

**R&S 112122**

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

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VINYL CHLORIDE PATHOLOGY REPORT

Submitted to  
Manufacturing Chemists Association  
Washington, D.C. 20009

January 9, 1979

Chemical Manufacturers Association

VINYL CHLORIDE PROJECT PANEL

Washington Hilton  
Georgetown West

0000359

March 18, 1980

11:00 a.m.

PROPOSED AGENDA

1. Introduction and Purpose of the Meeting
2. Background Information on Industrial BIO-TEST research project and an audit of this study by Experimental Pathology Laboratory
3. Disposition of Busey Report
4. Additional treatment and disposition of Industrial BIO-TEST data and tissues
5. Termination of Industrial BIO-TEST Contract and legal claim
6. Other follow-up work

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## VINYL CHLORIDE PATHOLOGY REPORT

## I. Introduction

At the request of the Manufacturing Chemists Association, Experimental Pathology Laboratories, Inc. provided a pathologist (Dr. William Busey) to assist in a partial pathology audit of a chronic inhalation study on vinyl chloride conducted at Industrial Bio-Test Laboratories in Decatur, Illinois. This audit was conducted during the week of February 20, 1978 at the IBT Laboratory in Decatur, Illinois. Dr. Busey participated as a member of the audit team and initially his responsibilities were to audit the histopathological findings. Because of the size of the study (2500 animals), and the number of tissues (31 organs per animal) called for to be examined in the protocol, the members of the audit task force were divided into three teams. Dr. Busey was assigned to audit team No. 1 along with Dr. G.K. Hatfield from Diamond Shamrock Corporation, and Drs. Sullivan and Vlaovic from IBT. The details of the tasks performed by audit team No. 1 are presented in the following section of this report.

Prior to the initiation of the audit, EPL was provided with a protocol of the study. The following table depicts the experimental design and group designations:

## Experimental Design for Vinyl Chloride Study

| Group   | Number of Animals |     |      |     |          |     | Specified Exposure Levels+ |
|---------|-------------------|-----|------|-----|----------|-----|----------------------------|
|         | Mice              |     | Rats |     | Hamsters |     |                            |
|         | 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    |

+Exposure levels have not been verified by audit team

\*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

The protocol as amended called for exposure of the above groups six hours per day, five days per week. Mice were to be exposed for nine months, rats and hamsters for twelve months. These groups were originally scheduled to be held for equal additional periods of time (nine or twelve months) but subsequently it was agreed they would be kept for their lifetime or sacrificed if seriously ill. All animals were to be necropsied either at the time of death or sacrifice and a specified set of tissues was to be preserved in 10% neutral buffered formalin. These tissues were to be examined from all animals in the control, T2 and T3 groups. If exposure related lesions were detected in the organs of the T2 or T3 groups, these same organs from the T1 group were to be examined.

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## II. Audit Tasks

Several tasks were assigned to audit team No. 1. These tasks were directed toward: (a) an assessment of the histopathology data developed by the IBT pathologists, (b) an enumeration of the neoplasms diagnosed by IBT, and (c) a verification of the number of tissues examined by IBT microscopically. In addition, EPL was asked to summarize the tissue counts performed by IBT from examination of all of the wet tissue bags, paraffin blocks and microscope slides. This latter task was subsequently performed at EPL.

### A. Examination of IBT Histopathology Data from Computer Printouts

The recorded diagnoses of the IBT pathologists had been input into a computer which in turn generated a series of printouts listing the findings and separating the neoplastic from the non-neoplastic diagnoses. Working with the IBT printout of the neoplastic diagnoses, summary neoplasm tables were generated by EPL for each of the three species. The number of organs indicated as examined by IBT pathologists was tabulated by the audit team, thus providing a denominator for comparative purposes. These neoplasm summaries are found in Tables I, II, and III.

In addition to summarizing all of the neoplasms, the audit team extracted all of the diagnoses of angiosarcoma and prepared a separate incidence table for this diagnosis. A summary of the diagnosis of angiosarcoma in any organ, expressed as a percentage of the number of animals examined, is found in Table IV.

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B. Microscopic Examination of Selected Neoplastic and Non-neoplastic Lesions Diagnosed by IBT Pathologists

Following examination of the computer printout containing the diagnoses rendered by the IBT pathologists for the various organs examined, selected tissues were examined microscopically. In general, this second microscopic examination correlated well with the original diagnoses and no discrepancies were noted. The only discrepancies noted were set of slides from apparently two different animals containing the same animal numbers. Since all of the slides were not examined, no assessment of the magnitude of this problem could be made.

C. Verification of Number of Tissues Examined Microscopically

During the audit selected neoplastic and non-neoplastic lesions were reexamined microscopically, and tissue counts were made from the microscope slides for selected animals. These counts were then checked against the rough pathology reports to assess whether all of the tissues available for microscopic examination were in fact examined. For these selected animals, no discrepancies were noted and the number of tissues available for microscopic examination correlated well with those that were reported.

D. Summarization of Counts of Wet Tissue, Paraffin Blocks and Microscope Slides Conducted by IBT Personnel

At the request of the vinyl chloride audit task force, IBT examined all of the wet tissues, paraffin blocks and slides from the animals used in the study. This examination consisted of the identi-

fication and counting of the various tissues that were available for possible microscopic evaluation. These counts were submitted on several individual forms and in order to properly evaluate these data, EPL summarized these counts by group, sex, and species. These summaries are presented in Tables V, VI, and VII.

### III. Summary and Recommendation

Inspection of the recorded IBT histopathologic findings clearly indicate that the inhalation exposure of rats, hamsters, and mice to vinyl chloride at 50, 200 and 2500 ppm results in a carcinogenic effect in the liver. This carcinogenic effect was manifest by the development of angiosarcomas, many of which metastasized to regional lymph nodes and the lung. Even though the histopathology is incomplete, the number of angiosarcomas observed clearly indicates the carcinogenicity of vinyl chloride to these three species of laboratory animals. Other neoplasms were observed and reported but because of the paucity of numbers of specific organs examined, conclusive statements about their relationship to vinyl chloride exposure cannot be made. Tumors of Zymbal's gland were seen in all of the exposure groups in the rats and probably are related to the exposure to vinyl chloride. However, only a small number of these organs were examined in each of the control and exposed groups. Malignant tumors of the mammary gland were seen to a greater degree in the exposed female rats; but, here again, the number of mammary glands examined was small and inconsistent. Therefore, conclusive statements

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cannot be made. Four tumors of the central nervous system were seen. One of these occurred in a Group II male and three occurred in Group III males. These are important findings in light of recent epidemiological data in man, but their relationship to the exposure to vinyl chloride in this study is undetermined because of the small number of brains examined.

Primary lung tumors occurred with greater frequency in both sexes of vinyl chloride exposed mice at all concentrations. These primary lung tumors were both benign and malignant and were diagnosed as alveolo-genic adenomas and carcinomas. Inspection of the IBT pathology reports indicates that approximately 50% of the lungs from the mice were examined microscopically. This number of lungs is sufficient to conclude that the inhalation exposure of vinyl chloride to male and female mice had a carcinogenic effect in the lungs.

Primary lung tumors were only seen in the male and female hamsters exposed to 2500 ppm of vinyl chloride. Two bronchiolar carcinomas were seen in the males and one in the females, and one bronchiolar adenoma was seen in the males. Primary lung tumors of the hamster are relatively rare; therefore, the presence of these five neoplasms may be meaningful and related to vinyl chloride exposure.

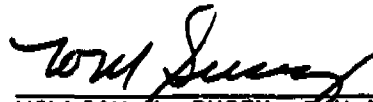
Since microscopic examination of a few selected neoplastic and non-neoplastic lesions diagnosed by the IBT pathologists did not reveal any meaningful discrepancies, it would appear that the histopathology conducted on the tissues from these animals was done accurately. Similar

spotchecks of the number of tissues reported to have been examined did not reveal any significant discrepancies.

Inspection of the tissue counts conducted by the IBT personnel of the wet tissue, paraffin blocks and microscope slides indicate that significantly fewer tissues were available for microscopic examination than were called for by the protocol. The reason for this discrepancy became apparent when the necropsy sheets and animal observation books were examined. The tissue from a large number of the animals in this study was not obtained. This discrepancy is unfortunate in light of the fact that the inhalation exposure of these three species of laboratory animals to vinyl chloride might have provided further definition of the pathology produced, the relationship to dose and the variation between species.

In conclusion, the results of this investigation revealed some rather severe deficiencies in the conduct of this study, primarily with regard to the numbers of tissues that were saved. The pathologic evaluation of the limited material that was available appears to have been conducted accurately. The available data indicate that vinyl chloride at 50, 200 and 2500 ppm has a carcinogenic effect on the liver of rats, mice and hamsters and a carcinogenic effect on the Zymbal's gland of the rat. Similarly, there appears to be a carcinogenic effect in the lungs of the mice. These conclusions are based upon the assumption that the concentrations expressed in this report were actually achieved

and maintained throughout the course of the study. Any significant excursions in the low level (50 ppm) may negate the conclusion of the carcinogenic effect of vinyl chloride at this level. Because of the serious deficiency in the number of tissues saved from animals in both the control and exposed groups, it is recommended to MCA that no further pathology work be done on this study.



WILLIAM M. BUSEY, D.V.M., Ph.D.  
Pathologist

1/9/77

WMB/sfh

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TABLE I  
RAT - TUMOR SUMMARY DATA

|                         | Control<br>Male | Control<br>Female | T1<br>Male | T1<br>Female | T2<br>Male | T2<br>Female |
|-------------------------|-----------------|-------------------|------------|--------------|------------|--------------|
| ADRENAL (No. Examined)  | (11)            | (26)              | (8)        | (9)          | (19)       | (7)          |
| Cortical Carcinoma      |                 | 1                 |            | 1            |            |              |
| Cortical Adenoma        |                 | 1                 |            |              |            |              |
| Medullary Carcinoma     |                 |                   |            |              |            |              |
| BRAIN (No. Examined)    | (10)            | (21)              | (8)        | (7)          | (18)       | (4)          |
| Neuroepithelioma        |                 |                   |            |              | 1          |              |
| CECUM (No. Examined)    | (10)            | (21)              | (8)        | (7)          | (17)       | (4)          |
| Lymphosarcoma           |                 |                   |            |              | 1          |              |
| DUODENUM (No. Examined) | (7)             | (9)               | (1)        | (6)          | (16)       | (4)          |
| Lymphosarcoma           |                 |                   |            |              | 1          |              |
| HEART (No. Examined)    | (69)            | (60)              | (74)       | (52)         | (64)       | (59)         |
| Angiosarcoma            |                 |                   |            |              |            |              |
| KIDNEYS (No. Examined)  | (70)            | (72)              | (75)       | (60)         | (68)       | (70)         |
| Lymphosarcoma           |                 |                   | 1          |              | 1          |              |
| Nephroblastoma          |                 |                   | 1          |              |            |              |
| Reticulum Cell Sarcoma  | 2               |                   | 1          | 1            |            |              |
| Tubular Adenoma         |                 |                   | 3          | 1            |            |              |
| Lipoma                  |                 |                   |            |              |            | 1            |
| Metastatic Angiosarcoma |                 |                   |            | 1            |            |              |
| LIVER (No. Examined)    | (70)            | (73)              | (77)       | (62)         | (69)       | (72)         |
| Angiosarcoma            |                 |                   | 11         | 17           | 35         | 47           |
| Heptocellular Carcinoma |                 |                   |            |              | 1          |              |
| Lymphosarcoma           |                 |                   | 1          |              | 2          |              |

