



CHEMICAL MANUFACTURERS ASSOCIATION

August 8, 1980

Mr. Fred Current, President
Industrial Bio-Test Laboratories, Inc.
1810 Frontage Road
Northbrook, IL 60062

*Michelle
for VC ch*

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Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

Dear Fred:

I was out of the office for the last couple of weeks and so apologize for not forwarding to you the information you requested during our meeting on July 16, 1980. The total cost to conduct the study at IBT and the estimated interest are summarized below:

\$169,825	Payments to IBT
20,147	Payments to Experimental Pathology Labs
4,000	Payments to Bob West Associates
9,908	CMA administrative expenses from 1973 to 1977
29,759	CMA administrative expenses from 1978 to present
15,000	Estimated expenses incurred by Panel members during various audits and related activities from 1978 to present
103,680	Estimated interest from 1976 to present
<u>\$352,319</u>	TOTAL

Please do not hesitate to call me if you need additional information.

I look forward to a mutually agreeable settlement of this issue.

Thank you.

Sincerely,

Hasmukh Shah

Hasmukh C. Shah, Ph.D.
Director, Special Projects

cc: Dr. Ted Torkelson
Dr. Zeb Bell
Mr. Roger Lockhead

CMA 001315

Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.

MANUFACTURING CHEMISTS ASSOCIATION

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

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14th Judicial District Court
Calcasieu Parish, Louisiana

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

Make
sure
This is
in TL
w/ all
~~the~~ docs
in appendixes

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

CMA 001316

February 1, 1

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).

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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.

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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 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 ~~the~~ (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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14th Judicial Parish,
Calcasieu

February 1, 1

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).

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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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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
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 (4-6 μ), stained with hematoxylin 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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MANUFACTURING CHEMISTS ASSOCIATION

1025 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.
1610 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) 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.

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Calcasieu Parish, Louisiana

CMA 001328

Dr. J. C. Calanora
May 18, 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. R. Carnes

Accepted for:

Industrial BIO-TEST
Laboratories, Inc.

Signed *J. T. Tschann*

Title President

Date May 22, 1973

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14th Judicial District Court
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CMA 001329

Sept. 7, 197

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

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.

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Calcasieu Parish, Louisiana

CMA 001330

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. S. Roman

Title Assistant to the President

Date September 7, 1973

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Calcasieu Parish, Louisiana

CMA 001331

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

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CMA 001332

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

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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
Corporate Medical Department

kjf

encl.

cc: Distribution List Attached.



CMA 001333

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. I. 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

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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

SURVIVING ANIMALS AT INT AS OF JAN. 20, 1975

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

() Indicates moribund or sick animals sacrificed this date.

* To be kept indefinitely.

** To be kept at least until March 10.

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Industrial BIO-TEST Laboratories, Inc.

DECATUR RESEARCH
1800 EAST PERSHING ROAD
DECATUR, ILLINOIS 62526

August 2, 1973

AREA CODE 217
TELEPHONE 877-9254

MENTAL SCIENCES
SCIENCES
SCIENCES

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

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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 001336

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

UG/dm

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Order in
Ross v. Conoco, Inc.,
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Calcasieu Parish, Louisiana

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MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N.W. WASHINGTON, D.C. 20001 (202) 463-0126

ALBERT C. CLARK
VICE PRESIDENT
GENERAL DIRECTOR

August 3, 1973

John W. Goode, Ph.D., Manager
Decatur Research Laboratories
Industrial Bio-Test Laboratories, Inc.
1800 East Pershing Road
Decatur, Illinois 62526

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Calcasieu Parish, Louisiana

Dear Dr. Goode:

Thank you for the courtesies extended to Mr. Harry Slatin and the representatives of our member companies, Dr. T. R. Kelson, 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 need.

MCA and its member representatives concur with you that a start 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,

Albert C. Clark

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Calcasieu Parish,, Louisiana

June 15, 1973

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

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 incompleeted 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:

1 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

CMA 001339

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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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.

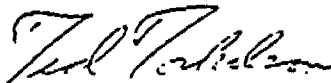
Everything appeared to be in order on shipment and delivery of samples and there was understanding what would be done to assure a supply on hand at all times.

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

la

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INTER-OFFICE CORRESPONDENCE

To: R. E. Widing

Date: August 6, 1973

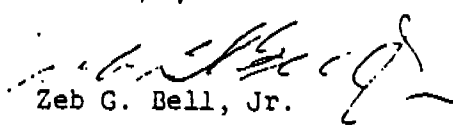
From: Zeb G. Bell, Jr.

Location: 12 East

Subject: Industrial Biotech
Laboratory Visit,
Decatur, Illinois

As a member of the MCA-VCM Technical Coordinators Task Group, the undersigned visited the Industrial Biotech Laboratory facility in Decatur, Illinois, where the MCA innelation 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 Biotech 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)
J. T. R. Torkelson (Dow)

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MANUFACTURING CHEMISTS ASSOCIATION

1925 CONNECTICUT AVENUE, N.W. WASHINGTON, D.C. 20009 (202) 483-6126

Memorandum

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

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

August 10, 1973
Subject to Protective Order in
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Calcasieu Parish, Louisiana

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	<u>MCA</u>	<u>IBL</u>
	Dr. T. R. Torkelson	Dr. J. W. Goode
	Dr. Z. G. Bell, Jr.	Mr. Ken Schadeberg
	Dr. W. D. Harris	Mr. Dennis Lindberg
	Mr. H. L. Kusnetz	
	Mr. H. L. Slatin	

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.

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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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TABLE I

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

NORTHBROOK, 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
1889 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)	IIS (s)		
1405 Male	AA (s)	HS (s)		2-25-74
1494 Male	AA (s)	HS (s)		3-22-74
1574 Female	AA (s)	IIS (s)		3-22-74
1531 Female		HS (s)	EC & MC (Femoral region)	3-23-74
1588 Female		HS (s)		3-25-74
1593 Female	AA (s)	HS (s)		3-30-74
1505 Female	AA (s)	IIS (s)		4-3-74
1565 Female	AA (s)	IIS (s)		4-3-74
1409 Male	AA (s)	IIS (s)		4-5-74
1543 Female	AA (s)	HS (s)		4-5-74
1544 Female	AA (s)	IIS		4-5-74
1546 Female	AA (s)	HS (s)	MC (Axillary region)	4-5-74
1535 Female	AA (s)	HS (s)		4-7-74
1432 Male	AA (s)			4-8-74
1477 Female	AA (s) Metastatic Skin Tumor?	HS (s)	EC (Para-Aural) MC (Abdomen) EC (Pelvic region)	4-9-74

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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)
- + Mammary Carcinoma of Skin (MC)
- ⊕ Lymphosarcoma of Thymus
- (s) Multiple tumors of indicated type

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