

(5-23-96)

2,4-D ACID

§83-2(b) Carcinogenicity - Mouse

**PRIMARY REVIEWER:** Jess Rowland, M.S, Toxicologist  
Section I, Toxicology Branch II (7509C)

**SECONDARY REVIEWER:** Yiannakis Ioannou, Ph.D, Head  
Section I, Toxicology Branch II (7509C)

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|------------------------|
| DATA EVALUATION RECORD |
|------------------------|

**STUDY TYPE:** Carcinogenicity Study - Mice.

**GUIDELINE:** §83-2(b)

**DP BARCODE(S):** D215600 & D222295

**SUBMISSION(S):** S487309 & S499298

**PC CODE:** 030001

**TOX.CHEM.No:** 315

**TEST MATERIAL:** 2,4-Dichlorophenoxyacetic acid (2,4-D)

**CITATION(S):** Study in Male Mice: Sott, WT, Johnson, KA, Gilbert, KS Ormand, JR, and Battjes, JE. "2,4-DICHLOROPHENOXYACETIC ACID: DIETARY ONCOGENICITY STUDY IN MALE B6C3F1 MICE - TWO YEAR FINAL REPORT" The Toxicology Research Laboratory, Dow Chemical Co., Midland, Michigan. Study ID: K-002372-063M. 11/16/95. **MRID No. 43879801.** Unpublished.

Study in Female Mice: Sott, WT, Johnson, KA, Gilbert, KS Ormand, JR, and Battjes, JE. "2,4-DICHLOROPHENOXYACETIC ACID: DIETARY ONCOGENICITY STUDY IN B6C3F1 MICE - TWO YEAR FINAL REPORT" The Toxicology Research Laboratory, Dow Chemical Co., Midland, Michigan. Study ID: K-002372-063F. 03/10/95. **MRID No. 43597201.** Unpublished.

**EXECUTIVE SUMMARY:** In a carcinogenicity study, 2,4-dichlorophenoxyacetic acid (96.4%) was administered in the diet for 104 weeks to male B6C3F1 mice (50/dose) at 0, 5, 62.5 or 125 mg/kg/day (MRID No. 43879801) and to female B6C3F1 mice (50/dose) at 0, 5, 150 or 300 mg/kg/day (MRID No. 43597201). In addition, 10 mice/sex/dose were sacrificed at 12 months. Parameters evaluated were: survival, body weight, food consumption, clinical signs of toxicity, hematology parameters at 12, 18 and 24 months, and organ weights and histopathology at 12 and 24 months.

In males, no treatment-related effects were seen on survival, body weight, body weight gain, clinical signs, hematology parameters, or gross pathology at any dose level. Females at 300 mg/kg/day exhibited 14% decreases in body weight gain at 3 months into the study but by study termination (24 months), body weight gains of these mice were similar to that of the controls. Treatment did not affect survival, induce clinical signs, alter hematology parameters,

or cause gross pathological changes at any dose level in females. Kidney was identified as the target organ for both sexes; dose-related increases in kidney weights and renal lesions were seen in males at 62.5 and 125 mg/kg/day and in females at 150 and 300 mg/kg/day.

Treatment-related organ weight changes were limited to kidney weights. In males, dose-related increases in absolute and relative kidney weights were seen only after 24 months; absolute weights were increased by 5% and 7% and relative weights by 6% and 10% at 62.5 and 125 mg/kg/day, respectively. In females, dose-related increases in absolute and relative kidney weights were seen after 12 and 24 months. After 12 months, absolute weights were increased by 14% and 17%, and relative weights by 22% and 30% at 150 and 300 mg/kg/day, respectively. After 24 months, absolute weights were increased by 14% and 22% and relative weights by 12% and 20% at 150 and 300 mg/kg/day, respectively. The increases in kidney weights were attributed to treatment due to corroborative dose-related renal lesions seen in both sexes after 12 and 24 months.

After 12 months of treatment (Interim-Sacrifice), dose-related renal lesions in male mice were degeneration with regeneration of the descending portion of the proximal tubule in 2/10 (20%) and 10/10 (100%) at 62.5 and 125 mg/kg/day, respectively and decreased vacuolation of the renal proximal tubule in 8/10 (80%) and 10/10 (100%) at 62.5 and 125 mg/kg/day, respectively. Neither of these lesions were seen in the control or at 5 mg/kg/day. In females, renal lesion was limited to hypercellularity of the descending portion of the proximal tubules seen in 8/10 (80%) and 10/10 (100%) mice at 150 and 300 mg/kg/day, respectively.

After 24 months of treatment (Terminal Sacrifice), dose-related renal lesions seen in males at 62.5 and 125 mg/kg/day comprised a constellation of changes that involved five different diagnoses. Degeneration with regeneration of the descending limb of the proximal tubule was seen in 25/50 (50%) and 48/50 (96%) at 62.5 and 125 mg/kg/day, respectively compared to none in the controls and at 5 mg/kg/day. Decreased vacuolation of the renal proximal tubule was seen in 39/50 (78%) and 48/50 (96%), respectively, at 62.5 and 125 mg/kg/day, compared to none in the controls and at 5 mg/kg/day. Both of these lesions were also seen in a dose-related manner at the interim (12-month) sacrifice. Also seen were, mineralization of the tubules in 29/50 (58%) and 36/50 (72%) and multifocal cortical cysts in 22/50 (44%) and 20/50 (40%) at 62.5 and 125 mg/kg/day, respectively. In females, renal lesions at 150 and 300 mg/kg/day were hypercellularity in 32/50 (64%) and 25/50 (50%) and degeneration with regeneration of the tubules in 38/50 (76%) and 34/50 (68%), respectively.

**Under the conditions of this study, for chronic toxicity, the NOEL is 5 mg/kg/day in both sexes. The LOEL is 62.5 mg/kg/day in males and 150 mg/kg/day in females. In both sexes, the LOEL is based on increases in absolute and/or relative kidney weights and histopathological lesions in the kidneys. At the doses tested, 2,4-D acid was not carcinogenic in male or female B6C3F1 mice.**

This carcinogenicity study in mice is classified as **Acceptable** and satisfies the Subdivision F guideline requirement for a carcinogenicity study in mice (§ 83-2b).