TABLE I  
RAT - TUMOR SUMMARY DATA

|                         | T3<br>Male | T3<br>Female | T4<br>Female | T4<br>Male<br>None |  |  |
|-------------------------|------------|--------------|--------------|--------------------|--|--|
| ADRENAL (No. Examined)  | (5)        | (5)          | (6)          |                    |  |  |
| Cortical Carcinoma      |            |              |              |                    |  |  |
| Cortical Adenoma        |            |              |              |                    |  |  |
| Medullary Carcinoma     |            |              | 1            |                    |  |  |
| BRAIN (No. Examined)    | (6)        | (0)          | (5)          |                    |  |  |
| Neuroepithelioma        | 3          |              |              |                    |  |  |
| CECUM (No. Examined)    | (3)        | (0)          | (5)          |                    |  |  |
| Lymphosarcoma           |            |              |              |                    |  |  |
| DUODENUM (No. Examined) | (3)        | (1)          | (5)          |                    |  |  |
| Lymphosarcoma           |            |              |              |                    |  |  |
| HEART (No. Examined)    | (71)       | (62)         | (64)         |                    |  |  |
| Angiosarcoma            |            |              | 1            |                    |  |  |
| KIDNEYS (No. Examined)  | (75)       | (69)         | (69)         |                    |  |  |
| Lymphosarcoma           |            | 1            |              |                    |  |  |
| Nephroblastoma          |            |              |              |                    |  |  |
| Reticulum Cell Sarcoma  |            |              |              |                    |  |  |
| Tubular Adenoma         |            |              |              |                    |  |  |
| Lipoma                  |            |              |              |                    |  |  |
| Metastatic Angiosarcoma |            |              |              |                    |  |  |
| LIVER (No. Examined)    | (78)       | (69)         | (70)         |                    |  |  |
| Angiosarcoma            | 51         | 63           | 49           |                    |  |  |
| Heptocellular Carcinoma |            |              |              |                    |  |  |
| Lymphosarcoma           |            |              |              |                    |  |  |

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TABLE I  
RAT - TUMOR SUMMARY DATA

|                                            | Control<br>Male | Control<br>Female | T1<br>Male | T1<br>Female | T2<br>Male | T2<br>Female |
|--------------------------------------------|-----------------|-------------------|------------|--------------|------------|--------------|
| LIVER (continued)                          |                 |                   |            |              |            |              |
| Reticulum Cell Sarcoma                     | 3               | 4                 | 2          | 1            |            |              |
| Metastatic Adreno-cortical<br>Carcinoma    |                 |                   |            | 1            |            |              |
| LUNG (No. Examined)                        | (73)            | (73)              | (77)       | (58)         | (71)       | (68)         |
| Alveologenic Adenoma                       |                 |                   | 1          |              |            |              |
| Bronchogenic Adenocarcinoma                |                 |                   |            |              | 1          |              |
| Bronchogenic Adenoma                       | 1               |                   | 1          |              | 1          |              |
| Bronchiolar-Alveolar Adenoma               |                 |                   | 1          |              | 1          |              |
| Angiosarcoma                               |                 |                   |            |              |            | 2            |
| Lymphosarcoma                              |                 |                   |            |              | 2          |              |
| Reticulum Cell Sarcoma                     | 2               | 4                 | 2          | 1            |            |              |
| Metastatic Angiosarcoma                    |                 |                   | 9          | 7            | 24         | 28           |
| Metastatic Hepatocellular<br>Carcinoma     |                 |                   |            |              | 1          |              |
| Metastatic Fibrosarcoma                    | 1               |                   |            |              |            |              |
| Metastatic Mammary Gland<br>Adenocarcinoma |                 | 1                 |            | 2            |            |              |
| Metastatic Zymbal's Gland<br>Carcinoma     |                 |                   |            |              |            | 1            |
| Metastatic Adreno-cortical<br>Carcinoma    |                 | 1                 |            |              |            |              |
| Metastatic Adenocarcinoma<br>N.O.S.        |                 |                   |            |              |            |              |
| MESENTERY (No. Examined)                   | (2)             | (3)               | (12)       | (11)         | (31)       | (43)         |
| Metastatic Hepatocellular<br>Carcinoma     |                 |                   |            |              | 1          |              |

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TABLE I  
RAT - TUMOR SUMMARY DATA

|                                            | T3<br>Male | T3<br>Female | T4<br>Female | T4<br>Male<br>None |  |  |
|--------------------------------------------|------------|--------------|--------------|--------------------|--|--|
| LIVER (continued)                          |            |              |              |                    |  |  |
| Reticulum Cell Sarcoma                     | 1          |              |              |                    |  |  |
| Metastatic Adreno-cortical<br>Carcinoma    |            |              |              |                    |  |  |
| LUNG (No. Examined)                        | (78)       | (70)         | (69)         |                    |  |  |
| Alveologenic Adenoma                       | 2          |              |              |                    |  |  |
| Bronchogenic Adenocarcinoma                |            |              |              |                    |  |  |
| Bronchogenic Adenoma                       |            |              |              |                    |  |  |
| Bronchiolar-Alveolar Adenoma               |            |              |              |                    |  |  |
| Angiosarcoma                               | 1          | 2            |              |                    |  |  |
| Lymphosarcoma                              |            |              |              |                    |  |  |
| Reticulum Cell Sarcoma                     | 1          |              |              |                    |  |  |
| Metastatic Angiosarcoma                    | 32         | 37           | 36           |                    |  |  |
| Metastatic Hepatocellular<br>Carcinoma     |            |              |              |                    |  |  |
| Metastatic Fibrosarcoma                    |            |              |              |                    |  |  |
| Metastatic Mammary Gland<br>Adenocarcinoma |            | 2            |              |                    |  |  |
| Metastatic Zymbal's Gland<br>Carcinoma     |            |              |              |                    |  |  |
| Metastatic Adreno-cortical<br>Carcinoma    |            |              |              |                    |  |  |
| Metastatic Adenocarcinoma<br>N.O.S.        |            |              | 1            |                    |  |  |
| MESENTERY (No. Examined)                   | (37)       | (37)         | (43)         |                    |  |  |
| Metastatic Hepatocellular<br>Carcinoma     |            |              |              |                    |  |  |

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TABLE I  
RAT - TUMOR SUMMARY DATA

|                            | Control<br>Male | Control<br>Female | T1<br>Male | T1<br>Female | T2<br>Male | T2<br>Female |
|----------------------------|-----------------|-------------------|------------|--------------|------------|--------------|
| MESENTERY (continued)      |                 |                   |            |              |            |              |
| Angiosarcoma               | 2               |                   |            | 12           | 29         | 42           |
| Reticulum Cell Sarcoma     |                 | 2                 | 1          |              |            |              |
| PANCREAS (No. Examined)    | (35)            | (39)              | (38)       | (23)         | (23)       | (8)          |
| Islet Cell Adenoma         | 7               | 1                 | 1          |              |            |              |
| PARATHYROID (No. Examined) | (6)             | (5)               | (2)        | (9)          | (8)        | (1)          |
| Adenoma                    | 1               |                   |            |              |            |              |
| PITUITARY (No. Examined)   | (9)             | (18)              | (9)        | (5)          | (12)       | (5)          |
| Chromophobe                | 8               | 14                | 4          | 3            | 5          |              |
| PLEURA (No. Examined)      | (0)             | (0)               | (0)        | (1)          | (4)        | (7)          |
| Angiosarcoma               |                 |                   |            |              | 4          | 5            |
| Reticulum Cell Sarcoma     |                 |                   |            |              |            |              |
| Metastatic Angiosarcoma    |                 |                   |            | 1            |            | 1            |
| PROSTATE (No. Examined)    | (9)             |                   | (10)       |              | (19)       |              |
| Adenocarcinoma             |                 |                   |            |              | 1          |              |
| SKIN (No. Examined)        | (19)            | (12)              | (12)       | (4)          | (17)       | (4)          |
| Fibroma                    | 7               | 1                 | 5          | 1            |            |              |
| Fibrosarcoma               | 2               | 2                 | 1          | 3            |            | 1            |
| Lipoma                     | 1               |                   |            |              |            |              |
| Liposarcoma                |                 |                   |            |              |            |              |
| Sarcoma, N.O.S.            | 1               | 1                 |            |              |            |              |
| Reticulum Cell Sarcoma     |                 |                   |            | 1            |            |              |
| Squamous Cell Carcinoma    | 2               |                   |            |              |            |              |

TABLE I  
RAT - TUMOR SUMMARY DATA

|                            | T3<br>Male | T3<br>Female | T4<br>Female | T4<br>Male<br>None |  |  |
|----------------------------|------------|--------------|--------------|--------------------|--|--|
| MESENTERY (continued)      |            |              |              |                    |  |  |
| Angiosarcoma               | 38         | 41           | 42           |                    |  |  |
| Reticulum Cell Sarcoma     |            |              |              |                    |  |  |
| PANCREAS (No. Examined)    | (4)        | (2)          | (4)          |                    |  |  |
| Islet Cell Adenoma         |            |              |              |                    |  |  |
| PARATHYROID (No. Examined) | (3)        | (2)          | (0)          |                    |  |  |
| Adenoma                    |            |              |              |                    |  |  |
| PITUITARY (No. Examined)   | (4)        | (0)          | (4)          |                    |  |  |
| Chromophobe                |            |              | 2            |                    |  |  |
| PLEURA (No. Examined)      | (4)        | (5)          | (4)          |                    |  |  |
| Angiosarcoma               | 3          | 4            | 4            |                    |  |  |
| Reticulum Cell Sarcoma     | 1          |              |              |                    |  |  |
| Metastatic Angiosarcoma    |            | 1            |              |                    |  |  |
| PROSTATE (No. Examined)    | (3)        |              |              |                    |  |  |
| Adenocarcinoma             | 3          |              |              |                    |  |  |
| SKIN (No. Examined)        | (3)        | (1)          | (3)          |                    |  |  |
| Fibroma                    |            |              |              |                    |  |  |
| Fibrosarcoma               | 1          |              |              |                    |  |  |
| Lipoma                     |            |              |              |                    |  |  |
| Liposarcoma                | 1          |              |              |                    |  |  |
| Sarcoma, N.O.S.            |            |              |              |                    |  |  |
| Reticulum Cell Sarcoma     |            |              |              |                    |  |  |
| Squamous Cell Carcinoma    | 1          | 1            |              |                    |  |  |

