

MCA

MANUFACTURING CHEMISTS ASSOCIATION

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CHEMICALS  
RESEARCH

MAY 19 1975

*C. K. to CLW*  
May 14, 1975

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TO: Technical Task Group on Vinyl Chloride Research

Gentlemen:

Attached for your perusal is Industrial BIO-TEST Laboratories' May 9, 1975 report on the "Chronic Vapor Inhalation Study with Vinyl Chloride (Ethylene Derived) in Albino Rats."

Sincerely,

*MF*  
Milton Freifeld,  
Project Manager

MF/etv

Attachment

VVC 000004458

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

REPORT TO  
MANUFACTURING CHEMISTS ASSOCIATION  
GROSS AND HISTOPATHOLOGIC FINDINGS  
ONE-YEAR INTERIM SACRIFICE  
CHRONIC VAPOR INHALATION STUDY WITH  
VINYL CHLORIDE (ETHYLENE DERIVED)  
IN ALBINO RATS

MAY 9, 1975

IBT NO. 663-03222

VVC 000004459

*Industrial* **BIO-TEST** *Laboratories, Inc.*

1810 FRONTAGE ROAD  
NORTHBROOK, ILLINOIS 60062

May 9, 1975

Mr. Milton Freifield  
Project Manager, Vinyl Chloride Research  
Manufacturing Chemists Association  
1825 Connecticut Avenue, N.W.  
Washington, D. C. 20009

Dear Mr. Freifield:

Re: IBT No. 663-03222 - Chronic Vapor Inhalation Study with  
Vinyl Chloride (Ethylene Derived) in Albino Rats - Gross  
and Histopathologic Findings - One-Year Interim Sacrifice

We are submitting herewith our laboratory report prepared  
in connection with the above study.

Very truly yours,



J. C. Calandra  
President

JCC:mcb

VVC 000004460

REPORT TO  
MANUFACTURING CHEMISTS ASSOCIATION  
GROSS AND HISTOPATHOLOGIC FINDINGS  
ONE-YEAR INTERIM SACRIFICE  
CHRONIC VAPOR INHALATION STUDY WITH  
VINYL CHLORIDE (ETHYLENE DERIVED)  
IN ALBINO RATS

MAY 9, 1975

IBT NO. 663-03222

I. Introduction

At the request of the Manufacturing Chemists Association, 40 rats (5 males and 5 females) from the control and test groups were sacrificed on September 5, 1974, to conduct cytogenetic studies on bone marrow specimens obtained at time of sacrifice. The purpose of this report is to present the gross and histopathological findings in other tissues from these animals.

## II. Summary

Treatment-related gross and/or histopathological findings were confined to the liver of test animals at exposure levels of 50, 200 and 2,500 ppm.

Gross pathologic findings ascribed to vinyl chloride were confined to the liver of 2 animals of the 200 ppm level (group T-II) and the liver of 5 animals of the 2,500 ppm level (group T-III). Findings consisted of solitary, dark red, nodular foci in the subcapsular region of single liver lobes. These nodules varied in size from approximately 4 mm to 4 cm in diameter and, on cross-section, they contained blood-filled cystic spaces.

Upon histopathological examination, the above lesions were identified as sites of hepatic angiosarcoma. In addition, there was focal hypertrophy and hyperplasia of hepatocytes in the liver sections from test animals at each exposure level. The incidence and relative severity of this finding could be correlated with the level of exposure to the test material. No extra-hepatic angiosarcomas were observed.

## Materials and Methods

All animals, selected at random for sacrifice, were rendered unconscious in a closed chamber by exposure to carbon dioxide gas and exsanguinated, and a complete necropsy examination was performed. The organs were weighed. Representative specimens of the following organs and tissues were placed in 10% neutral buffered formalin for fixation:

|                                                            |                                                  |
|------------------------------------------------------------|--------------------------------------------------|
| Adrenal Glands                                             | Pancreas                                         |
| All Gross Lesions                                          | Parathyroid Gland                                |
| Bone (femur and sternum)                                   | Pituitary Gland                                  |
| Bone Marrow (sternal)                                      | Prostate Gland                                   |
| Brain and Spinal Cord                                      | Salivary Gland                                   |
| Esophagus                                                  | Seminal Vesicles                                 |
| Eye                                                        | Skin                                             |
| Gonads (testes and ovaries)                                | Small Intestine (duodenum,<br>jejunum and ileum) |
| Kidneys                                                    | Spleen                                           |
| Large Intestine (caecum and colon)                         | Stomach                                          |
| Liver                                                      | Thymus                                           |
| Lungs                                                      | Thyroid Gland                                    |
| Lymph Nodes (tracheobronchial,<br>cervical and mesenteric) | Trachea                                          |
| Optic Nerve                                                | Urinary Bladder                                  |
|                                                            | Uterus                                           |

