

DATA EVALUATION RECORD

PYRACLOSTROBIN (BAS 500F)

Study Type: §83-1; Chronic Toxicity Study - Rats

Work Assignment No. 3-01-113D (MRID 45118329)

Prepared for

3/15/2001

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PYRACLOSTROBIN (BAS 500F)

Chronic Toxicity (§83-1(a))

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DATA EVALUATION RECORD

STUDY TYPE: Chronic Toxicity in Rats

OPPTS Number: 870.4100

OPP Guideline Number: §83-1a

DP BARCODE: D269669

P.C. CODE: 099100

SUBMISSION CODE: S583112

TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Pyraclostrobin (97.09% a.i.)

SYNONYMS: Methyl-N-[[[1-(4-chlorophenyl)pyrazol-3-yl]oxy]-o-tolyl]-N-methoxycarbamate;
BAS 500F; Reg. No. 304 428

CITATION: Mellert, W., Deckardt, K., Gembardt, Chr., et.al. (1999) BAS 500 F- Chronic Toxicity Study in Wistar Rats Administration in the Diet for 24 Months. BASF Aktiengesellschaft, Department of Toxicology, Ludwigshafen, Germany. Laboratory Project Id.: 82S0494/96085, November 9, 1999. MRID 45118329. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC

EXECUTIVE SUMMARY: In this chronic study (MRID 45118329), pyraclostrobin (97.09% a.i., Lot/Batch# J.-Nr. 27882/191/e) was administered continuously in the diet to 20 CrI:CD[®]BR rats/sex/group at nominal dose levels of 0, 25, 75, or 200 ppm (equivalent to [M/F] 0/0, 1.1/1.5, 3.4/4.6, and 9.0/12.3 mg/kg/day) for two years.

Mortality, clinical signs, body weight, food consumption, food efficiency, ophthalmoscopic findings, hematology, clinical chemistry, and urinalysis parameters, organ weights, gross pathology, and histopathology were unaffected by the test substance. No treatment-related findings were observed in the 25, 75, or 200 ppm dose groups.

At 200 ppm, cumulative body weight gains were decreased ($p \leq 0.05$) in the males at days 0-7 (16%) and 0-539 (111%) and in the females at days 0-483 (114%). These decreases were minor

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and not sustained throughout the study; overall (days 0-728) body weight gains were comparable between all treated groups and controls. Therefore, the decreases in body weight gains were considered not to be biologically important.

The LOAEL for this study was not observed.

The NOAEL for this study is 200 ppm (equivalent to 9.0 mg/kg/day in males and 12.3 mg/kg/day in females).

No treatment-related neoplastic findings were observed.

Under the conditions of this study, there was no evidence of carcinogenic potential.

The submitted study is classified as **unacceptable/guideline** (§83-1) and does not satisfy the requirements for a chronic toxicity study in rats. It appears that the animals could have tolerated a higher dose of the test substance.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Pyraclostrobin

Description: Viscous melting, red-brown, clear

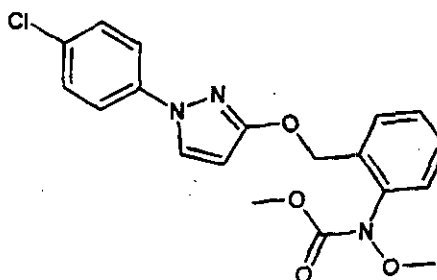
Lot/Batch #: J.-Nr. 27882/191/c

Purity: 97.09% a.i.

Stability of compound: The test substance was stable in the diet for 43 days at room temperature.

CAS #: 175013-18-0

Structure:

2. Vehicle: Diet3. Test animals: Species: Rat

Strain: Wistar Chbb:THOM (SPF)

Age and mean body weight at study initiation: Approximately 42 days old; males: 168-201 g (mean = 187 g) and females: 128-162 g (mean 144 g)

Source: Dr. Karl Thomae GmbH, Biberach/Riss, FRG

Housing: Individually, in stainless steel wire-mesh cages

Diet: Kilba maintenance diet, ad libitum except during overnight urine collection.

Water: Tap water, ad libitum except during overnight urine collection.