TABLE I  
RAT - TUMOR SUMMARY DATA

|                               | Control<br>Male | Control<br>Female | T1<br>Male | T1<br>Female | T2<br>Male | T2<br>Female |
|-------------------------------|-----------------|-------------------|------------|--------------|------------|--------------|
| MAMMARY GLAND (No. Examined)  | (1)             | (62)              | (4)        | (52)         | (3)        | (19)         |
| Fibroadenoma                  | 1               | 75                | 4          | 45           | 4          | 10           |
| Adenoma                       |                 | 23                |            | 8            |            | 7            |
| Adenocarcinoma                |                 | 5                 |            | 24           |            | 8            |
| ZYMBAL'S GLAND (No. Examined) | (9)             | (16)              | (7)        | (7)          | (17)       | (6)          |
| Carcinoma                     |                 |                   | 2          | 1            |            | 2            |
| SPLEEN (No. Examined)         | (65)            | (69)              | (66)       | (54)         | (62)       | (65)         |
| Angiosarcoma                  |                 |                   | 1          |              |            |              |
| Lymphosarcoma                 |                 |                   | 1          |              | 1          |              |
| Reticulum Cell Sarcoma        | 2               | 2                 | 2          | 1            |            |              |
| SKELETAL MUSCLE (No. Exam.)   | (9)             | (15)              | (6)        | (7)          | (14)       | (3)          |
| Metastatic Angioma            |                 |                   |            |              |            |              |
| STOMACH (No. Examined)        | (9)             | (20)              | (8)        | (7)          | (18)       | (4)          |
| Lymphosarcoma                 |                 |                   |            |              | 1          |              |
| TESTIS (No. Examined)         | (54)            |                   | (64)       |              | (41)       |              |
| Interstitial Cell Tumor       |                 |                   | 2          |              |            |              |
| Angioma                       |                 |                   |            |              | 1          |              |
| THYMUS (No. Examined)         | (1)             | (0)               | (0)        | (0)          | (2)        | (4)          |
| Lymphosarcoma                 |                 |                   |            |              | 2          |              |
| THYROID (No. Examined)        | (11)            | (22)              | (12)       | (11)         | (16)       | (4)          |
| Lymphosarcoma                 |                 |                   |            |              | 1          |              |
| C-Cell Adenoma                | 1               |                   |            |              |            |              |

TABLE I  
RAT - TUMOR SUMMARY DATA

|                               | T3<br>Male | T3<br>Female | T4<br>Female | T4<br>Male<br>None |  |  |
|-------------------------------|------------|--------------|--------------|--------------------|--|--|
| MAMMARY GLAND (No. Examined)  |            |              |              |                    |  |  |
| Fibroadenoma                  |            | 3            | 5            |                    |  |  |
| Adenoma                       |            | 1            | 2            |                    |  |  |
| Adenocarcinoma                | 1          | 8            | 14           |                    |  |  |
| ZYMBAL'S GLAND (No. Examined) | (8)        | (5)          |              |                    |  |  |
| Carcinoma                     | 9          | 4            | 4            |                    |  |  |
| SPLEEN (No. Examined)         | (71)       | (67)         | (0)          |                    |  |  |
| Angiosarcoma                  |            |              |              |                    |  |  |
| Lymphosarcoma                 |            |              |              |                    |  |  |
| Reticulum Cell Sarcoma        | 1          |              |              |                    |  |  |
| SKELETAL MUSCLE (No. Exam.)   | (1)        | (0)          | (0)          |                    |  |  |
| Metastatic Angioma            |            |              |              |                    |  |  |
| STOMACH (No. Examined)        | (3)        | (0)          | (0)          |                    |  |  |
| Lymphosarcoma                 |            |              |              |                    |  |  |
| TESTIS (No. Examined)         | (5)        |              |              |                    |  |  |
| Interstitial Cell Tumor       |            |              |              |                    |  |  |
| Angioma                       |            |              |              |                    |  |  |
| THYMUS (No. Examined)         | (0)        | (1)          | (0)          |                    |  |  |
| Lymphosarcoma                 |            |              |              |                    |  |  |
| THYROID (No. Examined)        | (3)        | (2)          | (0)          |                    |  |  |
| Lymphosarcoma                 |            |              |              |                    |  |  |
| C-Cell Adenoma                |            |              |              |                    |  |  |

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TABLE I  
RAT - TUMOR SUMMARY DATA

|                                      | Control<br>Male | Control<br>Female | T1<br>Male | T1<br>Female | T2<br>Male | T2<br>Female |
|--------------------------------------|-----------------|-------------------|------------|--------------|------------|--------------|
| THYROID (continued)                  |                 |                   |            |              |            |              |
| Follicular Adenoma                   |                 | 1                 |            |              |            |              |
| Follicular Adenocarcinoma            |                 | 1                 |            |              |            |              |
| TRACHEA (No. Examined)               | (14)            | (27)              | (17)       | (15)         | (23)       | (9)          |
| Lymphosarcoma                        |                 |                   |            |              | 1          |              |
| UTERUS (No. Examined)                |                 | (36)              |            | (35)         |            | (11)         |
| Reticulum Cell Sarcoma               |                 | 1                 |            |              |            |              |
| LYMPH NODE (No. Examined)            | (12)            | (21)              | (8)        | (7)          | (17)       | (5)          |
| Fibrosarcoma                         |                 |                   |            | 1            |            |              |
| Total Number Neoplasms               | 44              | 141               | 58         | 134          | 123        | 155          |
| No. Animals with Angiosarcomas       | S) 0            | 0                 | 1          | 2            | 7          | 3            |
|                                      | PM) 0           | 0                 | 12         | 13           | 33         | 62           |
|                                      | NR) 2           | 0                 | 0          | 0            | 0          | 4            |
|                                      | T) 2            | 0                 | 13         | 20           | 40         | 69           |
|                                      | %) 2.4          | 0                 | 15.7       | 26.7         | 52.6       | 84.1         |
| Total No. Primary<br>Angiosarcomas   | 2               | 0                 | 12         | 29           | 69         | 96           |
| No. Primary Angiosarcomas<br>per Rat | 0.0125          | 0                 | 0.145      | 0.387        | 0.908      | 1.170        |
| S=Sacrificed                         |                 |                   |            |              |            |              |
| PM=Died During Study                 |                 |                   |            |              |            |              |
| T=Total                              |                 |                   |            |              |            |              |
| NR=Newly Read                        |                 |                   |            |              |            |              |

TABLE I  
RAT - TUMOR SUMMARY DATA

|                                      | T3<br>Male | T3<br>Female | T4<br>Female | T4<br>Male<br>None |  |  |
|--------------------------------------|------------|--------------|--------------|--------------------|--|--|
| THYROID (continued)                  |            |              |              |                    |  |  |
| Follicular Adenoma                   |            |              |              |                    |  |  |
| Follicular Adenocarcinoma            |            |              |              |                    |  |  |
| TRACHEA (No. Examined)               | (4)        | (3)          | (0)          |                    |  |  |
| Lymphosarcoma                        |            |              |              |                    |  |  |
| UTERUS (No. Examined)                |            | (2)          | (0)          |                    |  |  |
| Reticulum Cell Sarcoma               |            |              |              |                    |  |  |
| LYMPH NODE (No. Examined)            | (3)        | (0)          | (0)          |                    |  |  |
| Fibrosarcoma                         |            |              |              |                    |  |  |
| Total Number Neoplasms               | 148        | 168          | 161          |                    |  |  |
| No. Animals with Angiosarcomas       | S) 10      | 8            | 5            |                    |  |  |
|                                      | PM) 41     | 50           | 53           |                    |  |  |
|                                      | NR) 2      | 8            | 3            |                    |  |  |
|                                      | T) 53      | 64           | 61           |                    |  |  |
|                                      | %) 63.9    | 79.0         | 81.3         |                    |  |  |
| Total No. Primary<br>Angiosarcomas   | 93         | 110          | 96           |                    |  |  |
| No. Primary Angiosarcomas<br>per Rat | 1.069      | 1.358        | 1.28         |                    |  |  |
| S=Sacrificed                         |            |              |              |                    |  |  |
| PM=Died During Study                 |            |              |              |                    |  |  |
| T=Total                              |            |              |              |                    |  |  |

NR=Newly Read

TABLE II  
MICE - TUMOR SUMMARY DATA

|                                       | Control<br>Male | Control<br>Female |  | T1<br>Male | T1<br>Female |  |
|---------------------------------------|-----------------|-------------------|--|------------|--------------|--|
| HEART (No. Examined)                  | (50)            | (45)              |  | (56)       | (58)         |  |
| Lymphosarcoma                         | 2               |                   |  | 1          |              |  |
| Angiosarcoma                          |                 |                   |  |            |              |  |
| KIDNEY (No. Examined)                 | (52)            | (45)              |  | (58)       | (62)         |  |
| Angiosarcoma                          |                 |                   |  | 3          | 7            |  |
| Lymphosarcoma                         | 3               | 2                 |  | 2          | 2            |  |
| Reticulum Cell Sarcoma                | 2               |                   |  | 1          |              |  |
| Metastatic Angiosarcoma               |                 |                   |  |            | 1            |  |
| LIVER (No. Examined)                  | (52)            | (45)              |  | (59)       | (62)         |  |
| Angiosarcoma                          |                 |                   |  | 18         | 28           |  |
| Hepatocellular Carcinoma              |                 |                   |  | 1          |              |  |
| Lymphosarcoma                         | 3               | 3                 |  | 2          | 1            |  |
| Reticulum Cell Sarcoma                | 1               | 1                 |  | 1          |              |  |
| Metastatic Mammary Carcinoma          |                 |                   |  |            |              |  |
| Hepatocellular Adenoma                | 1               |                   |  |            |              |  |
| Metastatic Squamous Cell<br>Carcinoma |                 |                   |  |            | 1            |  |
| LUNG (No. Examined)                   | (51)            | (45)              |  | (58)       | (62)         |  |
| Alveologenic Adenoma                  | 8               | 2                 |  | 68         | 34           |  |
| Alveologenic Carcinoma                | 1               |                   |  | 4          | 6            |  |
| Lymphosarcoma                         | 3               | 2                 |  | 2          | 2            |  |
| Reticulum Cell Sarcoma                | 2               |                   |  | 1          |              |  |
| Metastatic Mammary Carcinoma          |                 |                   |  |            | 7            |  |
| Metastatic Angiosarcoma               |                 |                   |  |            | 1            |  |
| Metastatic Squamous Cell<br>Carcinoma |                 |                   |  |            | 2            |  |

