: pmt

Record of Meeting Subject to Approval

January 16, 1979

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