## I. INTRODUCTION

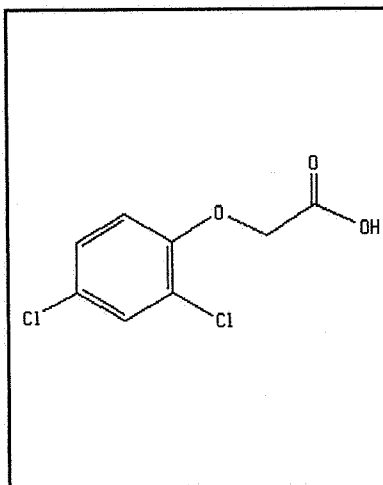
In 1988, the Agency required that rodent carcinogenicity testing with 2,4-dichlorophenoxyacetic acid (2,4-D) be repeated because a Maximum Tolerated Dose (MTD) had not been achieved in the Industry-sponsored studies. In the Data Call-In notice of 1989, the Agency formally requested that the carcinogenicity testing in rats and mice be repeated at higher doses. This Data Evaluation Report summarizes the results of a carcinogenicity study in mice.

## II. MATERIALS AND METHODS

### A. MATERIALS:

1. Test Material: 2,4-Dichlorophenoxyacetic acid  
Description: Solid  
Lot/Batch No.: 909  
Purity: Technical, 96.4%  
Stability  
of the compound: Concentrations of the active ingredient  
varied less than 1% between stability  
analyses conducted every 6 months over 2 years.  
CAS No.: 94-75-7

Structural Formula:



2. **Vehicle Control:** A basal diet of Purina Certified Chow #5002.

3. **Test Animals:**
- |                           |                                                                                                          |
|---------------------------|----------------------------------------------------------------------------------------------------------|
| Species:                  | Mouse                                                                                                    |
| Strain:                   | B6C3F1                                                                                                   |
| Sex:                      | Males & females                                                                                          |
| Age at Initiation:        | 7-8 weeks                                                                                                |
| Weight at Initiation:     | 22 g ♂ & 15 g ♀                                                                                          |
| Identification:           | S.C implanted transponder correlated to a unique i.d.number.                                             |
| Acclimation:              | 14 days                                                                                                  |
| Housing:                  | 1/cage in suspended stainless steel cages.                                                               |
| Food:                     | Purina Certified Rodent Chow #5002                                                                       |
| Water:                    | Tap water <u>ad libitum</u>                                                                              |
| Environmental Conditions: | Temperature, 18.8-24.7°C; Humidity, 30-94%; Light cycle, 12 hr.on/off; Air flow, 10-12 air changes/hour. |

B. **Study Design**

1. **In Life Dates:**
- |        |                  |                  |
|--------|------------------|------------------|
| Start: | Males - 5/19/93; | Females - 2/3/92 |
| End:   | - 5/23/95        | - 2/8/94         |

2. **Animal Assignment**

| Test Group | Dose Level<br>(mg/kg/day) |         | Main Study <sup>a</sup> |         | Interim Sacrifice<br>(12 Months) |         |
|------------|---------------------------|---------|-------------------------|---------|----------------------------------|---------|
|            | Males <sup>b</sup>        | Females | Males                   | Females | Males                            | Females |
| Control    | 0                         | 0       | 50                      | 50      | 10                               | 10      |
| Low Dose   | 5.0                       | 5.0     | 50                      | 50      | 10                               | 10      |
| Mid Dose   | 62.5                      | 150.0   | 50                      | 50      | 10                               | 10      |
| High Dose  | 125.0                     | 300.0   | 50                      | 50      | 10                               | 10      |

a = Hematology performed at 12, 18 and 24 months.

b = Initially, both sexes received the same doses of 2,4-D (i.e., 5, 150 or 300 mg/kg/day); however, due to severe body weight decrements in males at 150 and 300 mg/kg/day, a new study (MRID # 43879801) was conducted in males at lower doses (See 3. Dose Selection Rationale, below).

3. **Dose Selection Rationale:** In a subchronic toxicity study (MRID No. 41991502), B6C3F1 (10/sex/dose) were fed diets containing 2,4-D acid at 1, 15, 100 or 300 mg/kg/day for 90 days. At 100 mg/kg/day, treatment-related effects were decreases in glucose and thyroxine levels and increases in absolute and relative kidney weights. At 300 mg/kg/day, treatment-related effects were: transient decreases in food consumption; decreases in glucose and thyroxine levels; decreases in kidney-to-brain weight ratios; and histopathological lesions in the liver and kidneys. The NOEL was 15 mg/kg/day and the LOEL was 100 mg/kg/day.

Based on the results of the 90-day study, a carcinogenicity study was initiated at 0, 5, 150 or 300 mg/kg/day. During the course of the first year of the study, female mice at all dose levels had normal weight gain. However male mice at 150 and 300 mg/kg/day had significantly lower mean body weights and body weight gains when compared to controls; decrements in body weight gain were -7 to -11% at 150 mg/kg/day and -20 to -28% at 300 mg/kg/day ( $\leq 0.05$ ). Although there were no mortalities, body weight gain data indicated that for males, the 300 mg/kg/day was certainly too high and 150 mg/kg/day conceivably may lead to excessive toxicity as the study progressed. Therefore, in concurrence with the Agency, all male mice were terminated and a new study with males (MRID # 43879801) was initiated at lower doses (0, 62.5 or 125 mg/kg/day).

4. **Diet Preparation and Analysis:** The test material was air milled prior to mixing the diets. Test diets were prepared by serially diluting a premix (test material-feed concentrate). Test diets were prepared weekly during the first 13 weeks and at least once every two weeks for the remainder of the study. Concentration analyses of each dose level was determined for the first four weeks, and at least quarterly, thereafter. Homogeneity was initiated prior to the start of the study and validated analytically concurrently with the conduct of the study. Stability analysis was initiated with the start of the study.

**Results:** Concentration analysis indicated that the actual concentrations of 2,4-D in the low- mid- and high-dose test diets were within 83-127%, 88-106% and 92-114%, respectively, of the target for males, and 88-135%, 86-119% and 85-118%, respectively, in females. Homogeneity analyses showed that the diet mixes were homogeneously distributed with relative standard deviations of 2.65 to 14.52% for males and 2.9 to 38.17% for females. Stability analysis indicated the test material to be stable in the test diet for at least 49 days (91% of Day 0 value).