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TABLE II  
MICE - TUMOR SUMMARY DATA

|                                       | T2<br>Male | T2<br>Female |  | T3<br>Male | T3<br>Female |  |
|---------------------------------------|------------|--------------|--|------------|--------------|--|
| HEART (No. Examined)                  | (64)       | (59)         |  | (46)       | (40)         |  |
| Lymphosarcoma                         |            |              |  |            |              |  |
| Angiosarcoma                          |            | 1            |  |            |              |  |
| KIDNEY (No. Examined)                 | (69)       | (62)         |  | (50)       | (48)         |  |
| Angiosarcoma                          |            | 1            |  | 2          |              |  |
| Lymphosarcoma                         | 1          | 1            |  |            | 1            |  |
| Reticulum Cell Sarcoma                | 1          |              |  |            |              |  |
| Metastatic Angiosarcoma               |            |              |  | 2.         |              |  |
| LIVER (No. Examined)                  | (70)       | (64)         |  | (51)       | (50)         |  |
| Angiosarcoma                          | 71         | 60           |  | 52         | 61           |  |
| Hepatocellular Carcinoma              |            |              |  |            |              |  |
| Lymphosarcoma                         | 1          | 1            |  |            | 1            |  |
| Reticulum Cell Sarcoma                | 1          |              |  |            |              |  |
| Metastatic Mammary Carcinoma          |            |              |  |            | 1            |  |
| Hepatocellular Adenoma                |            |              |  |            | 1            |  |
| Metastatic Squamous Cell<br>Carcinoma |            |              |  |            |              |  |
| LUNG (No. Examined)                   | (70)       | (64)         |  | (51)       | (50)         |  |
| Alveologenic Adenoma                  | 66         | 53           |  | 92         | 61           |  |
| Alveologenic Carcinoma                | 1          | 3            |  | 10         | 8            |  |
| Lymphosarcoma                         | 1          |              |  |            | 1            |  |
| Reticulum Cell Sarcoma                | 1          |              |  |            |              |  |
| Metastatic Mammary Carcinoma          |            | 4            |  | 2          | 6            |  |
| Metastatic Angiosarcoma               |            | 1            |  | 4          | 5            |  |
| Metastatic Squamous Cell<br>Carcinoma |            |              |  |            |              |  |

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TABLE II  
MICE - TUMOR SUMMARY DATA

|                                | Control<br>Male | Control<br>Female |  | T1<br>Male | T1<br>Female |  |
|--------------------------------|-----------------|-------------------|--|------------|--------------|--|
| LYMPH NODE (No. Examined)      | (3)             | (2)               |  | (2)        | (2)          |  |
| Lymphosarcoma                  | 1               | 2                 |  |            |              |  |
| Angiosarcoma                   |                 |                   |  | 1          |              |  |
| Reticulum Cell Sarcoma         | 1               |                   |  |            |              |  |
| MESENTERY (No. Examined)       | (2)             | (2)               |  | (10)       | (27)         |  |
| Angiosarcoma                   |                 |                   |  | 7          | 29           |  |
| Lymphosarcoma                  | 1               | 1                 |  | 2          | 1            |  |
| Reticulum Cell Sarcoma         | 1               |                   |  | 1          |              |  |
| Fibrosarcoma                   |                 |                   |  |            | 1            |  |
| OVARY (No. Examined)           |                 | (10)              |  |            | (5)          |  |
| Angiosarcoma                   |                 | 1*                |  |            | 1            |  |
| PANCREAS (No. Examined)        | (4)             | (14)              |  | (11)       | (5)          |  |
| Angiosarcoma                   |                 |                   |  | 1          | 1            |  |
| Lymphosarcoma                  | 1               |                   |  |            |              |  |
| SALIVARY GLAND (No. Examined)  | (0)             | (0)               |  | (7)        | (1)          |  |
| Angiosarcoma                   |                 |                   |  |            |              |  |
| SKELETAL MUSCLE (No. Examined) | (0)             | (0)               |  | (6)        | (2)          |  |
| Lymphosarcoma                  |                 |                   |  |            |              |  |
| SKIN (No. Examined)            | (0)             | (3)               |  | (3)        | (4)          |  |
| Lymphosarcoma                  |                 |                   |  | 1          |              |  |
| Fibrosarcoma                   |                 | 1                 |  |            | 1            |  |
| Squamous Cell Carcinoma        |                 |                   |  |            | 1            |  |

\*Diagnosed angioma

TABLE II  
MICE - TUMOR SUMMARY DATA

|                                | T2<br>Male | T2<br>Female |  | T3<br>Male | T3<br>Female |  |
|--------------------------------|------------|--------------|--|------------|--------------|--|
| LYMPH NODE (No. Examined)      | (0)        | (2)          |  | (0)        | (1)          |  |
| Lymphosarcoma                  |            |              |  |            | 1            |  |
| Angiosarcoma                   |            |              |  |            |              |  |
| Reticulum Cell Sarcoma         |            |              |  |            |              |  |
| MESENTERY (No. Examined)       | (12)       | (10)         |  | (6)        | (7)          |  |
| Angiosarcoma                   | 11         | 10           |  | 10         | 8            |  |
| Lymphosarcoma                  | 1          |              |  |            |              |  |
| Reticulum Cell Sarcoma         |            |              |  |            |              |  |
| Fibrosarcoma                   |            |              |  |            |              |  |
| OVARY (No. Examined)           |            | (4)          |  |            | (1)          |  |
| Angiosarcoma                   |            | 1            |  |            |              |  |
| PANCREAS (No. Examined)        | (3)        | (4)          |  | (1)        | (1)          |  |
| Angiosarcoma                   |            |              |  |            |              |  |
| Lymphosarcoma                  |            |              |  |            |              |  |
| SALIVARY GLAND (No. Examined)  | (1)        | (1)          |  | (2)        | (0)          |  |
| Angiosarcoma                   |            | 1            |  |            |              |  |
| SKELETAL MUSCLE (No. Examined) | (1)        | (2)          |  | (0)        | (0)          |  |
| Lymphosarcoma                  | 1          |              |  |            |              |  |
| SKIN (No. Examined)            | (1)        | (2)          |  | (1)        | (1)          |  |
| Lymphosarcoma                  |            |              |  |            |              |  |
| Fibrosarcoma                   |            |              |  |            |              |  |
| Squamous Cell Carcinoma        |            | 2            |  | 1          |              |  |

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TABLE II  
MICE - TUMOR SUMMARY DATA

|                                 | Control<br>Male | Control<br>Female |  | T1<br>Male | T1<br>Female |  |
|---------------------------------|-----------------|-------------------|--|------------|--------------|--|
| MAMMARY GLAND (No. Examined)    | (0)             | (1)               |  | (1)        | (24)         |  |
| Adenosquamous Carcinoma         |                 | 1                 |  | 1          | 9            |  |
| Adenocarcinoma                  |                 |                   |  |            | 19           |  |
| SPLEEN (No. Examined)           | (46)            | (41)              |  | (57)       | (62)         |  |
| Angiosarcoma                    |                 |                   |  |            | 3            |  |
| Lymphosarcoma                   | 2               | 3                 |  | 2          | 2            |  |
| Reticulum Cell Sarcoma          | 1               | 1                 |  | 1          |              |  |
| Metastatic Angiosarcoma         |                 |                   |  |            |              |  |
| Metastatic Mammary Carcinoma    |                 |                   |  |            |              |  |
| STOMACH (No. Examined)          | (8)             | (17)              |  | (6)        | (2)          |  |
| Adenocarcinoma                  |                 |                   |  | 1          |              |  |
| Lymphosarcoma                   | 1               |                   |  |            |              |  |
| Reticulum Cell Sarcoma          | 1               |                   |  |            |              |  |
| URINARY BLADDER (No. Examined)  | (6)             | (8)               |  | (5)        | (1)          |  |
| Lymphosarcoma                   | 1               |                   |  |            |              |  |
| UTERUS (No. Examined)           |                 | (14)              |  |            | (5)          |  |
| Sarcoma, N.O.S.                 |                 | 1                 |  |            |              |  |
| Total Neoplasms                 | 31              | 19                |  | 120        | 145          |  |
| No. Animals with Angiosarcomas  | S) 0            | 0                 |  | 4          | 3            |  |
|                                 | PM) 0           | 0                 |  | 0          | 0            |  |
|                                 | T) 0            | 1                 |  | 20         | 40           |  |
|                                 | %) 0            | 2.2               |  | 33.3       | 61.5         |  |
| Total No. Primary Angiosarcomas | 0               | 1                 |  | 30         | 69           |  |
| No. Primary Angiosarcomas/Mouse | 0               | .02               |  | 0.5        | 1.06         |  |

S=Sacrificed, PM=Died During Study, T=Total

E P L

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TABLE II  
MICE - TUMOR SUMMARY DATA

|                                 | T2<br>Male | T2<br>Female |  | T3<br>Male | T3<br>Female |  |
|---------------------------------|------------|--------------|--|------------|--------------|--|
| MAMMARY GLAND (No. Examined)    | (0)        | (9)          |  | (3)        | (7)          |  |
| Adenosquamous Carcinoma         |            | 6            |  | 1          | 8            |  |
| Adenocarcinoma                  |            | 5            |  | 2          | 8            |  |
| SPLEEN (No. Examined)           | (68)       | (63)         |  | (47)       | (50)         |  |
| Angiosarcoma                    | 3          | 1            |  |            | 2            |  |
| Lymphosarcoma                   | 1          | 1            |  |            | 1            |  |
| Reticulum Cell Sarcoma          | 1          |              |  |            |              |  |
| Metastatic Angiosarcoma         | 1          |              |  |            |              |  |
| Metastatic Mammary Carcinoma    |            |              |  |            | 1            |  |
| STOMACH (No. Examined)          | (0)        | (2)          |  | (0)        | (1)          |  |
| Adenocarcinoma                  |            |              |  |            |              |  |
| Lymphosarcoma                   |            |              |  |            |              |  |
| Reticulum Cell Sarcoma          |            |              |  |            |              |  |
| URINARY BLADDER (No. Examined)  | (0)        | (1)          |  | (0)        | (0)          |  |
| Lymphosarcoma                   |            |              |  |            |              |  |
| UTERUS (No. Examined)           |            | (2)          |  |            | (0)          |  |
| Sarcoma, N.O.S.                 |            |              |  |            |              |  |
| Total Neoplasms                 | 152        | 136          |  | 160        | 127          |  |
| No. Animals with Angiosarcomas  | S) 3       | 0            |  | 9          | 12           |  |
|                                 | PM) 0      | 0            |  | 0          | 0            |  |
|                                 | T) 74      | 65           |  | 51         | 63           |  |
|                                 | %) 96.1    | 91.5         |  | 89.5       | 88.7         |  |
| Total No. Primary Angiosarcomas | 85         | 75           |  | 64         | 71           |  |
| No. Primary Angiosarcomas/Mouse | 1.10       | 1.05         |  | 1.12       | 1.0          |  |

S=Sacrificed, PM=Died During Study, T=Total

E P L

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TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