The above tissues from all animals were processed by conventional methods, embedded in Paraplast\*, sectioned at 4-6 microns, stained with Hematoxylin and Eosin and examined by light microscopy.

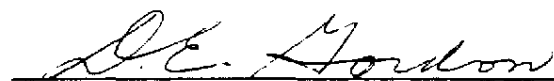
The gross pathologic findings are presented in Tables I through II.  
The histopathological findings are presented in Tables III and IV.

The pathologist's report is presented on pages 4 through 6.

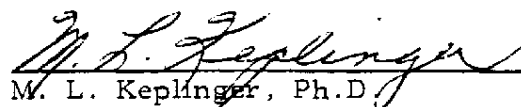
Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report prepared by:

  
Donovan E. Gordon, D.V.M., Ph.D.  
Section Head, Pathology

Report approved by:

  
M. L. Keplinger, Ph.D.  
Manager, Toxicology

mcb

\* Sherwood Medical Industries, St. Louis, Missouri 63103.

IBT No. 663-03222  
Manufacturing Chemists Association

February 27, 1975

A gross and histopathological examination was conducted on a series of tissues and organs from rats of the 12-month interim sacrifice of IBT No. 663-03222.

Treatment-related gross pathologic changes were confined to the liver of 2 T-II females (Nos. 550 and 599), 1 T-III male (No. 694) and 4 T-III females (Nos. 717, 732, 735 and 742). The lesions consisted of solitary, dark red nodules within the subcapsular region of 1 liver lobe. The nodules measured approximately 4 mm to 4 cm in diameter and contained blood-filled cystic spaces. There were fibrous adhesions between the capsular surface of some of these nodules and adjacent visceral structures. In 1 animal (No. 735), there were 2 different liver lobes with solitary nodular foci similar to the above. Upon histopathologic examination of the hepatic nodules, they were found to be angiosarcomas. A small amount of hemorrhagic fluid was present in the abdominal cavity of 1 animal (No. 59 ) as a result of hemorrhage from the surface of the liver tumor.

Treatment-related histopathologic findings were confined to the liver of 5 T-I animals and all of the T-II and T-III animals. There was an exposure-related incidence and severity of hypertrophy and hyperplasia of hepatocytes throughout the liver sections. The hypertrophied hepatocytes had an increase in cytoplasmic mass which had a light, eosinophilic staining appearance with a few basophilic condensations. In some sections, these cells formed small

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nodules with very little compression of the adjacent parenchymal cells of the liver. Some of the hyperplastic hepatocytes had prominent nuclei and nucleoli. They also formed small, discrete nodules in some areas. In addition, these cells often had a slightly increased cytoplasmic basophilia. In regard to the angiosarcomas, the early and more advanced stages of the tumor could be identified. In the early lesion, there was focal sinusoidal dilatation accompanied by hyperplastic and/or hypertrophied endothelial-like lining cells. The areas usually communicated with frank areas of angiosarcoma. The latter were characterized by the presence of blood-filled cystic sinusoidal spaces (peliotic foci) in which there were papillary projections of cords of liver cells that were covered by large, hyperchromatic to pleomorphic lining cells on the sinusoidal surface. The hepatocytes in the area adjacent to the tumor were also invaded by these tumor cells. In some areas, there was complete destruction of the enveloped liver cords and replacement by solid sheets of sarcomatous tumor cells which contained numerous mitotic figures and had anaplastic features. In most instances, the tumors were situated just beneath the capsular surface of the affected liver lobule and there was focal invasion of tumor cells into the capsule with hemorrhage into the peritoneal cavity at these sites. There were also fibrous adhesions to the adjacent visceral organs at the capsular surface of the tumors which correlated with the gross observations. In 2 animals (Nos. 663 and 668), the tumor foci were too small to be detected microscopically and they were in the early stages of development. In this study, there were no metastatic

tumor foci found in other organs, however; tumor emboli were present in some of the vessels of the larger liver tumors. All liver lesions, observed by light microscopy, summarized in Table III.