Environmental conditions:

Temperature: 20-24°C

Humidity: 30-70%

Air changes: Not reported

Photoperiod: 12 h dark/12 h light

Acclimation period: 9 days

B. STUDY DESIGN:

1. In life dates - start: 2/19/97 end: 2/26/99

2. Animal assignment: Animals were randomly assigned (stratified by weight) to treatment groups as indicated in Table 1.

Table 1. Study design ^a

| Test Group | Dose (ppm) | Achieved Dosage ^b M/F (mg/kg/day) | Males | Females |
|------------|------------|---|-------|---------|
| Control | 0 | 0/0 | 20 | 20 |
| Low | 25 | 1.1/1.5 | 20 | 20 |
| Mid | 75 | 3.4/4.6 | 20 | 20 |
| High | 200 | 9.0/12.3 | 20 | 20 |

a Adapted from the study report (MRID 45118329), page 24.

b Achieved dosages obtained from the study report (MRID 45118329), page 46.

3. Dose rationale: Dose selection was based on a previous subchronic toxicity study (MRID 45118321) in which the test substance was administered orally to 10 rats/sex/dose at dietary levels of 0, 50, 150, 500, 1000 or 1500 ppm for 3 months. Increased splenic extramedullary hematopoiesis and histiocytosis were observed at doses of 150 ppm and above. Decreases in food consumption, body weight, and body weight gains; changes in hematology and clinical chemistry parameters; increased absolute and relative (to body) liver, kidney, and spleen weights; and hepatocellular hypertrophy, distended sinusoids in the spleen, and mucosal hyperplasia in the duodenum were observed at doses of 500 ppm and above.

Based on the results of this range-finding study, the doses presented in Table 1 were chosen for the chronic study.

4. Test article preparation and analysis: Dose formulations were prepared weekly. A premix was made by freezing and crushing the test substance, dissolving it in acetone, spraying the acetone solution onto the diet, and evaporating the acetone. Subsequently, the premix was mixed with the appropriate amount of food to obtain the desired concentrations. Homogeneity and concentration analyses were performed in conjunction with a parallel carcinogenicity study. Homogeneity (top, middle, and bottom) was determined using the low and high dose formulations at 15 months after study initiation. Concentration analyses were performed on all dose formulations at study initiation and every 3 months thereafter. Stability analyses were conducted on a 20 mg/kg sample stored for 43 days at room temperature.

Results - Homogeneity analysis on triplicate samples of feed containing pyraclostrobin at 25 and 200 ppm: Mean % of nominal \pm SD = 92.9 \pm 2.0 and 93.9 \pm 1.5%, respectively.

Concentration analysis (range as % of nominal): 90.0-106.9%

Stability analysis (% of day 0): 104%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosages to the study animals was acceptable.

5. Dose administration - The test substance was administered continuously in the diet for the duration of the study. Control animals received the untreated diet only.
6. Statistical analyses: The following statistical tests were used ^a:

| Statistical Test | Parameters Investigated |
|--|---|
| One-way ANOVA followed by Dunnett's test ($p \leq 0.05$ and 0.01) | Body weight Body weight gains Food consumption Food efficiency |
| One-way Kruskal-Wallis test followed by Mann-Whitney U test ($p \leq 0.05$, 0.02 , and 0.002) | Hematology (except differential blood count) Clinical chemistry |
| Fisher's exact test ($p \leq 0.05$ and 0.01) | Urinalysis (except volume, color, turbidity, and specific gravity) |
| One-way Kruskal-Wallis test followed by Wilcoxon test ($p \leq 0.05$ and 0.01) | Organ weight |

a Extracted from the study report (MRID 45118329), pages 30, 38, and 42.

C. METHODS:

1. Observations - All animals were checked twice daily (once daily on weekends and holidays) for mortality clinical signs of toxicity. Detailed clinical examinations were performed weekly.
2. Body weight and body weight gain - All animals were weighed weekly through week 13. After the thirteenth week of treatment, all animals were weighed every fourth week and prior to necropsy. Mean cumulative body weight gains were calculated for each weighing day.
3. Food consumption, efficiency, and compound intake - Food consumption (g/animal/day) for each animal was determined weekly through week 13. After the thirteenth week of treatment, food consumption was determined every fourth week until study termination. Food efficiency was calculated based upon individual body weight gain and food

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consumption data. In addition, compound intake was calculated using individual food consumption and body weight determinations.