5. **Treatment:** Males were fed diets containing 2,4-D acid at 5, 62.5 or 125 mg/kg/day and females at 5, 75 or 150 mg/kg/day for a period of up to 24 months (732 to 734 days). Control animals received standard laboratory diet on the same schedule. The

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most recent group mean body weight and feed consumption data for each sex were used to adjust the concentration of the test material in the diet to maintain the targeted dose levels.

6. **Experimental Procedures:** Mortality/moribundity checks and cage-side observations for clinical signs of toxicity were performed twice daily. A detailed physical examination for signs of local or systemic toxicity, pharmacologic effects and palpation for tissue masses were conducted prior to initiation and weekly thereafter. Examination of central nervous system and behavior pattern of each animal included looking for signs of tremors, convulsions, salivation and diarrhea. Individual body weights and amount of feed consumed were recorded prior to initiation, weekly for the first 13 weeks, and at approximately monthly intervals, thereafter. Ophthalmologic examinations were conducted on all animals once prior to initiation and at scheduled necropsies. Blood was collected from 10 mice/sex/dose after approximately 12 and from 10 and 20 mice/sex/dose at 18 and 24 months, respectively for the following hematologic determinations: hematocrit; hemoglobin; erythrocyte count; total leukocyte count and platelet count. Blood smear examinations consisted of differential leukocyte counts on 100 leukocytes, as well as an assessment of erythrocyte, leukocyte and platelet morphology.
7. **Termination:** For the interim sacrifice 10 mice/sex/dose were sacrificed after 370 and 371 days of treatment for females and males, respectively. The surviving male and female mice were sacrificed between test days 732 and 734 (terminal sacrifice). Complete gross postmortem examination was performed on these animals as well as on animals dying spontaneously, accidentally, and sacrificed in a moribund condition. Postmortem procedures included: examination of the external surface; all orifices; the cranial cavity; carcass; the external and sectioned surfaces of the brain and spinal cord; nasal cavity and paranasal sinuses; the thoracic; abdominal and pelvic cavities and their viscera and the cervical tissue. Weights of brain, heart, kidneys and liver were recorded and the organ to final body weight and organ weight to brain weight ratios calculated for all animals.
8. **Histopathology:** The checked (x) tissues were trimmed and processed for histopathological examination of all mice in the control and high-dose groups and all mice from the intermediate and low dose groups terminated early. Microscopic examination of tissues from mice at the low-and mid-dose groups that survived until their scheduled termination of the study was limited to the liver, kidneys, lungs, gross lesions, and tissues routinely prepared with these protocol-designated tissues (i.e., gall bladder with liver, urinary bladder with the reproductive duct). In addition, due to observations made at necropsy (i.e., ovarian masses and cystic endometrial hyperplasia), the entire reproductive tract (cervix, vagina and oviducts in addition to ovaries and uterus) of these animals was examined histopathologically. When histopathology of protocol-defined organs at the low and mid-dose level mice from the terminal necropsy suggested lymphosarcoma, the spleen, thymus, mesenteric and mediastinal lymph nodes were also prepared and examined to establish a diagnosis.

| <u>Digestive System</u>                                                                                                                                                                                                                                                                                                                                                                | <u>Respiratory System</u>                                                                                                                                                                                                                                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>x Salivary glands<sup>a</sup></li> <li>x Esophagus<sup>a</sup></li> <li>x Stomach</li> <li>x Duodenum<sup>a</sup></li> <li>x Jejunum<sup>a</sup></li> <li>x Cecum<sup>a</sup></li> <li>x Colon<sup>a</sup></li> <li>x Ileum<sup>a</sup></li> <li>x Rectum<sup>a</sup></li> <li>x Liver<sup>a,c</sup></li> <li>x Pancreas<sup>a</sup></li> </ul> | <ul style="list-style-type: none"> <li>x Trachea<sup>a</sup></li> <li>x Lung<sup>a</sup></li> <li>Pharynx<sup>e</sup></li> <li>x Larynx<sup>a</sup></li> <li>Nose<sup>e</sup></li> <li>x Nasal Tissues</li> </ul>                                                                                                                               |
| <u>Nervous System</u>                                                                                                                                                                                                                                                                                                                                                                  | <u>Cardiovascular/Hematopoietic System</u>                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"> <li>x Brain [cerebrum, brain stem, cerebellum]<sup>a,c</sup></li> <li>x Pituitary<sup>a</sup></li> <li>x Peripheral nerve<sup>a,b</sup></li> <li>x Spinal cord (3 levels)<sup>a,b</sup></li> <li>x Eyes<sup>a,b</sup></li> </ul>                                                                                                                    | <ul style="list-style-type: none"> <li>x Aorta (thoracic)<sup>a</sup></li> <li>x Heart<sup>a</sup></li> <li>x Bone marrow<sup>a</sup></li> <li>x Lymph nodes<sup>a</sup></li> <li>x Spleen<sup>a</sup></li> <li>x Thymus<sup>a</sup></li> </ul>                                                                                                 |
| <u>Glandular System</u>                                                                                                                                                                                                                                                                                                                                                                | <u>Urogenital System</u>                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>x Adrenals<sup>a</sup></li> <li>x Lacrimal glands<sup>b</sup></li> <li>x Parathyroids<sup>a,d</sup></li> <li>x Thyroids<sup>a,d</sup></li> </ul>                                                                                                                                                                                                | <ul style="list-style-type: none"> <li>x Kidneys<sup>a,c</sup></li> <li>x Urinary bladder<sup>a</sup></li> <li>x Testes<sup>a,c</sup></li> <li>x Epididymides</li> <li>x Prostate</li> <li>x Seminal vesicles</li> <li>x Uterus<sup>a</sup></li> <li>x Ovaries<sup>a,c</sup></li> <li>x Vagina</li> <li>x Cervix</li> <li>x Oviducts</li> </ul> |
|                                                                                                                                                                                                                                                                                                                                                                                        | <u>Other</u>                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>x Skin</li> <li>x Mammary glands</li> <li>x All gross lesions and masses</li> <li>x Skeletal muscle<sup>a</sup></li> <li>x Mesenteric tissues</li> <li>x Mediastinal tissues</li> <li>x Oral tissue</li> <li>x Coagulating glands</li> <li>x Auditory sebaceous glands</li> </ul>                        |

a. Required for subchronic and chronic studies.

b. In subchronic studies examined only if indicated by toxicity or target organ involvement.

c. Organ weights required in subchronic and chronic studies.

d. Organ weights required for nonrodent studies.

e. Required for chronic inhalation study.