The other changes described in the liver and other tissues (Table IV) were regarded as lesions of naturally occurring diseases. The lesions were present, in most instances, among both control and test animals. The small (1-3 mm), red, subcapsular foci observed at necropsy in the liver of both control and test animals could be correlated with scattered foci of hepatocellular necrosis observed histologically in these animals.



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Donovan E. Gordon, D.V.M., Ph.D.  
Diplomate, American College of  
Veterinary Pathologists

TABLE I

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Individual Gross Pathologic Findings in the Liver - Males

| Group   | Animal Number | Gross Pathologic Findings                                                      |
|---------|---------------|--------------------------------------------------------------------------------|
| Control | 39            | 1 mm dark red foci in all lobes                                                |
|         | 54            | None                                                                           |
|         | 55            | Few 1 mm dark red foci in all lobes                                            |
|         | 69            | Numerous 1 mm dark red foci in all lobes                                       |
|         | 84            | None                                                                           |
| T-I     | 205           | Few 1 mm dark red foci in all lobes                                            |
|         | 256           | 1-3 mm dark red foci in all lobes                                              |
|         | 264           | None                                                                           |
|         | 279           | None                                                                           |
|         | 299           | Numerous 1-3 dark red depressed foci in all lobes                              |
| T-II    | 404           | Numerous 1-5 mm dark red depressed foci in all lobes                           |
|         | 433           | Few 1-3 mm dark red foci in all lobes                                          |
|         | 459           | Few 1 mm dark red foci in all lobes                                            |
|         | 469           | 1 mm dark red foci in all lobes                                                |
|         | 489           | 1 mm dark red foci in all lobes, slight pale discoloration                     |
| T-III   | 609           | None                                                                           |
|         | 639           | Numerous 1 mm dark red foci in all lobes                                       |
|         | 663           | Granular surface with numerous 1 mm dark red foci in all lobes                 |
|         | 668           | 1 mm dark red focus in 1 lobe                                                  |
|         | 694           | 0.5 cm dark red subcapsular nodule in 1 lobe with capsular adhesions to spleen |

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TABLE I continued

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Individual Gross Pathologic Findings in the Liver - Females

| Group   | Animal Number | Gross Pathologic Findings                                                                                                                              |
|---------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Control | 106           | 1-3 mm dark red foci in all lobes                                                                                                                      |
|         | 149           | Few 1 mm dark red foci in all lobes                                                                                                                    |
|         | 160           | None                                                                                                                                                   |
|         | 178           | Numerous 1 mm red foci in all lobes                                                                                                                    |
|         | 200           | Few 1 mm red foci in all lobes                                                                                                                         |
| T-I     | 303           | Few 1 mm dark red foci in all lobes                                                                                                                    |
|         | 349           | 1-3 mm dark red depressed foci in all lobes                                                                                                            |
|         | 369           | 1-3 mm dark red foci in all lobes                                                                                                                      |
|         | 381           | 1-3 mm dark red foci in all lobes                                                                                                                      |
|         | 397           | Few 1-2 mm dark red foci in all lobes                                                                                                                  |
| T-II    | 524           | Few 1-3 mm dark red foci in all lobes                                                                                                                  |
|         | 550           | 0.5 cm dark red nodule in 1 lobe                                                                                                                       |
|         | 569           | 1 mm dark red foci in all lobes                                                                                                                        |
|         | 594           | 1-2 mm dark red foci in all lobes                                                                                                                      |
|         | 599           | 4 cm subcapsular nodular focus in major lobe, capsular adhesions to diaphragm, spleen and serosal surface of small intestine                           |
| T-III   | 717           | 0.5 cm dark red focus in 1 lobe with capsular adhesions to mesentery                                                                                   |
|         | 728           | None                                                                                                                                                   |
|         | 732           | 1 cm dark red focus in 1 lobe                                                                                                                          |
|         | 735           | 3 cm nodule in 1 lobe; 0.5 cm dark red nodule in another lobe; focal capsular adhesions between nodule, small intestine, stomach, spleen and mesentery |
|         | 742           | 4 mm dark red depressions in 1 lobe, 1-5 mm dark red foci in all other lobes                                                                           |

