



CHEMICAL MANUFACTURERS ASSOCIATION

September 11, 1979

Mr. Fred R. Currant
Corporate Counsel
Industrial BIO-TEST Laboratories, Inc.
1810 Frontage Road
Northbrook, Illinois 60062

Dear Fred:

An agreement dated February 1, 1973, was signed between Industrial BIO-TEST Laboratories, Inc. (IBT) and the Chemical Manufacturers Association (CMA), formerly the Manufacturing Chemists Association, for IBT to conduct a "Chronic Vapor Inhalation Study with Vinyl Chloride". This agreement was extended to include an additional exposure group on May 22, 1973. References to this study in communications received by CMA from IBT bear the study identification of IBT No. 663-03222. The experimental design incorporated in the protocol appears in Appendix A, which is attached.

The Vinyl Chloride Audit Task Group and the pathologist serving as a consultant to CMA have expended in excess of 1,000 hours auditing and studying ways in which data of meaningful value might be salvaged from this research agreement. After their large expenditure of time and money, little or nothing of salvageable value has evolved, and it must be concluded the study has gross, irreparable deficiencies.

Little value can evolve from audits of other equally important records and research material, since inadequate pathologic studies and/or observations and insufficient numbers of tissues preclude scientifically valid conclusions on tumor incidence and dose-response relationships.

Data presented show that there is just cause that IBT (1) reimburse CMA for all costs of administering and auditing the agreement of February 1, 1973, as amended, (2) refund to CMA all funds paid to IBT against this agreement, and (3) supply funds required in excess of (2) to permit CMA to have the program, as amended, properly conducted at another laboratory.

Sincerely yours,

Edmund B. Frost
Vice President
and General Counsel

EBF:jbf
Enclosures

bcc: J. T. Seawell (Appendix A and your memo, 7/20/79, are enclosures)
1825 Connecticut Avenue, NW • Washington, DC 20009 • Telephone 202/328-4200 • Telex 89617 (CMA WSH)

URL 16180

APPENDIX A

Experimental Design for Vinyl Chloride Study

Group	Mice		Number of Animals Rats		Hamsters		Specified Exposure Levels
	M	F	M	F	M	F	
Control	100	100	100	100	100	100	-
T1*	100	100	100	100	100	100	50 ppm vinyl chloride
T2*	100	100	100	100	100	100	200 ppm vinyl chloride
T3*	100	100	100	100	100	100	2500 ppm vinyl chloride
T4**	-	-	100#		-	-	2500 ppm vinyl chloride

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

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

#All rats of same sex, females were exposed.

URL 16181

CMA INTEROFFICE MEMO

July 20, 1979

To: Edmund B. Frost

An agreement dated February 1, 1973 was signed between Industrial BIO-TEST Laboratories, Inc. (IBT) and the Chemical Manufacturers Association (CMA), formerly the Manufacturing Chemists Association, for IBT to conduct a "Chronic Vapor Inhalation Study with Vinyl Chloride". This agreement was extended to include an additional exposure group on May 22, 1973. References to this study in communications received by CMA from IBT bear the study identification of IBT No. 663-03222. The experimental design incorporated in the protocol appears in Appendix A, which is attached.

Calculations and compilations contributing to tissue accountability summaries presented in this communication were based primarily on the tissue inventory conducted by IBT personnel at the request of the Vinyl Chloride Audit Task Group (ATG). Allow me to emphasize that the ATG only partially validated the IBT inventory.

The ATG concerned itself initially with histology and histopathology rather than with other phases of this study since they recognized that conclusions relative to tumor incidence and to dose-response relationships would have little scientific validity without adequate histologic and pathologic materials and observation records. Therefore, the ATG has confined itself solely to a partial audit of existing tissues, tissue blocks, slides, and records of gross and histopathologic examinations. The initial audit efforts were concerned with a total organ accountability for each test animal based on necropsy sheets, histopathology sheets, and pertinent laboratory logs.

The IBT inventory of all tissues was completed after the transfer of all records and research material to IBT, Decatur, from IBT, Northbrook. The ATG was informed that the inventory includes all tissues, tissue blocks, and slides currently in storage. IBT inventory data are presented in the entry shown in the Tissue Accountability Summary (see Appendix B) under the caption "Total Tissues Available".

In the opinion of the ATG, the technical conduct of this study is grossly deficient as indicated by the following partial list of observations:

URL 16182

- 1) IBT failed to save most tissues as specified in the protocol.
- 2) IBT failed to conduct histopathologic examinations of many of the tissues that were saved.
- 3) Even though all currently available (according to the IBT conducted inventory) tissues were to be examined, the number would still be grossly inadequate to complete the objectives of the study.

As an example of observation 2) presented above, of 42 male rats in the top dose level (exposure concentration of 2,500 ppm) surviving at the end of one year exposure period, brains of only nine animals were saved for histopathologic examination. Of these, only four were made into microscopic slides and examined. Hence, 90% of the brains of those animals surviving to the most critical time period were never examined.

The overall deficiency is shown dramatically in the Tissue Availability Summary presented as Appendix B. The number of tissues per animal should range from 44 to 40 for males and 43 to 39 for females. Tissues from double organs (lung, kidney, testes, etc.) were often arranged on a single slide and this results in variations in the manner in which tissues from double organs are counted. Therefore, for purposes of total tissue accountability and relevant percentage computations, the ATG used the smaller of the two figures for each sex when computing data shown in Appendix B.

Percentages of total tissues examined by IBT and percentages of total tissues available as presented in the following discussions under specified test animals are all based on the respective protocol tissue requirements shown in Appendix B under the entries entitled "Tissues Required by Protocol".