9. **Statistical Analyses:** Differences in mortality patterns were tested by the Gehran-Wilcoxon procedure. Body weights, appropriate hematology parameter, and organ weight data were evaluated by Bartlett's test for equality of variance. Based on the outcome of Bartlett's test, exploratory data analysis was performed by a parametric or nonparametric ANOVA, followed respectively by Dunnett's test or the Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons. Statistical analysis of gross and histopathological lesions consisted of pair-wise comparisons of control and treated groups using the pair-wise chi-square test with Yate's continuity correction.
10. **Regulatory Compliances:** Signed and dated No Data Confidentiality Claim, Flagging, Good Laboratory Practices, and Quality Assurance statements were provided.

### III. RESULTS

- A. **Survival:** There was no treatment-related mortality in either sex throughout the study. As shown in Table 1, survival at 18 and 24 months exceeded the guideline requirement of not less than 50% and 25%, respectively, at these intervals.

Table 1. Survival Rate in B6C3F1 Mice Fed 2,4-D Acid for 2-years<sup>a</sup>.

| Percent Survival |                   |    |      |     |                     |    |     |     |
|------------------|-------------------|----|------|-----|---------------------|----|-----|-----|
| Interval         | Males (mg/kg/day) |    |      |     | Females (mg/kg/day) |    |     |     |
|                  | 0                 | 5  | 62.5 | 125 | 0                   | 5  | 150 | 300 |
| 12-Months        | 100               | 98 | 96   | 98  | 96                  | 96 | 96  | 96  |
| 18-Months        | 94                | 92 | 92   | 94  | 90                  | 92 | 92  | 94  |
| 24-Months        | 76                | 86 | 84   | 86  | 78                  | 84 | 84  | 70  |

a = Data obtained from Study Report Pages. 48 (♂), 47 & 48 (♀) .

- B. **Clinical Observations:** No treatment-related clinical signs of toxicity were seen in either sex at any dose level.
- C. **Ophthalmology Examination:** No treatment-related ophthalmological findings were seen in either sex at any dose level.

- D. Body Weight/Body Weight Gain:** Mean body weight data are presented in **Table 2**. Mean body weights of male mice at all dose levels were comparable to those of the controls throughout the study. Mean body weights of female mice at 150 mg/kg/day were generally lower (approximately 2-6%) than controls over a majority of the dosing period with the decreases reaching statistical significance ( $p < 0.05$ ) during Study Days 18 through 279. However, no significant differences were seen in body weights of treated females when compared to controls during Study Days 307 to 726.

**Table 2. Mean Body Weights (g) in B6C3F1 Mice Fed 2,4-D Acid For 2-Years<sup>a</sup>.**

| Interval   | Males (mg/kg/day) |      |      |      | Females (mg/kg/day) |       |      |       |
|------------|-------------------|------|------|------|---------------------|-------|------|-------|
|            | 0                 | 5    | 62.5 | 125  | 0                   | 5     | 5    | 300   |
| -3 Day     | 22.2              | 22.3 | 21.9 | 21.8 | 18.7                | 18.8  | 18.6 | 18.6  |
| ~ 3-Months | 29.2              | 28.9 | 29.3 | 29.5 | 25.8                | 25.2* | 25.3 | 24.7* |
| ~ 6-Months | 33.7              | 33.4 | 34.0 | 33.4 | 28.1                | 27.9  | 27.4 | 27.1* |
| 12-Months  | 36.3              | 35.7 | 36.1 | 36.1 | 31.5                | 32.1  | 30.8 | 30.2  |
| 18-Months  | 37.1              | 36.6 | 36.8 | 36.8 | 32.5                | 33.0  | 33.0 | 31.8  |
| 24-Months  | 34.5              | 34.6 | 34.5 | 33.5 | 30.6                | 32.1  | 31.9 | 31.3  |

a = Data obtained from Study Report Pages. 51-54 (♂) & 52-54 (♀)

\* Significantly different from controls at  $p < 0.05$ .

Mean body weight gain data are presented in **Table 3**. Mean body weight gain of male mice at all dose levels were comparable to those of the controls throughout the study. Female mice at 300 mg/kg/day showed consistent reductions in body weight gain when compared to controls; the decreases amounted to approximately -20 to 23% during Study Days 0-49, appeared to stabilize around Study Day 50, and ranged between -5 to 14% until 20 months into the study. At termination, body weight gain of mice at all treated groups were comparable to that of the controls.

**Table 3. Mean Body Weight Gain (G) in B6C3F1 Mice Fed 2,4-D Acid For 2-Years<sup>a</sup>.**

| Interval   | Males (mg/kg/day) |      |      |      | Females (mg/kg/day) |                           |              |               |
|------------|-------------------|------|------|------|---------------------|---------------------------|--------------|---------------|
|            | 0                 | 5    | 62.5 | 125  | 0                   | 5                         | 150          | 300           |
| ≈ 3-Months | 7.0               | 6.7  | 7.3  | 7.6* | 8.4                 | 7.8*<br>(-7) <sup>b</sup> | 7.9*<br>(-6) | 7.2*<br>(-14) |
| ≈ 6-Months | 11.5              | 11.2 | 12.1 | 11.5 | 10.6                | 10.5                      | 10.0         | 9.6*<br>(-9)  |
| 12-Months  | 14.1              | 13.5 | 14.2 | 14.3 | 14.1                | 14.7                      | 13.4         | 12.8*<br>(-9) |
| 18-Months  | 14.9              | 14.5 | 14.9 | 14.9 | 15.1                | 15.5                      | 15.5         | 14.4<br>(-5%) |
| 24-Months  | 12.2              | 12.4 | 12.7 | 11.6 | 13.2                | 14.7                      | 14.4         | 13.9          |

a = Data obtained from Study Report Pages. 57-60 (♂) & 56-60 (♀)

b = Values in parenthesis (% decrease vs. controls) were calculated by Reviewer.

\* Significantly different from controls at  $p < 0.05$ .