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|                                        | Control<br>Male | Control<br>Female |  | T1<br>Male | T1<br>Female |  |
|----------------------------------------|-----------------|-------------------|--|------------|--------------|--|
| ADRENAL (No. Examined)                 | (9)             | (4)               |  | (12)       | (4)          |  |
| Cortical Adenoma                       |                 |                   |  |            |              |  |
| Cortical Carcinoma                     |                 |                   |  | 1          |              |  |
| HEART (No. Examined)                   | (45)            | (32)              |  | (41)       | (30)         |  |
| Lymphosarcoma                          |                 |                   |  |            |              |  |
| KIDNEYS (No. Examined)                 | (53)            | (36)              |  | (43)       | (33)         |  |
| Angiosarcoma                           |                 |                   |  |            |              |  |
| Reticulum Cell Sarcoma                 |                 |                   |  | 1          |              |  |
| Tubular Adenoma                        |                 |                   |  | 1          | 1            |  |
| Metastatic Mammary Adeno-<br>carcinoma |                 |                   |  |            |              |  |
| LIVER (No. Examined)                   | (50)            | (33)              |  | (44)       | (30)         |  |
| Angiosarcoma                           |                 |                   |  | 5          | 2            |  |
| Lymphosarcoma                          |                 |                   |  |            |              |  |
| Metastatic Granulosa Cell              |                 |                   |  |            |              |  |
| Metastatic Mammary Adeno-<br>carcinoma |                 |                   |  |            |              |  |
| LUNG (No. Examined)                    | (49)            | (32)              |  | (42)       | (29)         |  |
| Alveolar Adenoma                       |                 |                   |  |            |              |  |
| Angiosarcoma                           |                 |                   |  |            |              |  |
| Bronchiolar Carcinoma                  |                 |                   |  |            |              |  |
| Bronchiolar Adenoma                    |                 |                   |  |            |              |  |
| Metastatic Angiosarcoma                |                 |                   |  |            |              |  |
| Metastatic Melanosarcoma               |                 |                   |  | 1          |              |  |
| Metastatic Adenocarcinoma              |                 |                   |  |            |              |  |

TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

|                                        | T2<br>Male | T2<br>Female |  | T3<br>Male | T3<br>Female |  |
|----------------------------------------|------------|--------------|--|------------|--------------|--|
| ADRENAL (No. Examined)                 | (18)       | (11)         |  | (5)        | (2)          |  |
| Cortical Adenoma                       |            | 1            |  | 1          |              |  |
| Cortical Carcinoma                     | 1          |              |  |            |              |  |
| HEART (No. Examined)                   | (35)       | (51)         |  | (45)       | (23)         |  |
| Lymphosarcoma                          |            |              |  | 1          |              |  |
| KIDNEYS (No. Examined)                 | (40)       | (57)         |  | (50)       | (24)         |  |
| Angiosarcoma                           | 2          |              |  |            |              |  |
| Reticulum Cell Sarcoma                 |            |              |  |            |              |  |
| Tubular Adenoma                        |            |              |  |            |              |  |
| Metastatic Mammary Adeno-<br>carcinoma |            | 1            |  |            |              |  |
| LIVER (No. Examined)                   | (36)       | (52)         |  | (48)       | (26)         |  |
| Angiosarcoma                           | 1          | 11           |  | 38         | 18           |  |
| Lymphosarcoma                          |            |              |  | 1          |              |  |
| Metastatic Granulosa Cell              |            | 1            |  |            |              |  |
| Metastatic Mammary Adeno-<br>carcinoma |            | 1            |  |            |              |  |
| LUNG (No. Examined)                    | (36)       | (49)         |  | (44)       | (26)         |  |
| Alveolar Adenoma                       |            |              |  | 1          |              |  |
| Angiosarcoma                           |            |              |  | 2          |              |  |
| Bronchiolar Carcinoma                  |            |              |  | 2          | 1            |  |
| Bronchiolar Adenoma                    |            |              |  | 1          |              |  |
| Metastatic Angiosarcoma                | 1          | 2            |  | 7          | 4            |  |
| Metastatic Melanosarcoma               | 1          |              |  |            |              |  |
| Metastatic Adenocarcinoma              |            | 1            |  |            |              |  |

TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

|                                        | Control<br>Male | Control<br>Female |  | T1<br>Male | T1<br>Female |  |
|----------------------------------------|-----------------|-------------------|--|------------|--------------|--|
| LUNG (Continued)                       |                 |                   |  |            |              |  |
| Metastatic Mammary Adeno-<br>carcinoma |                 |                   |  |            |              |  |
| Metastatic Uterine Adeno-<br>carcinoma |                 |                   |  |            |              |  |
| MESENTERY (No. Examined)               | (0)             | (0)               |  | (5)        | (3)          |  |
| Angiosarcoma                           |                 |                   |  | 1          | 1            |  |
| Melanosarcoma                          |                 |                   |  | 1          |              |  |
| Adenocarcinoma, N.O.S.                 |                 |                   |  |            |              |  |
| ESOPHAGUS (No. Examined)               | (7)             | (2)               |  | (7)        | (3)          |  |
| Papilloma                              |                 |                   |  |            |              |  |
| OVARIES (No. Examined)                 |                 | (16)              |  |            | (13)         |  |
| Granulosa Cell, Malignant              |                 |                   |  |            |              |  |
| Thecal Cell                            |                 | 1                 |  |            | 1            |  |
| PANCREAS (No. Examined)                | (14)            | (4)               |  | (20)       | (11)         |  |
| Islet Cell Adenoma                     |                 |                   |  | 1          |              |  |
| PLEURA (No. Examined)                  | (0)             | (0)               |  | (0)        | (0)          |  |
| Metastatic Angiosarcoma                |                 |                   |  |            |              |  |
| SKELETAL MUSCLE (No. Examined)         | (3)             | (3)               |  | (7)        | (2)          |  |
| Lymphosarcoma                          |                 |                   |  |            |              |  |
| SKIN (No. Examined)                    | (5)             | (2)               |  | (7)        | (4)          |  |
| Angiosarcoma                           |                 |                   |  |            |              |  |

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TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

|                                        | T2<br>Male | T2<br>Female |  | T3<br>Male | T3<br>Female |  |
|----------------------------------------|------------|--------------|--|------------|--------------|--|
| LUNG (Continued)                       |            |              |  |            |              |  |
| Metastatic Mammary Adeno-<br>carcinoma |            | 2            |  |            |              |  |
| Metastatic Uterine Adeno-<br>carcinoma |            | 1            |  |            |              |  |
| MESENTERY (No. Examined)               | (11)       | (3)          |  | (8)        | (4)          |  |
| Angiosarcoma                           | 2          | 3            |  | 7          | 4            |  |
| Melanosarcoma                          |            |              |  |            |              |  |
| Adenocarcinoma, N.O.S.                 |            | 1            |  |            |              |  |
| ESOPHAGUS (No. Examined)               | (14)       | (9)          |  | (4)        | (3)          |  |
| Papilloma                              |            | 1            |  |            |              |  |
| OVARIES (No. Examined)                 |            | (16)         |  |            | (2)          |  |
| Granulosa Cell, Malignant              |            | 1            |  |            |              |  |
| Thecal Cell                            |            | 1            |  |            |              |  |
| PANCREAS (No. Examined)                | (16)       | (12)         |  | (4)        | (3)          |  |
| Islet Cell Adenoma                     | 1          |              |  |            | 1            |  |
| PLEURA (No. Examined)                  | (0)        | (0)          |  | (1)        | (0)          |  |
| Metastatic Angiosarcoma                |            |              |  | 1          |              |  |
| SKELETAL MUSCLE (No. Examined)         | (16)       | (5)          |  | (5)        | (3)          |  |
| Lymphosarcoma                          |            |              |  | 1          |              |  |
| SKIN (No. Examined)                    | (16)       | (12)         |  | (7)        | (3)          |  |
| Angiosarcoma                           | 2          |              |  |            |              |  |

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TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

|                                        | Control<br>Male | Control<br>Female |  | T1<br>Male | T1<br>Female |  |
|----------------------------------------|-----------------|-------------------|--|------------|--------------|--|
| SKIN (Continued)                       |                 |                   |  |            |              |  |
| Fibroma                                |                 |                   |  |            |              |  |
| Fibrosarcoma                           |                 |                   |  |            |              |  |
| Melanosarcoma                          |                 |                   |  |            | 1            |  |
| Metastatic Uterine Adeno-<br>carcinoma |                 |                   |  |            | 1            |  |
| MAMMARY GLAND (No. Examined)           | (0)             | (2)               |  | (0)        | (4)          |  |
| Adenocarcinoma                         |                 |                   |  |            |              |  |
| Adenoma                                |                 |                   |  |            |              |  |
| SPLEEN (No. Examined)                  | (40)            | (31)              |  | (36)       | (26)         |  |
| Angiosarcoma                           |                 |                   |  | 3          | 2            |  |
| Metastatic Mammary Adeno-<br>carcinoma |                 |                   |  |            |              |  |
| Lymphosarcoma                          |                 |                   |  |            |              |  |
| STOMACH (No. Examined)                 | (3)             | (3)               |  | (8)        | (3)          |  |
| Papilloma                              | 1               |                   |  | 3          |              |  |
| THYMUS (No. Examined)                  | (0)             | (0)               |  | (0)        | (0)          |  |
| Lymphosarcoma                          |                 |                   |  |            |              |  |
| UTERUS (No. Examined)                  |                 | (22)              |  |            | (15)         |  |
| Adenocarcinoma                         |                 |                   |  |            |              |  |
| Angiosarcoma                           |                 | 1*                |  |            |              |  |
| Papilloma                              |                 |                   |  |            |              |  |

\* Diagnosed as angioma.

TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

|                                        | T2<br>Male | T2<br>Female |  | T3<br>Male | T3<br>Female |  |
|----------------------------------------|------------|--------------|--|------------|--------------|--|
| SKIN (Continued)                       |            |              |  |            |              |  |
| Fibroma                                |            | 1            |  |            |              |  |
| Fibrosarcoma                           |            | 2            |  |            |              |  |
| Melanosarcoma                          |            |              |  |            |              |  |
| Metastatic Uterine Adeno-<br>carcinoma |            |              |  |            |              |  |
| MAMMARY GLAND (No. Examined)           | (0)        | (12)         |  | (0)        | (3)          |  |
| Adenocarcinoma                         |            | 3            |  |            | 1            |  |
| Adenoma                                |            | 1            |  |            |              |  |
| SPLEEN (No. Examined)                  | (34)       | (47)         |  | (41)       | (22)         |  |
| Angiosarcoma                           | 5          | 11           |  | 8          | 9            |  |
| Metastatic Mammary Adeno-<br>carcinoma |            | 1            |  |            |              |  |
| Lymphosarcoma                          |            |              |  | 1          |              |  |
| STOMACH (No. Examined)                 | (16)       | (14)         |  | (7)        | (4)          |  |
| Papilloma                              | 1          | 10           |  | 2          | 2            |  |
| THYMUS (No. Examined)                  | (2)        | (3)          |  | (2)        | (0)          |  |
| Lymphosarcoma                          |            |              |  | 1          |              |  |
| UTERUS (No. Examined)                  |            | (33)         |  |            | (4)          |  |
| Adenocarcinoma                         |            | 2            |  |            |              |  |
| Angiosarcoma                           |            | 1            |  |            | 1            |  |
| Papilloma                              |            | 1            |  |            |              |  |

TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

|                                                          | Control<br>Male | Control<br>Female |  | T1<br>Male | T1<br>Female |  |
|----------------------------------------------------------|-----------------|-------------------|--|------------|--------------|--|
| Total Neoplasms                                          | 2               | 2                 |  | 18         | 9            |  |
| No. Animals with Angiosarcomas                           | S) 0            | 1                 |  | 2          | 1            |  |
|                                                          | PM) 0           | 0                 |  | 5          | 3            |  |
|                                                          | T) 0            | 1                 |  | 7          | 4            |  |
|                                                          | %) 0            | 2.7               |  | 15.21      | 12.9         |  |
| Total No. Primary Angiosarcomas                          | 0               | 1                 |  | 9          | 5            |  |
| No. Primary Angiosarcomas/<br>Hamster                    | 0               | 0.027             |  | 1.28       | 1.25         |  |
| <p>S=Sacrificed<br/>PM=Died During Study<br/>T=Total</p> |                 |                   |  |            |              |  |

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TABLE III  
HAMSTERS - TUMOR SUMMARY DATA

|                                                          | T2<br>Male | T2<br>Female |  | T3<br>Male | T3<br>Female |  |
|----------------------------------------------------------|------------|--------------|--|------------|--------------|--|
| Total Neoplasms                                          | 17         | 61           |  | 75         | 41           |  |
| No. Animals with Angiosarcomas S)                        | 3          | 2            |  | 8          | 4            |  |
| PM)                                                      | 5          | 15           |  | 31         | 16           |  |
| T)                                                       | 8          | 17           |  | 39         | 20           |  |
| %)                                                       | 21.6       | 26.98        |  | 75.0       | 64.5         |  |
| Total No. Primary Angiosarcomas                          | 12         | 25           |  | 55         | 32           |  |
| No. Primary Angiosarcomas/<br>Hamster                    | 1.50       | 1.47         |  | 1.40       | 1.60         |  |
| <p>S=Sacrificed<br/>PM=Died During Study<br/>T=Total</p> |            |              |  |            |              |  |

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TABLE IV

## PERCENTAGE OF ANIMALS WITH PRIMARY ANGIOSARCOMAS

|          | <u>Untreated<br/>Control</u> | <u>T1</u> | <u>T2</u> | <u>T3</u> | <u>T4*</u> |
|----------|------------------------------|-----------|-----------|-----------|------------|
| RATS     |                              |           |           |           |            |
| Male     | 2.4                          | 15.7      | 52.6      | 63.9      | -          |
| Female   | 0                            | 26.7      | 84.1      | 79.0      | 81.3       |
| MICE     |                              |           |           |           |            |
| Male     | 0                            | 33.3      | 96.1      | 89.5      | -          |
| Female   | 2.2                          | 61.5      | 91.5      | 88.7      | -          |
| HAMSTERS |                              |           |           |           |            |
| Male     | 0                            | 15.2      | 21.6      | 75.0      | -          |
| Female   | 2.7                          | 12.9      | 27.0      | 64.5      | -          |

\*Allowed feed and bedding during exposure

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TABLE V  
TISSUE COUNTS - MALE RATS

|                   | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-------------------|----------------------|-----|-----|-----|--|--|
| Number of Animals | 81                   | 82  | 75  | 86  |  |  |
| ADRENAL           | 18                   | 15  | 22  | 22  |  |  |
| BONE              | 18                   | 15  | 23  | 24  |  |  |
| BRAIN             | 19                   | 15  | 23  | 23  |  |  |
| EPIDIDYMIS        | 79                   | 79  | 73  | 81  |  |  |
| ESOPHAGUS         | 59                   | 69  | 63  | 73  |  |  |
| EXT. & MID. EAR   | 10                   | 6   | 19  | 0   |  |  |
| EYES              | 19                   | 15  | 22  | 24  |  |  |
| HEART             | 81                   | 80  | 74  | 86  |  |  |
| KIDNEYS           | 81                   | 80  | 73  | 86  |  |  |
| LIVER             | 81                   | 80  | 74  | 86  |  |  |
| LUNG & BRONCHI    | 81                   | 81  | 74  | 86  |  |  |
| MUSCLE            | 19                   | 17  | 23  | 22  |  |  |
| OVARIES           |                      | 1   |     |     |  |  |
| PANCREAS          | 69                   | 65  | 65  | 71  |  |  |

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TABLE V  
TISSUE COUNTS - MALE RATS

|                 | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-----------------|----------------------|-----|-----|-----|--|--|
| PITUITARY       | 14                   | 13  | 16  | 21  |  |  |
| PROSTATE        | 11                   | 15  | 23  | 8   |  |  |
| SALIVARY GLAND  | 17                   | 15  | 23  | 22  |  |  |
| SEMINAL VESICLE | 8                    | 5   | 14  | 0   |  |  |
| SKIN            | 24                   | 14  | 25  | 22  |  |  |
| SPINAL CORD     | 17                   | 13  | 21  | 20  |  |  |
| SPLEEN          | 81                   | 78  | 73  | 85  |  |  |
| STOMACH         | 19                   | 15  | 25  | 20  |  |  |
| TESTIS          | 78                   | 79  | 73  | 81  |  |  |
| THYMUS          | 4                    | 3   | 1   | 8   |  |  |
| THYROID         | 26                   | 27  | 30  | 36  |  |  |
| TISSUE MASS     | 21                   | 24  | 37  | 62  |  |  |
| TRACHEA         | 49                   | 48  | 49  | 52  |  |  |
| URINARY BLADDER | 18                   | 15  | 25  | 20  |  |  |
| UTERUS          |                      | 1   |     |     |  |  |

TABLE V  
TISSUE COUNTS - MALE RATS

|                  | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|------------------|----------------------|-----|-----|-----|--|--|
| AORTA            | 18                   | 13  | 19  | 17  |  |  |
| OPTIC NERVE      | 16                   | 13  | 15  | 20  |  |  |
| INTESTINES       | 21                   | 15  | 24  | 23  |  |  |
| LYMPH NODE       | 32                   | 32  | 38  | 54  |  |  |
| PERIPHERAL NERVE | 18                   | 13  | 21  | 16  |  |  |
| STERNUM          | 15                   | 14  | 23  | 8   |  |  |
| TONGUE           | 18                   | 15  | 22  | 22  |  |  |
| NOSE             | 9                    | 12  | 23  | 16  |  |  |
| DIAPHRAGM        | 1                    | 0   | 0   | 2   |  |  |
| FAT              | 1                    | 0   | 0   | 0   |  |  |
| UNKNOWN          | 40                   | 47  | 39  | 35  |  |  |
| ZYMBAL'S GLAND   | 0                    | 0   | 0   | 0   |  |  |
| SKULL            | 0                    | 13  | 22  | 0   |  |  |

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TABLE V  
TISSUE COUNTS - FEMALE RATS

|                   | Untreated<br>Control | T-1 | T-2 | T-3 | T-4 |            |
|-------------------|----------------------|-----|-----|-----|-----|------------|
| Number of Animals | 92                   | 76  | 79  | 79  | 74  | R&S 112161 |
| ADRENAL           | 30                   | 12  | 10  | 15  | 9   |            |
| BONE              | 28                   | 13  | 10  | 16  | 10  |            |
| BRAIN             | 28                   | 14  | 10  | 17  | 11  |            |
| EPIDIDYMIS        |                      |     |     |     |     |            |
| ESOPHAGUS         | 60                   | 54  | 71  | 75  | 67  |            |
| EXT. & MID. EAR   | 18                   | 7   | 5   | 3   | 1   |            |
| EYES              | 28                   | 13  | 11  | 18  | 11  |            |
| HEART             | 79                   | 65  | 73  | 78  | 73  |            |
| KIDNEYS           | 78                   | 65  | 74  | 77  | 72  |            |
| LIVER             | 77                   | 65  | 75  | 79  | 72  |            |
| LUNG & BRONCHI    | 78                   | 63  | 74  | 78  | 73  |            |
| MUSCLE            | 30                   | 15  | 12  | 11  | 10  |            |
| OVARIES           | 72                   | 62  | 71  | 69  | 67  |            |
| PANCREAS          | 69                   | 56  | 67  | 61  | 50  |            |

TABLE V  
TISSUE COUNTS - FEMALE RATS

|                 | Untreated<br>Control | T-1 | T-2 | T-3 | T-4 |  |
|-----------------|----------------------|-----|-----|-----|-----|--|
| PITUITARY       | 24                   | 9   | 11  | 12  | 8   |  |
| PROSTATE        |                      |     |     |     |     |  |
| SALIVARY GLAND  | 33                   | 12  | 13  | 17  | 10  |  |
| SEMINAL VESICLE |                      |     |     |     |     |  |
| SKIN            | 58                   | 29  | 19  | 13  | 12  |  |
| SPINAL CORD     | 26                   | 13  | 8   | 14  | 9   |  |
| SPLEEN          | 78                   | 64  | 74  | 79  | 70  |  |
| STOMACH         | 34                   | 14  | 11  | 12  | 13  |  |
| TESTIS          |                      |     |     |     |     |  |
| THYMUS          | 2                    | 1   | 2   | 3   | 2   |  |
| THYROID         | 31                   | 21  | 29  | 32  | 22  |  |
| TISSUE MASS     | 60                   | 61  | 69  | 67  | 67  |  |
| TRACHEA         | 55                   | 47  | 56  | 19  | 44  |  |
| URINARY BLADDER | 28                   | 14  | 11  | 13  | 14  |  |
| UTERUS          | 75                   | 64  | 71  | 73  | 66  |  |

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TABLE V  
TISSUE COUNTS - FEMALE RATS

|                  | Untreated<br>Control | T-1 | T-2 | T-3 | T-4 |  |
|------------------|----------------------|-----|-----|-----|-----|--|
| AORTA            | 27                   | 9   | 9   | 15  | 5   |  |
| OPTIC NERVE      | 26                   | 10  | 7   | 15  | 9   |  |
| INTESTINES       | 31                   | 17  | 10  | 15  | 13  |  |
| LYMPH NODE       | 41                   | 28  | 38  | 62  | 51  |  |
| PERIPHERAL NERVE | 21                   | 8   | 7   | 9   | 9   |  |
| STERNUM          | 26                   | 10  | 9   | 5   | 5   |  |
| TONGUE           | 24                   | 11  | 11  | 10  | 9   |  |
| NOSE             | 16                   | 13  | 10  | 8   | 6   |  |
| DIAPHRAGM        | 0                    | 0   | 0   | 0   | 0   |  |
| FAT              | 0                    | 0   | 0   | 0   | 0   |  |
| UNKNOWN          | 65                   | 59  | 48  | 38  | 53  |  |
| ZYMBAL'S GLAND   | 7                    | 1   | 0   | 0   | 0   |  |
| SKULL            | 14                   | 9   | 10  | 10  | 8   |  |