The following examples of observations relevant to Appendix B are summarized under the respective test animals:

Rats-Male

According to IBT's own inventory, of test Groups II and III, only 26.5% and 27.6% of the tissues required by the protocol are currently available. Of these, only 17.6% and 9.6%, respectively, of the tissues required by the protocol were examined by IBT pathologist(s).

Rats-Female

In test Groups II and III only 23% and 25%, respectively, are available according to IBT's inventory. Of these, only 10% and 8%, respectively, were examined histologically.

Thus, for rats, the highest percentage of tissues available is 28%, far below the generally recognized minimum acceptable level of 95% accountability.

Mice-Male

Again in the crucial test Groups T-II and T-III the total tissues currently available are 18% and 19%, respectively, and of these tissues only 7% and 5%, respectively, were examined by an IBT pathologist(s).

Mice-Female

In the same above-mentioned test Groups, T-II and T-III, the total tissues available are only 24% and 23%, respectively, and of these, 7% and 5%, respectively, were examined by an IBT pathologist(s).

Thus, for the two top levels for this species, the highest percentage of tissues available is 71% below the generally recognized minimum acceptable level.

Hamsters-Male

Only 19%, of the total tissues required by the protocol are available for test Groups T-II and T-III, and of these, only 11% and 8% respectively, were examined.

Hamsters-Female

In test Groups T-II and T-III only 17% and 12%, respectively, of the total tissues required by the protocol are available. Of these, only 12% and 4%, respectively, were examined.

Therefore, for the two highest exposure levels for this test species, the highest percentage of tissues available is 76% below the minimum acceptable level.

Controls-All Test Animals

The percentages of tissues available as required by the protocol for all control animals (as shown in Appendix B) ranges from a "high" 32% to a low of 10%. Therefore, for the control groups for all test animals the highest percentage of tissues available is 63% below the minimum acceptable level of 95%.

Summary

The Vinyl Chloride Audit Task Group and the pathologist serving as a consultant to CMA have expended in excess of 1,000 hours auditing and studying ways in which data of meaningful value might be salvaged from this research agreement. After their large expenditure of time and money, little or nothing of salvageable value has evolved, and it must be concluded the study has gross, irreparable deficiencies.

Little value can evolve from audits of other equally important records and research material, since inadequate pathologic studies and/or observations and insufficient numbers of tissues preclude scientifically valid conclusions on tumor incidence and dose-response relationships.


J. T. Seawell

JTS:pmt
Attachments

URL 16185

APPENDIX A

Experimental Design for Vinyl Chloride Study

Group	Mice		Number of Animals Rats		Hamsters		Specified Exposure Levels
	M	F	M	F	M	F	
Control	100	100	100	100	100	100	-
T1*	100	100	100	100	100	100	50 ppm vinyl chloride
T2*	100	100	100	100	100	100	200 ppm vinyl chloride
T3*	100	100	100	100	100	100	2500 ppm vinyl chloride
T4**	-	-	100#		-	-	2500 ppm vinyl chloride

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

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

#All rats of same sex, females were exposed.

APPENDIX B

TISSUE ACCOUNTABILITY SUMMARY

According to:

- I. Tissues Required by Protocol
- II. Tissues Examined by IBT
- III. Total Tissues Available According to IBT Inventory

	<u>Untreated Controls</u>		<u>Group T-1</u>		<u>Group T-2</u>		<u>Group T-3</u>		<u>Group T-4</u>	
	<u>Totals</u>	<u>Per Cent</u>	<u>Totals</u>	<u>Per Cent</u>	<u>Totals</u>	<u>Per Cent</u>	<u>Totals</u>	<u>Per Cent</u>	<u>Totals</u>	<u>Per Cent</u>
<u>RATS - MALE</u>										
Tissues Required by Protocol	4,000		4,000		4,000		4,000			
Total Tissues Examined by IBT	590	14.75	588	14.70	706	17.65	386	9.65		
Total Tissues Available	998	24.95	930	23.25	1,061	26.52	1,103	27.57		
<u>RATS - FEMALE</u>										
Tissues Required by Protocol	3,900		3,900		3,900		3,900		3,900	
Total Tissues Examined by IBT	815	20.89	475	12.17	395	10.12	299	7.66	377	9.66
Total Tissues Available	1,263	32.38	853	21.87	908	23.28	970	24.87	856	21.94
<u>MICE - MALE</u>										
Tissues Required by Protocol	4,000		4,000		4,000		4,000			
Total Tissues Examined by IBT	262	6.55	349	8.72	284	7.10	205	5.12		
Total Tissues Available	497	12.42	548	13.70	739	18.47	766	19.15		
<u>MICE - FEMALE</u>										
Tissues Required by Protocol	3,900		3,900		3,900		3,900			
Total Tissues Examined by IBT	314	8.05	295	7.56	289	7.41	208	5.33		
Total Tissues Available	402	10.30	599	15.35	942	24.15	910	23.33		
<u>HAMSTERS - MALE</u>										
Tissues Required by Protocol	4,000		4,000		4,000		4,000			
Total Tissues Examined by IBT	333	8.32	384	9.60	453	11.32	315	7.87		
Total Tissues Available	511	12.77	485	12.12	743	18.57	761	19.02		
<u>HAMSTERS - FEMALE</u>										
Tissues Required by Protocol	3,900		3,900		3,900		3,900			
Total Tissues Examined by IBT	222	5.69	217	5.56	485	12.43	167	4.28		
Total Tissues Available	372	9.53	406	10.41	677	17.35	454	11.64		