- E. **Food and Compound Consumption:** No consistent changes in food consumption of treated mice relative to controls was observed either in males or in females in spite of the decreased body weights in this sex at the high-dose. The average dosages received by male mice were 5.0, 61.9 or 128.6 mg/kg/day for the targeted doses of 5, 62.5 or 125 mg/kg/day, respectively and by the female mice were 5.01, 149.83 or 310.01 mg/kg/day for the targeted doses of 5, 150 or 300 mg/kg/day, respectively.
- F. **Hematology:** No treatment-or statistically significant differences in any of the hematological parameters (RBC, HGB, HCT, WBC or platelet number) were observed in either sex at any interval (12, 18 or 24 month).
- G. **Organ Weights:** Treatment related changes observed in kidney weights are presented in **Table 4**. In males at 62.5 and 125 mg/kg/day, dose-related increases in absolute and relative kidney weights were seen only after 24 months. In females at 150 and 300 mg/kg/day dose-related increases in absolute and relative kidney weights were seen after 12 and 24 months. The increases in kidney weights corroborated with histopathological lesions in the kidneys in both sexes and were thus determined to be treatment related. In contrast, the decreases (-5 to -10%) in absolute/relative heart weights and the increase (6%) in relative testes weights of males at 125 mg/kg/day and the increase (6%) in relative liver weights in females at 150 mg/kg/day were not attributed to treatment due to lack of dose- and/or time-response and corroborative histopathological lesions in these organs.

**Table 4. Kidney Weights at the Interim & Terminal Sacrifices<sup>a</sup>.**

| Males                       |       |       |       |       |                  |                             |                  |                  |
|-----------------------------|-------|-------|-------|-------|------------------|-----------------------------|------------------|------------------|
| Dose (mg/kg/day)            | 0     |       | 5     |       | 62.5             |                             | 125              |                  |
| Sacrifice Interval (Months) | 12    | 24    | 12    | 24    | 12               | 24                          | 12               | 24               |
| Absolute (g) Weights        | 0.710 | 0.744 | 0.729 | 0.721 | 0.687            | 0.778<br>(+5%) <sup>b</sup> | 0.710            | 0.797*<br>(+7%)  |
| Relative (g/100) weights    | 1.915 | 2.123 | 1.970 | 2.085 | 1.921            | 2.239*<br>(+6)              | 2.006            | 2.343*<br>(+10)  |
| Females                     |       |       |       |       |                  |                             |                  |                  |
| Dose (mg/kg/day)            | 0     |       | 5     |       | 150              |                             | 300              |                  |
| Sacrifice Interval (Months) | 12    | 24    | 12    | 24    | 12               | 24                          | 12               | 24               |
| Absolute (g) weights        | 0.428 | 0.486 | 0.421 | 0.478 | 0.486*<br>(+14%) | 0.554*<br>(+14%)            | 0.500*<br>(+17%) | 0.595*<br>(+22%) |
| Relative (g/100) weights    | 1.324 | 1.560 | 1.351 | 1.487 | 1.616*<br>(+22%) | 1.740*<br>(+12%)            | 1.719*<br>(+30%) | 1.872*<br>(+20%) |

a = Data obtained from Study Report Pages. 82 and 83 (♂) & 81 and 83 (♀)

b = Values in parenthesis (% increase vs. controls) were calculated by the reviewer.

H. **Gross Pathology:** No treatment-related gross necropsy findings were seen in either sex at any dose level either at the interim or the terminal sacrifice. Necropsy findings in the control and treated groups occurred with comparable frequency and were similar to those commonly seen in this age/strain of mice .

I. **Histopathology - Interim Sacrifice (12-months)**

1. **Non-neoplastic Lesions:** Treatment-related non-neoplastic lesions observed at the 12-month interim sacrifice are presented in **Table 5**. Lesions were limited to the kidneys of both sexes of mice at the mid-and high doses and to the liver of females at the high dose.
2. **Neoplastic Lesions:** Neoplasms observed in males were: 2 undifferentiated subcutaneous sarcomas and 1 testicular gonadal stromal tumor in the control; a bronchioalveolar adenoma at 62.5 mg/kg/day; and a thyroid follicular cell adenoma and a lacrimal gland adenoma at 125 mg/kg/day. Neoplasms observed in females were: a lung adenoma and an abdominal hemangioma in the control and a lung adenoma and a pituitary adenoma at 150 mg/kg/day. These tumors were not attributed to treatment since the incidences were similar in number and frequency to those seen in this strain/age of mice.

**Table 5. Treatment-Related Non-Neoplastic Lesions in B6C3F1 Mice at the INTERIM Sacrifice<sup>a</sup>.**

| No. Examined: 10/Dose                                                  |                                                                            | Males (mg/kg/day)   |   |            |              |
|------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------|---|------------|--------------|
| Tissue/Lesion                                                          |                                                                            | 0                   | 5 | 62.5       | 125          |
| <b>Kidneys:</b>                                                        | - degeneration/regeneration, descending proximal tubule-very slight/slight | 0                   | 0 | 2<br>(20%) | 10<br>(100%) |
|                                                                        | - vacuolation - decreased, proximal tubule(s)                              | 0                   | 0 | 8<br>(80%) | 10<br>(100%) |
| No. Examined: 10/Dose                                                  |                                                                            | Females (mg/kg/day) |   |            |              |
| Tissue/Lesion                                                          |                                                                            | 0                   | 5 | 150        | 300          |
| <b>Kidneys:</b> hypercellular, proximal tubule-descending part, slight |                                                                            | 0                   | 0 | 8<br>(80%) | 10<br>(100%) |
| <b>Liver:</b> hyperchromic nuclei, midzonal, slight                    |                                                                            | 1                   | 0 | 2          | 5            |

a = Data obtained from Study Report Pages. 104 & 105 (♂) and 111 \* 112 (♀)

In males, dose-related kidney lesions were degeneration with regeneration of the descending portion of the proximal tubule seen in 2/10 (20%) and 10/10 (100%) at 62.5 and 125 mg/kg/day, respectively and vacuolation of the proximal tubules seen in 8/10 (80%) and 10/10 (100%) at 62.5 and 125 mg/kg/day respectively, when compared to 0% for both lesions in control males.