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TABLE VI  
TISSUE COUNTS - MALE MICE

|                   | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-------------------|----------------------|-----|-----|-----|--|--|
| Number of Animals | 61                   | 61  | 82  | 71  |  |  |
| ADRENAL           | 14                   | 27  | 51  | 52  |  |  |
| BONE              | 6                    | 13  | 7   | 16  |  |  |
| BRAIN             | 5                    | 13  | 3   | 14  |  |  |
| EPIDIDYMIS        | 56                   | 57  | 81  | 66  |  |  |
| ESOPHAGUS         | 2                    | 3   | 13  | 22  |  |  |
| EXT. & MID. EAR   | 1                    | 0   | 1   | 6   |  |  |
| EYES              | 6                    | 7   | 2   | 13  |  |  |
| GALL BLADDER      | 8                    | 6   | 5   | 16  |  |  |
| HEART             | 60                   | 60  | 82  | 71  |  |  |
| KIDNEYS           | 61                   | 60  | 82  | 70  |  |  |
| LIVER             | 60                   | 61  | 82  | 71  |  |  |
| LUNG              | 60                   | 61  | 82  | 71  |  |  |
| MUSCLE            | 6                    | 13  | 7   | 13  |  |  |
| NASAL CAVITY      | 0                    | 0   | 1   | 12  |  |  |

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TABLE VI  
TISSUE COUNTS - MALE MICE

|                 | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-----------------|----------------------|-----|-----|-----|--|--|
| OVARIES         |                      |     |     |     |  |  |
| PANCREAS        | 26                   | 17  | 36  | 69  |  |  |
| PITUITARY       | 0                    | 0   | 3   | 12  |  |  |
| PROSTATE        | 8                    | 8   | 0   | 0   |  |  |
| SALIVARY GLAND  | 3                    | 9   | 5   | 14  |  |  |
| SEMINAL VESICLE | 6                    | 5   | 0   | 0   |  |  |
| SKIN            | 7                    | 11  | 10  | 13  |  |  |
| SPINAL CORD     | 2                    | 9   | 4   | 12  |  |  |
| SPLEEN          | 60                   | 58  | 79  | 71  |  |  |
| STOMACH         | 51                   | 60  | 82  | 67  |  |  |
| TESTIS          | 52                   | 57  | 81  | 64  |  |  |
| THYMUS          | 0                    | 0   | 0   | 0   |  |  |
| THYROID         | 0                    | 3   | 1   | 1   |  |  |
| TISSUE MASS     | 4                    | 4   | 19  | 12  |  |  |
| TRACHEA         | 12                   | 8   | 9   | 22  |  |  |

TABLE VI  
TISSUE COUNTS - MALE MICE

|                  | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|------------------|----------------------|-----|-----|-----|--|--|
| URINARY BLADDER  | 46                   | 47  | 77  | 65  |  |  |
| UTERUS           |                      |     |     |     |  |  |
| AORTA            | 2                    | 1   | 1   | 1   |  |  |
| INTESTINES       | 53                   | 59  | 82  | 70  |  |  |
| LYMPH NODE       | 11                   | 6   | 33  | 33  |  |  |
| PERIPHERAL NERVE | 0                    | 5   | 1   | 5   |  |  |
| STERNUM          | 0                    | 7   | 0   | 0   |  |  |
| TONGUE           | 2                    | 1   | 3   | 11  |  |  |
| SKULL            | 3                    | 6   | 4   | 9   |  |  |
| UNKNOWN          | 3                    | 11  | 20  | 10  |  |  |
| OPTIC NERVE      | 6                    | 7   | 0   | 0   |  |  |
| FEET             | 0                    | 0   | 0   | 0   |  |  |
| LEGS             | 0                    | 0   | 0   | 0   |  |  |
| LIMBS            | 0                    | 0   | 1   | 0   |  |  |
| ZYMBAL'S GLAND   | 0                    | 0   | 0   | 6   |  |  |

TABLE VI  
TISSUE COUNTS - FEMALE MICE

|                   | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-------------------|----------------------|-----|-----|-----|--|--|
| Number of Animals | 45                   | 76  | 77  | 72  |  |  |
| ADRENAL           | 20                   | 29  | 77  | 64  |  |  |
| BONE              | 6                    | 9   | 9   | 16  |  |  |
| BRAIN             | 2                    | 6   | 8   | 13  |  |  |
| EPIDIDYMIS        |                      |     |     |     |  |  |
| ESOPHAGUS         | 7                    | 2   | 48  | 39  |  |  |
| EXT. & MID. EAR   | 0                    | 2   | 3   | 3   |  |  |
| EYES              | 1                    | 5   | 8   | 14  |  |  |
| GALL BLADDER      | 16                   | 6   | 38  | 19  |  |  |
| HEART             | 43                   | 75  | 75  | 71  |  |  |
| KIDNEYS           | 44                   | 75  | 77  | 72  |  |  |
| LIVER             | 44                   | 76  | 77  | 72  |  |  |
| LUNG              | 44                   | 75  | 76  | 72  |  |  |
| MUSCLE            | 9                    | 11  | 5   | 14  |  |  |
| NASAL CAVITY      | 0                    | 0   | 5   | 12  |  |  |

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TABLE VI  
TISSUE COUNTS - FEMALE MICE

|                 | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-----------------|----------------------|-----|-----|-----|--|--|
| OVARIES         | 28                   | 53  | 68  | 64  |  |  |
| PANCREAS        | 20                   | 10  | 71  | 69  |  |  |
| PITUITARY       | 1                    | 1   | 5   | 10  |  |  |
| PROSTATE        |                      |     |     |     |  |  |
| SALIVARY GLAND  | 0                    | 2   | 8   | 15  |  |  |
| SEMINAL VESICLE |                      |     |     |     |  |  |
| SKIN            | 3                    | 18  | 11  | 19  |  |  |
| SPINAL CORD     | 3                    | 3   | 8   | 13  |  |  |
| SPLEEN          | 43                   | 75  | 75  | 71  |  |  |
| STOMACH         | 44                   | 74  | 76  | 70  |  |  |
| TESTIS          |                      |     |     |     |  |  |
| THYMUS          | 0                    | 0   | 2   | 2   |  |  |
| THYROID         | 4                    | 1   | 6   | 5   |  |  |
| TISSUE MASS     | 3                    | 52  | 21  | 27  |  |  |
| TRACHEA         | 12                   | 3   | 37  | 33  |  |  |

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TABLE VI  
TISSUE COUNTS - FEMALE MICE

|                  | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|------------------|----------------------|-----|-----|-----|--|--|
| URINARY BLADDER  | 23                   | 30  | 64  | 60  |  |  |
| UTERUS           | 38                   | 48  | 75  | 69  |  |  |
| AORTA            | 1                    | 0   | 4   | 5   |  |  |
| INTESTINES       | 43                   | 73  | 74  | 72  |  |  |
| LYMPH NODE       | 11                   | 2   | 53  | 50  |  |  |
| PERIPHERAL NERVE | 0                    | 2   | 1   | 8   |  |  |
| STERNUM          | 2                    | 3   | 1   | 0   |  |  |
| TONGUE           | 1                    | 0   | 8   | 8   |  |  |
| SKULL            | 1                    | 10  | 5   | 8   |  |  |
| UNKNOWN          | 3                    | 45  | 19  | 19  |  |  |
| OPTIC NERVE      | 1                    | 5   | 7   | 0   |  |  |
| FEET             | 1                    | 0   | 0   | 1   |  |  |
| LEGS             | 0                    | 2   | 0   | 0   |  |  |
| LIMBS            | 0                    | 0   | 0   | 0   |  |  |
| ZYMBAL'S GLAND   | 0                    | 0   | 0   | 8   |  |  |

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TABLE VII  
TISSUE COUNTS - MALE HAMSTERS

|                         | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-------------------------|----------------------|-----|-----|-----|--|--|
| Total Number of Animals | 57                   | 45  | 46  | 61  |  |  |
| ADRENAL                 | 13                   | 12  | 21  | 9   |  |  |
| BONE                    | 5                    | 7   | 17  | 9   |  |  |
| BRAIN                   | 5                    | 7   | 17  | 9   |  |  |
| EPIDIDYMIS              | 56                   | 41  | 45  | 56  |  |  |
| ESOPHAGUS               | 10                   | 9   | 17  | 11  |  |  |
| EXT. & MID. EAR         | 2                    | 7   | 15  | 4   |  |  |
| EYES                    | 4                    | 7   | 17  | 9   |  |  |
| GALL BLADDER            | 24                   | 26  | 25  | 21  |  |  |
| HEART                   | 57                   | 45  | 46  | 61  |  |  |
| KIDNEYS                 | 57                   | 45  | 46  | 61  |  |  |
| LIVER                   | 57                   | 45  | 46  | 61  |  |  |
| LUNG & BRONCHI          | 57                   | 45  | 46  | 61  |  |  |
| MUSCLE                  | 3                    | 8   | 19  | 9   |  |  |
| NASAL CAVITY (NOSE)     |                      | 2   |     |     |  |  |

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TABLE VII  
TISSUE COUNTS - MALE HAMSTERS

|                 | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-----------------|----------------------|-----|-----|-----|--|--|
| OVARIES         |                      |     |     |     |  |  |
| PANCREAS        | 24                   | 28  | 27  | 21  |  |  |
| PITUITARY       | 0                    | 5   | 7   | 0   |  |  |
| PROSTATE        | 13                   | 12  | 20  | 11  |  |  |
| RIB (JUNCTION)  |                      | 1   |     |     |  |  |
| SALIVARY GLAND  | 3                    | 8   | 17  | 8   |  |  |
| SEMINAL VESICLE | 7                    | 10  | 19  | 11  |  |  |
| SKIN            | 5                    | 6   | 17  | 8   |  |  |
| SPINAL CORD     | 4                    | 8   | 16  | 4   |  |  |
| SPLEEN          | 52                   | 41  | 43  | 59  |  |  |
| STOMACH         | 10                   | 14  | 31  | 41  |  |  |
| TESTIS          | 55                   | 41  | 44  | 54  |  |  |
| THYMUS          | 1                    | 2   | 2   | 1   |  |  |
| THYROID         | 6                    | 9   | 11  | 4   |  |  |
| TISSUE MASS     | 3                    | 2   | 7   | 4   |  |  |

TABLE VII  
TISSUE COUNTS - MALE HAMSTERS

|                      | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|----------------------|----------------------|-----|-----|-----|--|--|
| TRACHEA              | 18                   | 17  | 23  | 30  |  |  |
| URINARY BLADDER      | 12                   | 19  | 30  | 36  |  |  |
| UTERUS               |                      |     |     |     |  |  |
| AORTA                | 22                   | 20  | 10  | 4   |  |  |
| OPTIC NERVE          | 2                    | 5   | 9   |     |  |  |
| INTESTINES           | 16                   | 13  | 32  | 46  |  |  |
| LYMPH NODE           | 3                    | 7   | 15  | 2   |  |  |
| PERIPHERAL NERVE     | 1                    | 3   | 7   | 1   |  |  |
| STERNUM              | 4                    | 3   | 15  | 7   |  |  |
| TONGUE               | 3                    | 6   | 16  | 8   |  |  |
| SKULL                | 1                    | 5   | 15  | 2   |  |  |
| UNKNOWN              | 13                   | 14  | 10  | 16  |  |  |
| PAPILLARY PROJECTION |                      | 2   | 3   | 6   |  |  |
| FEET                 |                      | 1   | 2   |     |  |  |
| CYST                 |                      |     |     |     |  |  |