4. Water consumption - Water consumption was not determined.
5. Ophthalmoscopic examination - Ophthalmoscopic examinations were performed on all animals prior to dose initiation and on all surviving control and high-dose animals prior study termination.
6. Blood analyses - Blood was collected for hematology and clinical chemistry evaluations from the retroorbital venous plexus of all animals (non-fasted) on days 92, 187, 362, 551, and 722. The CHECKED (X) parameters below were evaluated in each blood sample.

a. Hematology:

| | | | |
|---|---|---|---------------------------------|
| X | Hematocrit (HCT)* | X | Leukocyte differential count* |
| X | Hemoglobin (HGB)* | X | Mean corpuscular HGB (MCH)* |
| X | Leukocyte count (WBC)* | X | Mean corpusc. HGB conc.(MCHC)* |
| X | Erythrocyte count (RBC)* | X | Mean corpusc. volume (MCV)* |
| X | Platelet count* | | Reticulocyte count ¹ |
| X | Blood clotting measurements* (Thromboplastin time) | | |
| X | (Prothrombin time) | | |

*-Guideline required parameters to be examined.

¹-Reticulocytes, as well as blood smears, were prepared and stained, but not evaluated.

b. Clinical chemistry:

| ELECTROLYTES | | OTHER | |
|--------------|---|-------|-----------------------------|
| X | Calcium* | X | Albumin* |
| X | Chloride* | X | Blood creatinine* |
| X | Magnesium | X | Blood urea nitrogen* |
| X | Inorganic phosphate* | X | Total Cholesterol* |
| X | Potassium* | X | Globulins |
| X | Sodium* | X | Glucose* |
| | | X | Total bilirubin* |
| | | X | Total serum protein (TP)* |
| | | X | Triglycerides |
| | | | Serum protein electrophores |
| ENZYMES | | | |
| X | Alkaline phosphatase (AP)* | | |
| X | Serum cholinesterase (ChE) | | |
| | Creatine phosphokinase | | |
| | Lactic acid dehydrogenase | | |
| X | Serum alanine aminotransferase (ALT)* | | |
| X | Serum aspartate aminotransferase (AST)* | | |
| X | Gamma glutamyltransferase (GGT)* | | |
| | Glutamate dehydrogenase (GLDH) | | |

*-Guideline required parameters to be examined.

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7. Urinalysis - Urine was collected overnight from all animals on days 85, 181, 356, 545, and 713. The following CHECKED (X) parameters were evaluated.

| | | | |
|---|------------------------|---|--------------|
| X | Appearance* | X | Glucose* |
| X | Volume* | X | Ketones |
| X | Specific gravity* | X | Bilirubin |
| X | pH* | X | Blood* |
| X | Sediment (microscopic) | X | Nitrite |
| X | Protein* | X | Urobilinogen |

*- Guideline required parameters to be evaluated.

8. Sacrifice and pathology - Upon study termination, all surviving rats were anesthetized by CO₂, sacrificed by decapitation, and necropsied. The following CHECKED (X) tissues were collected from all animals and preserved in 4% formaldehyde; all slides were stained using Hematoxylin and Eosin. The (XX) organs were weighed. The tissues that are followed by an * were examined histologically from all dose groups; all remaining tissues were examined in the control and high dose groups in addition to tissues with gross lesions from the low and mid-dose animals.