In females, the dose-related kidney lesion was hypercellularity of the descending portion of the proximal tubule seen in 8/10 (80%) and 10/10 (100%) at 150 and 300 mg/kg/day, respectively. The lesion was of minimal degree and necrosis or indications of repair (i.e., mitotic figures) were not present. This renal lesion correlated with the increases in absolute/relative kidney weights observed at these dose levels. The other kidney lesion was the slightly increased incidence of minimal tubular degeneration with regeneration of the cortical tubules seen only at 150 mg/kg/day 4/10 (40%) compared to 1/10 (10%) in the controls.

In the liver of female mice, there was an increase in the incidence of hyperchromic nuclei at 300 mg/kg/day (5/10 (50%) compared to controls (1/10, 10%). This lesion/change may be considered to be equivocal, since there are normally some nuclear size variability and tinctorial changes (increased basophilic staining) of hepatocytes from the midzonal to centrilobular areas, particularly in sections from the right and caudate lobes, in mice of this strain and age.

The other non-neoplastic lesions observed at the interim sacrifice were similar in number and frequency of those seen in this strain//sex/age of mice.

**Histopathology - Terminal Sacrifice (24-months)**

1. **Non-neoplastic Lesions:** Treatment-related non-neoplastic lesions observed at the 24-month terminal sacrifice are presented in Table 6. Kidney lesions, similar to those seen in both sexes of mice at the mid- and high-dose groups at the interim sacrifice were also seen at the terminal sacrifice. These lesions were of minimal degree (very slight or slight) and considered unlikely to have an effect on renal function.

**Table 6. Treatment-Related Non-Neoplastic Lesions in B6C3F1 Mice at the TERMINAL Sacrifice<sup>a</sup>.**

| No. Examined: 50/Dose |                                                                                                                  | Males (mg/kg/day)   |             |              |                           |
|-----------------------|------------------------------------------------------------------------------------------------------------------|---------------------|-------------|--------------|---------------------------|
| Tissue/Lesion         |                                                                                                                  | 0                   | 5           | 62.5         | 125                       |
| Kidneys               | - degeneration/regeneration, descending proximal tubule-<br>- any severity                                       | 0                   | 0           | 25*<br>(50%) | 48*<br>(96%)              |
|                       | - vacuolation - decreased, proximal tubule(s)                                                                    | 0                   | 0           | 39*<br>(78%) | 48*<br>(96%)              |
|                       | -mineralization, tubule(s), multifocal - very slight-                                                            | 16<br>(32%)         | 19<br>(38%) | 29*<br>(58%) | 36* <sup>T</sup><br>(72%) |
|                       | - cyst, cortex, focal or multifocal                                                                              | 9                   | 9           | 22*<br>(44%) | 20* <sup>T</sup><br>(40%) |
|                       | -degeneration/regeneration, cortex, multifocal                                                                   | 39                  | 43          | 43           | 45                        |
| Liver                 | -aggregates of RE cells frequently adjacent of degenerative<br>or necrotic hepatocytes, multifocal, any severity | 12<br>(24%)         | 16<br>(32%) | 17<br>(34%)  | 25* <sup>T</sup><br>(50%) |
| No. Examined: 50/Dose |                                                                                                                  | Females (mg/kg/day) |             |              |                           |
| Tissue/Lesion         |                                                                                                                  | 0                   | 5           | 150          | 300                       |
| Kidneys               | -hypercellular, proximal tubule-descending part - slight                                                         | 0                   | 0           | 32*<br>(64%) | 25* <sup>T</sup><br>(50%) |
|                       | -degeneration/regeneration, tubule, multifocal - very slight<br>- slight                                         | 7<br>0              | 3<br>0      | 35*<br>3     | 26* <sup>T</sup><br>8*    |
|                       | -mineralization, tubule(s), multifocal - very slight                                                             | 0                   | 0           | 1            | 7* <sup>T</sup>           |
| Spleen                | -extramedullary hematopoiesis, - very slight                                                                     | 2                   | 0           | 3            | 8*                        |
|                       | - slight                                                                                                         | 3                   | 3           | 3            | 7                         |
|                       | - moderate                                                                                                       | 2                   | 4           | 3            | 5                         |
|                       | - severe                                                                                                         | 1                   | 0           | 0            | 0                         |

a = Data obtained from Study Report Pages. 117-121 (♂) and 123, 124, 138 (♀)

\* = Significantly different from controls; T = Trend

In males, the dose-related renal lesions, degeneration with regeneration of the descending portion of the proximal tubules and decreased vacuolation of the proximal tubules, observed at 62.5 and 125 mg/kg/day at the interim sacrifice were also dose-related at the terminal sacrifice. Also dose-related at 62.5 and 125 mg/kg/day was the increase in the multifocal, mineralization of scattered tubules (also known as microlithiasis). Multifocal cortical cysts were increased (not dose-related) at 62.5 and 125 mg/kg/day. Tubular degeneration/regeneration of the cortex was seen in all treated groups including the controls.

The degeneration/ regeneration changes were restricted to the outer stripe of the outer zone of the medulla but usually involved all the tubules in which this segment was present in the plane of section. When graded as slight, the change was manifested by increased number of epithelial cells in the straight descending portion of the proximal tubule with minimal nuclear pleomorphism and rare enlarge nuclei. The tubular lumens were more evident apparently due to loss of the brush border of the epithelium and there was basophilia of the cytoplasm of affected tubules. Necrosis or indications of repair (i.e., mitotic figures) were not present. When graded as very slight, the change was primarily hypercellularity of the descending portion of the proximal tubules with equivocal evidence of the other characteristics above.

The decreased vacuolation of the renal proximal tubules seen after 12 and 24 months may represent a lesion of uncertain significance and etiology. Male mice normally have large, clearly demarcated vacuoles in some of the proximal tubular epithelial cells. The vacuoles normally occur in the proximal convoluted portion of the tubules and are noted histologically in clusters in the cortex. Therefore, this lesions may not have been related to tubular degeneration.

The mineralization of scattered tubule and the multifocal cortical cysts, although attributed to treatment, can be considered to be of minimal functional significance.

The tubular degeneration with regeneration of the renal tubules in the cortex seen in both the control and treated groups are an exacerbation of a geriatric change commonly seen in untreated aged mice and is not attributed to treatment.

In the liver, there was an increase in the aggregates of RE cells frequently adjacent to degenerative or necrotic hepatocytes at all dose levels with the increase reaching statistical significance only at 125 mg/kg/day.