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TABLE VII  
TISSUE COUNTS - FEMALE HAMSTERS

|                         | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-------------------------|----------------------|-----|-----|-----|--|--|
| Total Number of Animals | 35                   | 36  | 61  | 31  |  |  |
| ADRENAL                 | 6                    | 7   | 7   | 9   |  |  |
| BONE                    | 3                    | 5   | 8   | 7   |  |  |
| BRAIN                   | 3                    | 5   | 8   | 8   |  |  |
| EPIDIDYMISS             |                      |     |     |     |  |  |
| ESOPHAGUS               | 7                    | 6   | 10  | 8   |  |  |
| EXT. & MID. EAR         | 1                    | 5   | 8   | 3   |  |  |
| EYES                    | 4                    | 5   | 7   | 7   |  |  |
| GALL BLADDER            | 8                    | 14  | 23  | 12  |  |  |
| HEART                   | 35                   | 36  | 60  | 31  |  |  |
| KIDNEYS                 | 35                   | 36  | 60  | 31  |  |  |
| LIVER                   | 35                   | 36  | 60  | 31  |  |  |
| LUNG & BRONCHI          | 35                   | 36  | 59  | 31  |  |  |
| MUSCLE                  | 3                    | 4   | 7   | 4   |  |  |
| NASAL CAVITY (NOSE)     |                      |     |     |     |  |  |

R&S 112173

TABLE VII  
TISSUE COUNTS - FEMALE HAMSTERS

|                 | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|-----------------|----------------------|-----|-----|-----|--|--|
| OVARIES         | 18                   | 22  | 34  | 18  |  |  |
| PANCREAS        | 17                   | 20  | 27  | 13  |  |  |
| PITUITARY       | 0                    | 2   | 2   | 1   |  |  |
| PROSTATE        |                      |     |     |     |  |  |
| RIB (JUNCTION)  |                      |     |     |     |  |  |
| SALIVARY GLAND  | 3                    | 5   | 12  | 5   |  |  |
| SEMINAL VESICLE |                      |     |     |     |  |  |
| SKIN            | 3                    | 3   | 12  | 5   |  |  |
| SPINAL CORD     | 3                    | 4   | 7   | 4   |  |  |
| SPLEEN          | 34                   | 34  | 57  | 30  |  |  |
| STOMACH         | 15                   | 14  | 30  | 26  |  |  |
| TESTIS          |                      |     |     |     |  |  |
| THYMUS          | 4                    | 0   | 2   | 1   |  |  |
| THYROID         | 3                    | 3   | 7   | 2   |  |  |
| TISSUE MASS     | 3                    | 3   | 4   | 3   |  |  |

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TABLE VII  
TISSUE COUNTS - FEMALE HAMSTERS

|                      | Untreated<br>Control | T-1 | T-2 | T-3 |  |  |
|----------------------|----------------------|-----|-----|-----|--|--|
| TRACHEA              | 12                   | 14  | 18  | 19  |  |  |
| URINARY BLADDER      | 16                   | 12  | 21  | 22  |  |  |
| UTERUS               | 32                   | 34  | 50  | 28  |  |  |
| AORTA                | 2                    | 6   | 20  | 6   |  |  |
| OPTIC NERVE          | 3                    | 2   | 6   |     |  |  |
| INTESTINES           | 18                   | 18  | 30  | 28  |  |  |
| LYMPH NODE           | 3                    | 3   | 8   | 3   |  |  |
| PERIPHERAL NERVE     | 2                    | 3   | 3   | 1   |  |  |
| STERNUM              | 2                    | 4   | 7   | 4   |  |  |
| TONGUE               | 2                    | 3   | 6   | 4   |  |  |
| SKULL                | 2                    | 4   | 3   | 3   |  |  |
| UNKNOWN              | 3                    | 2   | 20  | 6   |  |  |
| PAPILLARY PROJECTION | 1                    |     | 13  | 2   |  |  |
| FEET                 |                      |     |     |     |  |  |
| CYST                 |                      | 1   |     |     |  |  |

R&S 112175

[illegible]

Meetings of the Task Group for Audit of Vinyl Chloride (VC)  
Chronic Inhalation Study at the Sheraton Inn

R&S 112177

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:

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 - PathologyAudit Parameters

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

- . 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.

## 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)

- . 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

- . 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

-11-

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

- . 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

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

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:

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

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  
Record Subject to Approval  
March 31, 1978

R&S 112192



# MANUFACTURING CHEMISTS ASSOCIATION

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

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

R&S 112193

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

### 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

R&S 112194

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.

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.

R&S 112198

February 1, 1972

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).

R&S 112199

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<br>(Ethylene derived) | TE-I Low level -<br>50 ppm            | 100                      | 100            | 100          | 100            | 100             | 100            |
|                                      | TE-II Intermediate level -<br>500 ppm | 100                      | 100            | 100          | 100            | 100             | 100            |
|                                      | TE-III High level -<br>5000 ppm       | 100                      | 100            | 100          | 100            | 100             | 100            |

## II. Chamber Parameters

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

## III. Animal Parameters

### A. Clinical Observations

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

## B. Body Weights

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

## C. Clinical Pathology

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

## D. Anatomic Pathology

### 1. Methods of Sacrifice

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

### 2. Gross Pathology

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

### 3. Histopathology

Representative specimens of the following organs

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

Adrenal Glands  
All Gross Lesions  
Bone (femur, tarsal and metatarsal, including long bones of  
all four limbs)  
Bone Marrow (sternal)  
Brain  
Both Ears (external auditory canal with ceruminous (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 $\mu$ ), stained with hema-  
toxylin and eosin, and evaluated by light microscopy. If

R&S 112203

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

# 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.  
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) 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.

R&S 112205

Dr. J. C. Calandra  
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,



Accepted for:

Industrial BIO-TEST  
Laboratories, Inc.

Signed J. T. Tealander

Title President

Date May 22, 1973

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

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.

R&S 112207

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,

*JC*

Accepted for:

Industrial BIO-TEST  
Laboratories, Inc.

Signed

*R. Q. Roman*

Title Assistant to the President

Date September 7, 1973

R&S 112208

TABLE I (Revised August 31, 1973)

## 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<br>(Ethylene derived) | TE-I* Low level -<br>50 ppm            | 100                      | 100            | 100          | 100            | 100             | 100            |
|                                      | TE-II* Intermediate level -<br>200 ppm | 100                      | 100            | 100          | 100            | 100             | 100            |
|                                      | TE-III* High level -<br>2,500 ppm      | 100                      | 100            | 100          | 100            | 100             | 100            |
|                                      | TE-IV** High level -<br>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

R&S 112210

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

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 hold 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.

R&S 112211



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

R&S 112212

SURVIVING ANIMALS AT INC AS OF JAN. 20, 1975

| Inhaled Concentration<br>OF Vinyl Chloride | Hamsters |        | Mice |        | Rats |        |                        |
|--------------------------------------------|----------|--------|------|--------|------|--------|------------------------|
|                                            | Male     | Female | Male | Female | Male | Female | Female<br>with<br>Food |
| 2500 ppm                                   | 16       | 0(3)   | 0    | 0      | 0(4) | 0      | 0(7)                   |
| 200 ppm                                    | 26       | 41     | 0    | 0      | 54   | 13*    | --                     |
| 40 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.

*Industrial BIO-TEST Laboratories, Inc.*

DECATUR RESEARCH  
1800 EAST PERSHING ROAD  
DECATUR, ILLINOIS 62526

August 2, 1973

AREA CODE 217  
TELEPHONE 877-8254

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

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.

R&S 112214

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

R&S 112215

MANUFACTURING CHEMISTS ASSOCIATION

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

LENT 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

Dear Dr. Goode:

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

*Levent*

R&S 112216

June 15, 1973

Zeb Bell  
Walter Harris  
Russ Maycock  
Maurey Johnson  
Bill Rinehart  
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 Kusnetz (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 incomplected 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

R&amp;S 112218

2 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.

3 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.

4 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.

5 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.

6 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.

7 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.

8 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.

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

R&S 112219



## INTER-OFFICE CORRESPONDENCE

R&amp;S 112220

To: R. E. Widing

Date: August 6, 1973

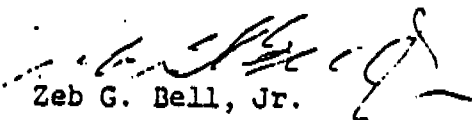
From: Zeb G. Bell, Jr.

Location: 12 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 inhalation 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)



# 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

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 | <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.

R&S 112221

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

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 IISummary of Tumors in Vinyl Chloride Exposed MiceIBT 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<br>Skin Tumor    |              | EC (para-aural)                                       | 3-20-74              |
| 1119 Female                   |                                     | HS (s)       |                                                       | 3-24-74              |
| 1200 Female                   | Metastatic Skin<br>Tumor            |              | EC & MC+ (Femoral<br>region)                          | 3-30-74              |
| T-II                          |                                     |              |                                                       |                      |
| 1347 Female                   | Metastatic Skin<br>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<br>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)                              | HS (s)       |                                                       | 3-22-74              |
| 1531 Female                   |                                     | HS (s)       | EC & MC (Femoral<br>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)                              | HS (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<br>region)                               | 4-5-74               |
| 1535 Female                   | AA (s)                              | HS (s)       |                                                       | 4-7-74               |
| 1432 Male                     | AA (s)                              |              |                                                       | 4-8-74               |
| 1477 Female                   | AA (s)<br>Metastatic Skin<br>Tumor? | HS (s)       | EC (Para-Aural)<br>MC (Abdomen)<br>EC (Pelvic region) | 4-9-74               |

TABLE III

*Industrial BIO-TEST Laboratories, Inc.*1810 FRONTAGE ROAD  
NORTHBROOK, ILLINOIS 60062

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Summary 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 → Lu |
| 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

# MANUFACTURING CHEMISTS ASSOCIATION

1825 CONNECTICUT AVENUE, N.W. WASHINGTON, D. C. 20003 (202) 483-6126

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<br>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                                      |

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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.

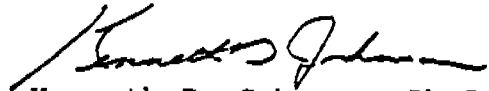
It was further moved, seconded and carried that the chairman appoint a group to begin investigating the cost and availability of facilities of new experiments to be conducted at lower levels of exposure, with larger groups of animals. He was asked specifically to seek to encourage the National Center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

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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