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TABLE II

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Summary of Gross Pathologic Findings in All Tissues Except Liver

| Organ          | Findings                                             | Group:            | Control                  | T-I                      | T-II                     | T-III                    |
|----------------|------------------------------------------------------|-------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                |                                                      | Number per Group: | 10/10                    | 10/10                    | 10/10                    | 10/10                    |
|                |                                                      |                   | Male/Female<br>Incidence | Male/Female<br>Incidence | Male/Female<br>Incidence | Male/Female<br>Incidence |
| Lung           | Focal adhesions to diaphragm or thorax               |                   | 3/0                      | 1/0                      | 2/0                      | 0/0                      |
|                | Few pin-point red foci in all lobes                  |                   | 1/0                      | 0/0                      | 0/0                      | 1/0                      |
|                | Focal consolidation of 1 or more lobes               |                   | 0/1                      | 0/0                      | 0/1                      | 1/0                      |
|                | Abscesses in parenchyma                              |                   | 0/0                      | 1/0                      | 0/0                      | 0/0                      |
| Kidneys        | Unilateral hydronephrosis                            |                   | 0/0                      | 1/0                      | 0/0                      | 0/0                      |
|                | Bilateral hydronephrosis                             |                   | 1/0                      | 0/0                      | 0/0                      | 0/0                      |
| Ovaries        | Unilateral or bilateral follicular cysts             |                   | 2                        | 2                        | 0                        | 1                        |
| Adrenal glands | Small (1 mm) blood-filled cysts in cortex of 1 gland |                   | 0/1                      | 0/0                      | 0/0                      | 0/0                      |
|                | Enlarged and dark red color                          |                   | 0/0                      | 0/0                      | 0/1                      | 0/0                      |
| Uterine horns  | Hydrometra                                           |                   | 2                        | 0                        | 0                        | 0                        |

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TABLE II continued

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Summary of Gross Pathologic Findings in All Tissues Except Liver

| Organ            | Findings                                   | Group:            | Control                  | T-I                      | T-II                     | T-III                    |
|------------------|--------------------------------------------|-------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                  |                                            | Number per Group: | 10/10                    | 10/10                    | 10/10                    | 10/10                    |
|                  |                                            |                   | Male/Female<br>Incidence | Male/Female<br>Incidence | Male/Female<br>Incidence | Male/Female<br>Incidence |
| Pituitary gland  | Hemorrhagic focus                          |                   | 0/0                      | 1/0                      | 0/0                      | 0/0                      |
| Spleen           | Few adhesions to mesentery                 |                   | 0/0                      | 0/0                      | 1/0                      | 1/0                      |
|                  | Enlarged (3 times normal size)             |                   | 0/0                      | 0/0                      | 0/1                      | 0/0                      |
| Abdominal cavity | Small amount of blood in peritoneal cavity |                   | 0/0                      | 0/0                      | 0/1                      | 0/0                      |

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TABLE III

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Summary of Liver Lesions\* - Males