| | DIGESTIVE SYSTEM | | CARDIOVASC./HEMAT. | | NEUROLOGIC |
|----|------------------------------|----|------------------------------|----|---|
| X | Tongue | X | Aorta ¹ | XX | Brain ^{1,2} |
| X | Salivary glands ¹ | X | Heart ^{1,2} | X | Periph. nerve ¹ |
| X | Esophagus ¹ | X | Bone marrow ¹ | X | Spina ¹ cord (3 levels) ¹ |
| X | Stomach ^{1*} | X | Lymph nodes ¹ | X | Pituitary ¹ |
| X | Duodenum ^{1*} | X | Spleen ^{1,2*} | X | Eyes ¹ |
| X | Jejunum ¹ | X | Thymus* | | |
| X | Ileum ¹ | | | | |
| X | Cecum ¹ | | | | |
| X | Colon ¹ | | | | |
| X | Rectum ¹ | | | | |
| XX | Liver ^{1,2*} | XX | UROGENITAL | XX | GLANDULAR |
| X | Pancreas ¹ | X | Kidneys ^{1,2*} | X | Adrenal gland ^{1,2*} |
| | | X | Urinary bladder ¹ | X | Lacrimal gland |
| | | XX | Testes ^{1,2*} | X | Mammary gland ^{1*} |
| | | X | Epididymides ^{1,2} | X | Thyroids w/ parathyroids ¹ |
| | | X | Prostate ¹ | | |
| | RESPIRATORY | X | Seminal vesicle ¹ | X | OTHER |
| X | Trachea ¹ | XX | Ovaries ^{1,2*} | X | Bone (including joint) |
| X | Lung ^{1*} | X | Uterus ^{1,2} | X | Skeletal muscle |
| | Pharynx ¹ | | | X | Skin ¹ |
| | Larynx ¹ | | | X | All gross lesions and masses ¹ |
| | Nose ¹ | | | X | Vagina |
| | | | | X | Oviducts |

1-Guideline required tissues to be examined in the control and high dose groups.
 2-Guideline required organs to be weighed.

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II. RESULTS

A. Observations:

1. Mortality - No differences in survival were observed in either sex of the treated groups throughout the study when compared to the respective control groups. After 24 months of dosing, survival was 80-95% in the males and 65-80% in the females, which exceeded the guideline requirement (not less than 25%) for this interval.
2. Clinical signs - No treatment-related clinical signs were observed in any treated group when compared to concurrent controls.

B. Body weight and body weight gain - No treatment-related decreases in body weight or cumulative body weight gains (Table 2) were observed in any treated group. At 200 ppm, cumulative body weight gains were decreased ($p \leq 0.05$) in the males at days 0-7 (16%) and 0-539 (111%) and in the females at days 0-483 (114%). These decreases were minor and not sustained throughout the study; overall (days 0-728) body weight gains were comparable between all treated groups and controls. Therefore, the decreases in body weight gains were considered not to be biologically important.

Table 2. Mean cumulative body weight gains (g) at selected intervals in rats dosed with pyraclostrobin for two years. ^a

| Interval (days) | Dose (ppm) | | | |
|-----------------|------------|------------|------------|-------------------|
| | 0 | 25 | 75 | 200 |
| Males | | | | |
| 0-7 | 53.9±4.4 | 52.3±5.1 | 50.6±3.6 | 50.4*±4.2 (16) |
| 0-539 | 530.8±73.9 | 530.0±74.1 | 519.4±89.1 | 472.5*±56.8 (111) |
| Overall (0-728) | 517.8±84.1 | 514.8±70.9 | 521.1±94.4 | 489.4±66.9 |
| Females | | | | |
| 0-7 | 19.0±5.6 | 19.3±4.7 | 20.9±5.8 | 17.5±4.7 |
| 0-483 | 205.8±36.0 | 205.3±36.1 | 206.0±40.9 | 177.9*±25.5 (114) |
| Overall (0-728) | 230.0±28.6 | 231.8±38.0 | 226.8±52.9 | 207.4±41.2 |

^a Data obtained from the study report, Tables IA025 through IA032, pages 89 through 96; n=18-20. Percent difference from controls is listed parenthetically.