In females, the dose-related renal lesion, hypercellularity of the descending portion of the proximal tubules, observed at 150 and 300 mg/kg/day at the interim sacrifice was also dose-related at these doses at the terminal sacrifice.

The other treatment-related but not dose-related renal changes were the degeneration with regeneration of the cortical tubules seen at 150 and 300 mg/kg/day and mineralization of scattered tubules seen only at 300 mg/kg/day. These renal changes may correlate with the increases in absolute and relative kidney weights observed at the terminal sacrifice in mice at these dose levels.

Hypercellularity of the descending portion of the proximal tubule was characterized by increased numbers of epithelial cells in the straight descending portion of the proximal tubules. These cells appeared to be somewhat shorter than normal and may have contributed to the hypercellular appearance. Necrosis or indications of repair (i.e., mitotic figures) were not present. Mineralization of scattered tubules (also known as microlithiasis) was seen only at 300 mg/kg/day. In the spleen, the increase in extramedullary hematopoiesis showed statistical significance only for the very slight grade with no statistical significance for the slight, moderate or severe grades. Since no statistically-identified anemia or other blood cell differences were seen at the 12, 18 or 24 months, the splenic hematopoiesis was considered to be equivocal and may be attributed to a secondary effect to treatment.

2. **Neoplastic Lesions:** Histopathology revealed a variety of benign and malignant tumors at different sites in both treated and control animals, but none showed statistical significance in individual tumor types in any treated group of either sex. Neoplastic lesions observed were similar in number and type commonly seen in this strain/age mice. A summary of the neoplastic lesions presented in Tables 34 for males (Study Report Pages 142 to 145) and 35 for females (Study Report Pages 151 to 156) are appended to this DER (Appendix 1).

#### IV. DISCUSSION

The purpose of this discussion that follows is to compare the findings of the 1987 (Hazleton) and the 1995 (Dow) carcinogenicity studies conducted with 2,4-D acid in B6C3F1 mice. In the 1987 study, 50/sex/dose were fed diets containing 2,4-D acid technical (97.5%) at 0, 1, 15 or 45 mg/kg/day for 104 weeks, and in the 1995 study, 2,4-D acid (96.45%) was administered in the diet at 0, 5, 62.5 or 125 mg/kg/day to males and at 0, 5, 150 or 300 mg/kg/day to females for 104 weeks.

- A. **Survival:** As shown below in **Table 7**, no treatment-related effect was seen on survival in either study.

**Table 7. Survival (%) in B6C3F1 Mice In The Two Studies<sup>a</sup>.**

| Sex     | Months | Dose (mg/kg/day) |          |          |          |           |           |                   |            |                   |            |
|---------|--------|------------------|----------|----------|----------|-----------|-----------|-------------------|------------|-------------------|------------|
|         |        | 0<br>(H)         | 0<br>(D) | 1<br>(H) | 5<br>(D) | 15<br>(H) | 45<br>(H) | 62.5<br>(D)       | 125<br>(D) | 150<br>(D)        | 300<br>(D) |
| Males   | 12     | 98               | 100      | 100      | 98       | 96        | 90        | 96                | 98         | NOT<br>APPLICABLE |            |
|         | 24     | 80               | 94       | 88       | 86       | 80        | 76        | 84                | 86         |                   |            |
| Females | 12     | 97               | 96       | 93       | 96       | 92        | 97        | NOT<br>APPLICABLE |            | 96                | 96         |
|         | 24     | 76               | 78       | 78       | 84       | 72        | 70        |                   |            | 84                | 70         |

a = Data obtained from 1987 Study Report Pages. 94-102 & Table 1 of this DER  
H = 1987 Hazleton Study. D = 1995 Dow Study

- B. **Body Weights:** Cumulative body weight gain data for both studies are presented in **Table 8**. In the 1987 decreases (-9% to 16%) in mean cumulative (0-104 weeks) body weight gain was seen in males at all dose levels; a similar effect was not seen in females. In the 1995 study, no treatment-related effects on body weight gain were seen in males at much higher doses. Decrements in body weight gain (-5% to -15%) were seen in females at 300 mg/kg/day until 20 months into the study. Terminal body weights at this dose were comparable to those of the controls.

**Table 8. Cumulative Body Weight Gain (g) in B6CF1 Mice In The Two Studies<sup>a</sup>.**

| Sex     | Months | Dose (mg/kg/day) |          |                |          |                 |                 |              |            |              |            |
|---------|--------|------------------|----------|----------------|----------|-----------------|-----------------|--------------|------------|--------------|------------|
|         |        | 0<br>(H)         | 0<br>(D) | 1<br>(H)       | 5<br>(D) | 15<br>(H)       | 45<br>(H)       | 62.5<br>(D)  | 125<br>(D) | 150<br>(D)   | 300<br>(D) |
| Males   | 12     | 14.3             | 14.1     | 13.6           | 14.5     | 14.2            | 13.8            | 14.2         | 14.3       | NOT<br>DOSED |            |
|         | 24     | 14.1             | 12.2     | 12.8*<br>(-9%) | 12.4     | 12.6*<br>(-11%) | 11.8*<br>(-16%) | 12.7         | 11.6       |              |            |
| Females | 12     | 13.3             | 14.1     | 12.5           | 14.7     | 12.4            | 12.8            | NOT<br>DOSED |            | 15.5         | 14.4       |
|         | 24     | 12.9             | 13.2     | 11.9           | 14.7     | 12.4            | 12.5            |              |            | 14.4         | 13.9       |

a = Data obtained from the 1987 Study Report Pages. 94-104 & Table 3.

\* =  $p \geq 0.05$ . H = 1987 Hazleton Study D = 1995 Dow Study

- C. **Food Consumption:** No treatment-related changes associated with food consumption were seen in either study.
- D. **Ophthalmology:** No ocular toxicity was seen in either study.
- E. **Hematology:** No treatment-related effects were observed in any of the hematological parameters in either study.
- F. **Organ Weights:** In both studies, treatment-related changes were limited to kidney weights in both sexes. In the 1987 study, relative kidney weights were increased in females at 15 mg/kg/day, absolute kidney weights were increased in males at 45 mg/kg/day, and the relative kidney weights were increased in males and females at 45 mg/kg/day. In the 1995 study, dose-related increases in absolute and relative kidney weights were seen in males at 62.5 and 125 mg/kg/day only after 24 months. Whereas dose-related increases in absolute and relative kidney weights were seen in females at 150 and 300 mg/kg/day after 12 and 24 month. In both studies, the increases in kidney weights corroborated with histopathological lesions in the kidneys in both sexes and were thus determined to be treatment related.
- G. **Gross Pathology:** No treatment-related gross pathological lesions were seen in either study.
- H. **Histopathology**
1. **Non-neoplastic Lesions:** In both studies, kidneys were the target organ with renal lesions seen at the interim and terminal sacrifices.  
  