| Group and Animal Number | Bile Duct Proliferation | Portal to Sinusoidal Extrahepatic Hematopoiesis | Necrosis of Hepatocytes | Cytoplasmic Lipid Vacuoles in Hepatocytes | Hypertrophy of Hepatocytes | Hypertrophy and Hyperplasia of Hepatocytes | Sinusoidal Dilatation |                    | Blood-Filled Cystic Spaces (Peliosis) | Angiosarcoma |
|-------------------------|-------------------------|-------------------------------------------------|-------------------------|-------------------------------------------|----------------------------|--------------------------------------------|-----------------------|--------------------|---------------------------------------|--------------|
|                         |                         |                                                 |                         |                                           |                            |                                            | Region Only           | Section Throughout |                                       |              |
| Control                 |                         |                                                 |                         |                                           |                            |                                            |                       |                    |                                       |              |
| 39                      |                         |                                                 | 2/M                     |                                           |                            |                                            |                       |                    |                                       |              |
| 54                      |                         | 1-2                                             |                         |                                           |                            |                                            |                       |                    | 1-2                                   |              |
| 55                      |                         |                                                 | 1-2/M                   |                                           |                            |                                            | 1                     |                    |                                       |              |
| 69                      |                         |                                                 | 2/M                     |                                           |                            |                                            |                       |                    |                                       |              |
| 84                      |                         |                                                 | 1                       |                                           |                            |                                            |                       |                    | 1                                     |              |
| T-I                     |                         |                                                 |                         |                                           |                            |                                            |                       |                    |                                       |              |
| 205                     | 1                       |                                                 | 1-2/M                   | 1 (few)                                   |                            |                                            |                       |                    | 1                                     |              |
| 256                     |                         |                                                 | 1-2                     |                                           |                            |                                            |                       |                    | 1                                     |              |
| 264                     |                         |                                                 | 1-2                     | 1                                         |                            |                                            |                       |                    | 1-2                                   |              |
| 279                     |                         | 1                                               |                         | 1-2                                       | 1 (few)                    |                                            |                       |                    |                                       |              |
| 299                     |                         | 1                                               | 1-2                     | 4/D (1 lobe)                              |                            | 1                                          | 1-2                   |                    |                                       |              |
| T-II                    |                         |                                                 |                         |                                           |                            |                                            |                       |                    |                                       |              |
| 404                     | 1-2                     | 2                                               | 1                       |                                           |                            | 1-2                                        |                       |                    | 1                                     |              |
| 433                     |                         |                                                 | 2/M                     | 2                                         |                            | 1-2                                        |                       |                    | 1                                     |              |
| 459                     |                         |                                                 | 1-2                     |                                           |                            | 1                                          | 1-2                   |                    |                                       |              |
| 469                     | 1                       |                                                 | 2/M                     |                                           |                            | 1-2                                        | 1                     |                    | 1-2                                   |              |
| 489                     | 1                       |                                                 | 2/M                     |                                           |                            | 1-2                                        |                       |                    | 2                                     |              |
| T-III                   |                         |                                                 |                         |                                           |                            |                                            |                       |                    |                                       |              |
| 609                     | 1                       |                                                 | 2                       | 1                                         |                            | 2/M                                        |                       |                    |                                       |              |
| 639                     | 1                       |                                                 | 2/M                     | 2                                         |                            | 1-2/M                                      | 1                     |                    |                                       |              |
| 663                     | 1                       |                                                 | 2                       | 1                                         |                            | 2/M                                        |                       |                    | 1                                     | P            |
| 668                     | 1-2                     |                                                 | 2                       | 1                                         |                            | 2-3/M                                      | 2                     |                    | P                                     | P            |
| 694                     | 1                       |                                                 | 1-2/M                   |                                           |                            | 2/M                                        |                       |                    | P                                     | P            |

\* All lesions are focal unless otherwise indicated.

## Grading System and Abbreviations

1 = minimal in severity

2 = mild in severity

3 = moderate in severity

4 = marked in severity

5 = extreme in severity

P = Present, no grade

M = multifocal

D = diffuse

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TABLE III continued  
 TEST MATERIAL: Vinyl Chloride (Ethylene Derived)  
 Chronic Vapor Inhalation Study - Albino Rats  
 One-Year Interim Sacrifice  
 Summary of Liver Lesions\* - Females