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

- C. Food consumption and efficiency - No treatment-related differences in food consumption or efficiency were observed. At 200 ppm, decreased ($p \leq 0.05$) food consumption was observed in the males on day 7 (↓5%) and in the females on days 343 and 455 (↓7-9%); however, these decreases were minor, incidental, and considered unrelated to treatment. Increased ($p \leq 0.05$) food consumption was observed sporadically in the 25 and 75 ppm females (↑5-7%); however, these minor increases were not dose-dependent and considered not to be adverse. Occasional differences ($p \leq 0.05$) in food efficiency were observed during the study; however, these differences were sporadic and incidental and were considered not to be treatment-related.
- D. Ophthalmoscopic examination - There were no treatment related ophthalmological findings detected in any treated group.
- E. Blood analyses
1. Hematology - No treatment-related differences in hematology parameters were observed during this study. The following differences ($p \leq 0.02$) from concurrent controls were noted, but were minor and/or not dose-dependent and considered unrelated to treatment: (i) increased platelets in the 75 and 200 ppm males (↑8% each) on day 187; (ii) increased platelets in the 25 ppm males (↑12%) on day 551; and (iii) increased leukocytes in the 25 ppm (↑39%) and 200 ppm (↑36%) females on day 723.
 2. Clinical chemistry - No treatment-related differences in clinical chemistry parameters were observed during this study. Decreased ($p \leq 0.002$, 0.02, or 0.05) alanine aminotransferase was noted in the 200 ppm males at all time points (↓12-18%) and in the 25 and 75 ppm males on day 92 (↓12-15%); however, these findings lacked corroborating evidence of liver toxicity and were considered not to be toxicologically important. Likewise, decreased ($p \leq 0.002$, 0.02, or 0.05) alkaline phosphatase was observed in the 200 ppm males (↓9-18%) and females (↓13-22%) at all time points; however, these findings were not corroborated by other evidence of liver toxicity, and were also considered not to be toxicologically important. Other differences ($p \leq 0.002$, 0.02, or 0.05) in clinical chemistry parameters were noted, but were minor, not sustained over time, and/or not dose-dependent and considered unrelated to treatment: (i) increased alkaline phosphatase in the 25 and 75 ppm males on day 722 (↑12-19%); (ii) increased serum cholinesterase in the 200 ppm females on days 363 and 554 (↑17-24%) and in the 25 ppm females on day 554 (↑19%); (iii) decreased potassium (↓4%), creatinine (↓6%), and globulins (↓6%) in the 200 ppm males on day 187; (iv) increased inorganic phosphate in the 25 ppm females on day 188 (↑12%) and in all treated females on day 554 (↑13-17%); (v) increased magnesium in the 25 and 75 ppm females on day 188 (↑5-6%); and (vi) increased albumin in the 200 ppm females on day 363 (↑4%).
- F. Urinalysis - There were no treatment-related differences in urinalysis parameters between treated groups and concurrent controls. Increased ($p \leq 0.05$ or 0.01) urine protein was

observed in the 200 ppm males on day 356 (140%), 25 ppm males on day 545 (150%), all treated males on day 713 (143-50%), and 200 ppm females on day 546 (150%); however, these increases were not consistent over time and were considered not to be adverse. Other differences ($p < 0.05$ or 0.01) from concurrent controls which were neither dose-dependent nor consistent over time included increased nitrite in the 25 ppm males on day 545 (1113%) and increased blood in the urine in the 75 ppm females on day 546 (133%).

G. Sacrifice and pathology:

1. Organ weights - Absolute and relative (to body weight) organ weights were comparable between treated and control animals.
2. Gross pathology - At 25, 75, and 200 ppm ($n=20$), dose-dependently increased incidences of liver (50, 50, and 60%, respectively vs. 40% controls) and pituitary gland (20, 30, and 35%, respectively vs. 15% controls) foci in the females and cystic degeneration of the testes in the males (25, 30, and 35%, respectively vs. 15% controls) were noted.
3. Microscopic pathology at necropsy:
 - a) Non-neoplastic - No treatment-related non-neoplastic findings were observed. All microscopic lesions occurred at incidences that were comparable to concurrent controls. Inflammatory foci, clear and basophilic foci, and biliary cysts were among the common liver findings in the control and all treated animals; however, these findings were not dose-related. Other observations (in the control, low, mid- and high-dose, respectively) include increased testicular tubular degeneration (1/20, 7/20, 7/20, and 6/20) and mineralization (1/20, 4/20, 6/20, 4/20) and increased uterine endometrial cysts (3/20, 5/14, 4/15, 9/20) and squamous cysts (1/20, 2/14, 3/15, and 6/20) (MRID 45118329, Table IC 31-32, pp.231-232). However, these changes were neither dose-dependent nor were they corroborated by findings in the accompanying oncogenicity rat study (MRID 45118331).
 - b) Neoplastic - No treatment-related neoplastic findings were observed. The following tumors occurred at higher incidences at 200 ppm than concurrent controls; however, the incidences were not dose-dependent (data presented as # affected animals): (i) pituitary gland adenoma in the females (19/20 treated vs. 17/20 controls); (ii) pheochromocytoma in the males (6/20 treated vs. 3/20); and (iii) mammary gland fibroadenoma in the females (8/20 treated vs. 5/20 controls).