In the 1987 study, renal lesions, characterized as a cytoplasmic homogeneity seen in the renal tubule epithelium, were seen only in males at the mid- and high-dose groups; the incidences were 11/60 (18%), 15/60 (25%), 48/60 (80%,  $p < 0.0001$ ) and 58/59 (98%,  $p < 0.0001$ ) at 0, 1, 15 and 45 mg/kg/day, respectively. This change was associated with the reduction of cytoplasmic vacuoles that are normally present in the renal tubular epithelium.  
  
In the 1995 study, renal lesions were seen in both sexes at the mid-and high-dose groups. In males at 62.5 and 125 mg/kg/day renal lesions comprised a constellation of changes that involved five different diagnoses. The primary lesion, degeneration with regeneration of the descending limb of the proximal tubule, was seen at 12 and 24 months. Mineralization of the tubules and multiple cortical cysts were seen only after 24 months. Decreased vacuolation of the renal proximal tubules were seen after 12 and 24 months. In females, renal lesions seen at 150 and 300 mg/kg/day comprised of hypercellularity of the descending portion of the proximal tubules and degeneration with regeneration of cortical tubules.
  2. **Neoplastic Lesions:** No treatment-related neoplastic lesions were seen in either

study.

#### VI. ADEQUACY OF THE DOSE LEVELS TESTED TO ASSESS CARCINOGENICITY

In males, the high dose (125 mg/kg/day) did not cause any adverse effect on survival, body weight decrements, clinical signs, or alterations in hematology but did increase the absolute and relative kidney weights and induced histopathological lesions in the kidneys. In the original design of this study when male mice were fed higher doses (150 and 300 mg/kg/day), the study had to be "aborted" after 419 days due to significant decrements in body weight gain; 7 to 11% at 150 mg/kg/day and 20 to 27% at 300 mg/kg/day ( $\leq 0.05$ ). Thus, it is apparent that for males, while a dose of 300 mg/kg/day was definitely excessive, 150 mg/kg/day was also approaching, and possibly exceeding an adequate dose. Consequently, based on the body weight data of the "aborted study" and the renal effects (dose-related increases in absolute/relative kidney weights and renal lesions) seen at 125 mg/kg/day in the present study, it is determined that the high-dose tested was adequate to assess the carcinogenicity of 2,4-D in male B6C3F1 mice.

In females, the high dose (300 mg/kg/day), did not alter survival, induce clinical signs or change hematology parameters, but decreased body weight gain by 14% at 3 months, 9% at 6 and 12 months and 5% at 20 months, increased the absolute and relative kidney weights, and induced renal lesions after 12 and 24 months of treatment. Renal effects were also seen at 150 mg/kg/day. Therefore, it is determined that the dose levels tested were adequate to assess the carcinogenicity of 2,4-D in female B6C3F1 mice.

Under the conditions of this study, for chronic toxicity, the NOEL is 5 mg/kg/day for both sexes and the LOEL is 62.5 mg/kg/day in males and 150 mg/kg/day in females. In both sexes, the LOEL is based on increases in absolute/relative kidney weights and histopathological lesions in the kidneys.

In this study, at the dose levels tested, **2,4-D acid was not carcinogenic in male or female B6C3F1 mice.**

**APPENDIX - 1**

**NEOPLASTIC LESIONS OBSERVED IN B6C3F1 MICE FED 2,4-D ACID FOR 24 MONTHS**

**THE DOW CHEMICAL COMPANY**

**STUDY ID; K-002372-063MF**

## 2,4-D ACID

## 83-2(b) Carcinogenicity - Mouse

PC Code: 03001 Tox Chem No. 315

File Last Updated

Current Date

2,4-Dichlorophenoxyacetic acid

STUDY/LAB/STUDY #/DATE

MATERIAL

EPA MRID NO.

RESULTS: LD50, LC50, PIS, NOEL, LEL

TOX CATEGORY

CORE GRADE/DOC. #

|                                                                                                                                                          |                                |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------------|
| 83-2(b)<br>Carcinogenicity<br>Species: Mice<br>Tox.Res.Labs<br>K-002372-063M (males)<br>K-002372-063F (females)<br>11/16/95 (Males)<br>3/10/95 (Females) | 2,4-D acid<br>96.4%, Technical | 43879801 (Male)<br>43597201 (Female) | <p>Dose levels: 0, 5, 62.5 or 125 mg/kg/day for males and 0, 5, 150 or 300 mg/kg/day for females. Treatment-related had no adverse effect on survival, body weight, bodyweight gain, clinical signs, food consumption or hematology in males. In females, body weight gain was decreased by 14% at 3 months, however, by study termination (24 months) body weight gains were similar to that of the controls. Males at 62.5 and 125 mg/kg/day and females at 150 and 300 mg/kg/day exhibited increases in absolute and/or relative weights at 12 and/or 24 months and histopathological lesions in the kidneys after 12 and 24 months of treatment. Renal lesions in males were degeneration with regeneration of the descending portion of the proximal tubule, degeneration with regeneration of the cortical tubules, decreased vacuolation of the proximal tubules, and increased incidence of mineralization of renal tubules and multifocal cysts. Renal lesions in females were hypercellularity of the descending portion of the proximal tubules and degeneration with regeneration of cortical tubules. For chronic toxicity, the NOEL = 5 mg/kg/day in both sexes. The LOEL = 62.5 mg/kg/day in males and 150 mg/kg/day in females. In both sexes, the LOEL is based on increases in kidney weight and renal lesions. There was no evidence of carcinogenicity in either sex.</p> | NA | Acceptable |
|                                                                                                                                                          |                                |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |            |
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2,4-D ACID

Sign-off date: 05/23/96  
DP Barcode: D222295  
HED DOC Number: 011934  
Toxicology Branch: TB2

§83-2(b) Carcinogenicity - Mouse