| Group and Animal Number | Bile Duct Proliferation | Portal to Sinusoidal Extramedullary Hematopoiesis | Necrosis of Hepatocytes | Cytoplasmic Lipid Vacuoles in Hepatocytes | Hypertrophy of Hepatocytes | Hypertrophy and Hyperplasia of Hepatocytes | Sinusoidal Dilatation Subcapsular Region Only | Throughout Section | Blood-Filled Cystic Spaces (Peliosis) | Angiosarcoma |
|-------------------------|-------------------------|---------------------------------------------------|-------------------------|-------------------------------------------|----------------------------|--------------------------------------------|-----------------------------------------------|--------------------|---------------------------------------|--------------|
| Control                 |                         |                                                   |                         |                                           |                            |                                            |                                               |                    |                                       |              |
| 106                     | 1                       |                                                   |                         |                                           |                            |                                            | 1                                             |                    |                                       |              |
| 149                     |                         |                                                   | 1-2/M                   |                                           |                            |                                            |                                               |                    |                                       |              |
| 160                     |                         |                                                   |                         |                                           |                            |                                            |                                               | 1                  |                                       |              |
| 178                     |                         |                                                   | 2                       |                                           |                            |                                            |                                               | 1                  |                                       |              |
| 200                     |                         | 1                                                 | 1                       |                                           |                            |                                            |                                               | 1                  |                                       |              |
| T-I                     |                         |                                                   |                         |                                           |                            |                                            |                                               |                    |                                       |              |
| 303                     |                         |                                                   |                         |                                           |                            |                                            |                                               | 1-2                |                                       |              |
| 349                     |                         |                                                   |                         |                                           | 1                          |                                            |                                               | 1-2                |                                       |              |
| 369                     |                         |                                                   |                         |                                           |                            | 1                                          |                                               | 1-2                |                                       |              |
| 381                     | 1                       |                                                   |                         |                                           |                            | 1                                          |                                               | 1-2                |                                       |              |
| 397                     |                         |                                                   | 1-2 (few)               |                                           |                            | 1                                          |                                               | 1                  |                                       |              |
| T-II                    |                         |                                                   |                         |                                           |                            |                                            |                                               |                    |                                       |              |
| 524                     | 1                       | 1                                                 |                         | 1-2                                       |                            | 1                                          |                                               | 1                  |                                       |              |
| 550                     | 1                       |                                                   |                         |                                           | 1                          |                                            |                                               | 2                  | P                                     | P            |
| 569                     | 1                       | 1                                                 |                         |                                           |                            | 1-2                                        |                                               | 1-3                |                                       |              |
| 594                     |                         |                                                   |                         |                                           |                            | 1-2/M                                      | 2                                             |                    |                                       |              |
| 599                     |                         | 1-2                                               |                         |                                           |                            | 2/M                                        |                                               |                    | P                                     | P            |
| T-III                   |                         |                                                   |                         |                                           |                            |                                            |                                               |                    |                                       |              |
| 717                     | 1                       | 1                                                 | 2                       | 1                                         |                            | 2/M                                        |                                               | 2                  | P                                     | P            |
| 728                     | 1                       | 1                                                 |                         |                                           |                            | 2-3/M                                      |                                               | 1-2                |                                       |              |
| 732                     | 1                       |                                                   |                         | 1-2                                       |                            | 2-3/M                                      |                                               | 2                  | P                                     | P            |
| 735                     | 1-3                     | 1-2                                               |                         |                                           |                            | 2-3/M                                      |                                               | 2                  | P                                     | P            |
| 742                     |                         | 1                                                 |                         | 1                                         |                            | 2/M                                        |                                               | 2                  | P                                     | P            |

\* All lesions are focal unless otherwise indicated.

Grading System and Abbreviations

1 = minimal in severity  
 2 = mild in severity  
 3 = moderate in severity  
 4 = marked in severity  
 5 = extreme in severity

P = Present, no grade  
 M = multifocal  
 D = diffuse

VVC 000004472

TABLE IV

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Incidental Histopathologic Changes in Tissues Other Than Liver - Males

| Organ           | Findings                                                                                                                                   | Group:<br>Number Examined: | Control<br>10 |                  | T-I<br>10 |                  | T-II<br>10 |                  | T-III<br>10 |                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------|------------------|-----------|------------------|------------|------------------|-------------|------------------|
|                 |                                                                                                                                            |                            | Incidence     | Average<br>Grade | Incidence | Average<br>Grade | Incidence  | Average<br>Grade | Incidence   | Average<br>Grade |
| Trachea         | Chronic tracheitis                                                                                                                         |                            | 2             | 2.0              | 3         | 1.0              | 2          | 1.8              | 3           | 1.7              |
| Lung            | Chronic focal murine pneumonia                                                                                                             |                            | 3             | 1.3              | 5         | 1.3              | 2          | 1.5              | 5           | 1.3              |
|                 | Focal aggregates of alveolar macrophages                                                                                                   |                            | 2             | 1.0              |           |                  | 1          | 1.0              | 2           | 1.0              |
|                 | Acute focal bronchopneumonia                                                                                                               |                            |               |                  | 1         | 2.0              |            |                  |             |                  |
| Heart           | Focal myocardial degeneration and fibrosis                                                                                                 |                            | 2             | 1.0              | 2         | 1.0              | 1          | 1.0              |             |                  |
| Kidney          | Bilateral focal proteinaceous tubular casts                                                                                                |                            | 3             | 1.2              | 2         | 1.0              | 2          | 1.8              | 4           | 1.5              |
|                 | Bilateral focal tubular nephrosis                                                                                                          |                            | 1             | 1.5              |           |                  | 2          | 1.8              | 3           | 1.7              |
|                 | Bilateral focal interstitial lymphoid infiltrations                                                                                        |                            |               |                  | 1         | 1.0              |            |                  | 1           | 1.0              |
|                 | Bilateral chronic focal nephritis                                                                                                          |                            | 2             | 1.0              | 1         | 1.5              |            |                  |             |                  |
|                 | Bilateral focal mineralized microconcretions in tubules                                                                                    |                            |               |                  |           |                  | 1          | 1.0              |             |                  |
|                 | Unilateral hydronephrosis                                                                                                                  |                            |               |                  | 1         | 2.0              |            |                  |             |                  |
|                 | Bilateral hydronephrosis                                                                                                                   |                            | 1             | 2.5              |           |                  |            |                  |             |                  |
| Urinary bladder | Proteinaceous plug in lumen                                                                                                                |                            | 2             | 1.0              | 1         | 1.0              | 3          | 1.0              | 4           | 1.0              |
| Prostate gland  | Focal interstitial lymphoid infiltrations                                                                                                  |                            |               |                  |           |                  | 1          | 1.0              |             |                  |
| Testes          | Unilateral focal testicular degeneration                                                                                                   |                            |               |                  |           |                  | 1          | 1.0              |             |                  |
|                 | Unilateral focal testicular degeneration with spermatocoeles, spermatoc granuleomas and dystrophic mineralization of some affected tubules |                            |               |                  |           |                  | 1          | 3.5              |             |                  |

VVC 000004473

TABLE IV continued

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Incidental Histopathologic Changes in Tissues Other Than Liver - Males

| Organ           | Findings                                                                | Group:           |         | T-I       |               | T-II      |               | T-III     |               |
|-----------------|-------------------------------------------------------------------------|------------------|---------|-----------|---------------|-----------|---------------|-----------|---------------|
|                 |                                                                         | Number Examined: | Control | Incidence | Average Grade | Incidence | Average Grade | Incidence | Average Grade |
|                 |                                                                         |                  | 10      |           | 10            | 10        |               | 10        |               |
| Pituitary gland | Focal cytoplasmic vacuolation of basophils<br>Small chromophobe adenoma | 2                | 1.0     | 2         | 1.0           | 1         | 1.0           | 1         | 1.0           |
| Adrenal glands  | Unilateral focus of lipomatous degeneration<br>in cortex                | 2                | 1.0     |           |               | 1         | 1.5           | 1         | 1.0           |
| Thyroid glands  | Bilateral diffuse hypertrophy of follicular<br>epithelial cells         |                  |         |           |               | 1         | 2.0           |           |               |
| Colon           | Nematode parasites in lumen (nematodiasis)                              | 1                |         |           |               |           |               |           |               |
| Bone            | Focal medial hypertrophy of arterioles in<br>femoral marrow             | 1                | 3.0     | 1         | 2.0           | 1         | 1.0           | 1         | 2.0           |

Grading System

1.0 = minimal in severity  
 2.0 = mild in severity  
 3.0 = moderate in severity  
 4.0 = marked in severity  
 5.0 = extreme in severity  
 P = Present, no grade

TABLE IV continued

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Incidental Histopathologic Changes in Tissues Other Than Liver - Females

| Organ   | Findings                                                                                                                       | Group: Control   |               | T-I       |               | T-II      |               | T-III     |               |
|---------|--------------------------------------------------------------------------------------------------------------------------------|------------------|---------------|-----------|---------------|-----------|---------------|-----------|---------------|
|         |                                                                                                                                | Number Examined: | Average Grade | Incidence | Average Grade | Incidence | Average Grade | Incidence | Average Grade |
|         |                                                                                                                                | 10               |               | 10        |               | 10        |               | 10        |               |
| Trachea | Chronic tracheitis                                                                                                             | 3                | 1.8           | 3         | 1.5           | 2         | 1.8           | 1         | 1.0           |
| Lung    | Chronic focal murine pneumonia                                                                                                 | 5                | 1.2           | 4         | 1.0           | 4         | 1.6           | 4         | 1.1           |
|         | Focal aggregates of alveolar macrophages                                                                                       | 2                | 1.0           |           |               |           |               | 1         | 1.0           |
|         | Diffuse hemorrhage and edema (agonal)                                                                                          | 1                | 3.0           |           |               |           |               |           |               |
|         | Focal suppurative bronchiolitis                                                                                                | 1                | 1.0           |           |               | 1         | 2.0           |           |               |
| Heart   | Few small foci of chronic myocarditis                                                                                          |                  |               |           |               |           |               | 1         | 1.0           |
| Kidneys | Unilateral focal proteinaceous tubular casts                                                                                   | 1                | 1.0           |           |               | 1         | 1.0           |           |               |
|         | Bilateral focal proteinaceous tubular casts                                                                                    | 1                | 2.0           |           |               | 3         | 2.0           | 1         | 1.0           |
|         | Bilateral focal tubular nephrosis                                                                                              | 1                | 1.5           |           |               | 1         | 1.0           |           |               |
|         | Unilateral chronic focal nephritis                                                                                             | 1                | 1.0           |           |               |           |               |           |               |
|         | Unilateral focal mineralized microconcretions in tubules                                                                       |                  |               |           |               |           |               | 1         | 1.0           |
|         | Bilateral focal mineralized microconcretions in tubules                                                                        | 4                | 1.9           | 3         | 1.0           | 4         | 1.6           | 4         | 1.9           |
| Spleen  | Unilateral large tubular cyst in cortex                                                                                        |                  |               |           |               |           |               |           |               |
|         | Bilateral diffuse brown granular pigment and protein resorption droplets within cytoplasm of cortical tubular epithelial cells |                  |               |           |               | 1         | 1.5           | 1         | P             |
|         | Increased hemosiderin pigment                                                                                                  | 2                | 1.5           | 2         | 1.5           | 1         | 1.0           | 2         | 1.0           |
| Uterus  | Diffuse increased extramedullary hematopoiesis                                                                                 |                  |               |           |               | 1         | 3.0           | 1         | 2.0           |
|         | Hydronephra                                                                                                                    | 1                | 3.0           |           |               |           |               |           |               |
|         | Suppurative metritis with endometrial abscesses                                                                                |                  |               |           |               | 1         | 2.0           | 1         | 2.0           |
|         | Suppurative metritis                                                                                                           |                  |               |           |               |           |               |           |               |

TEST MATERIAL: Vinyl Chloride (Ethylene Derived)

Chronic Vapor Inhalation Study - Albino Rats

One-Year Interim Sacrifice

Incidental Histopathologic Changes in Tissues Other Than Liver - Females

TABLE IV continued

| Organ           | Findings                                                     | Number Examined: |     |           |         | Average   |     |           |     |
|-----------------|--------------------------------------------------------------|------------------|-----|-----------|---------|-----------|-----|-----------|-----|
|                 |                                                              | Group:           |     | Incidence |         | Incidence |     | Incidence |     |
|                 |                                                              | Control          | T-I | 10        | Average | T-II      | 10  | Average   | 10  |
| Ovaries         | Bilateral focal follicular cysts                             |                  | 1   |           | P       | 1         |     | P         |     |
|                 | Unilateral focal follicular cysts                            |                  | 1   |           | P       |           |     |           | 2   |
| Pituitary gland | Focal hyperplasia of chromophobe cells                       |                  |     |           |         | 2         |     |           |     |
| Adrenal glands  | Unilateral focus of lipomatous degeneration in cortex        | 1                | 1   | 4.0       | 1.0     | 2         | 2.8 | 1.0       | 1   |
|                 | Unilateral focal hematocysts in cortex                       |                  |     |           |         | 1         | 1.0 |           | 2.0 |
| Pancreas        | Focal atrophy of acinar cells                                | 1                |     | 1.0       |         | 1         | 1.0 |           | 2.0 |
| Thyroid gland   | Bilateral diffuse hypertrophy of follicular epithelial cells |                  |     |           |         |           |     |           | 1.0 |
| Eye             | Unilateral chronic focal dacryadenitis                       | 1                |     | 1.0       |         |           |     |           |     |
|                 | Unilateral focal retinal degeneration                        |                  | 1   |           | 1.0     |           |     |           |     |
| Colon           | Nematode parasites in lumen (nematodiasis)                   |                  |     |           |         |           |     |           | 2   |

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