The following tumors occurred at low incidences (5%, $n=20$) in the 200 ppm animals but not in any other animal including concurrent controls (0%, $n=20$): (i) cholangioma (female); (ii) pancreatic acinar adenoma (male); (iii) tubular carcinoma of the kidney (male); (iv) yolk sac carcinoma (female); (v) squamous carcinoma of the skin (male); and (vi) osteosarcoma (male).

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III. DISCUSSION

- A. Investigators conclusions - It was concluded that oral administration of pyraclostrobin for approximately two years produced decreased body weights, body weight gains, and alkaline phosphatase in both sexes and decreased alanine aminotransferase in the males at 200 ppm. The NOAEL for this study was designated as 75 ppm.
- B. Reviewer's discussion/conclusions - In this chronic study, pyraclostrobin was administered continuously in the diet to 20 CrI:CD®BR rats/sex/group at nominal dose levels of 0, 25, 75, or 200 ppm (equivalent to [M/F] 0/0, 1.1/1.5, 3.4/4.6, and 9.0/12.3 mg/kg/day) for two years. Analysis of the test substance indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable. Furthermore, the results confirmed the stability of the test substance for a period of 43 days at room temperature.

Mortality, clinical signs, body weight, food consumption, food efficiency, ophthalmoscopic findings, hematology, clinical chemistry, and urinalysis parameters, organ weights, and histopathology were unaffected by the test substance. No treatment-related findings were observed in the 25, 75, or 200 ppm dose groups.

At 200 ppm, cumulative body weight gains were decreased ($p \leq 0.05$) in the males at days 0-7 (↓6%) and 0-539 (↓11%) and in the females at days 0-483 (↓14%). These decreases were minor and not sustained throughout the study; overall (days 0-728) body weight gains were comparable between all treated groups and controls. Therefore, the decreases in body weight gains were considered not to be biologically significant.

The LOAEL for this study was not observed.

The NOAEL for this study is 200 ppm (equivalent to 9.0 mg/kg/day in males and 12.3 mg/kg/day in females).

No treatment-related neoplastic findings were observed. The following tumors occurred at higher incidences at 200 ppm than concurrent controls; however, the incidences were not dose-dependent (data presented as # affected animals): (i) pituitary gland adenoma in the females (19/20 treated vs. 17/20 controls); (ii) pheochromocytoma in the males (6/20 treated vs. 3/20 controls); and (iii) mammary gland fibroadenoma in the females (8/20 treated vs. 5/20 controls).

The following tumors occurred at low incidences (5%, n=20) in the 200 ppm animals but not in any other animal including concurrent controls (0%, n=20): (i) cholangioma (female); (ii) pancreatic acinar adenoma (male); (iii) tubular carcinoma of the kidney (male); (iv) yolk sac carcinoma (female); (v) squamous carcinoma of the skin (male); and (vi) osteosarcoma (male).

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Under the conditions of this study, there was no evidence of carcinogenic potential.

The submitted study is classified as **unacceptable/guideline (§83-1)** and **does not** satisfy the requirements for a chronic toxicity study in rats. It appears that the animals could have tolerated a higher dose of the test substance.

C. Study deficiencies -

1. It appears that the animals could have tolerated a higher dose of the test substance.
2. The nose, pharynx, and larynx were not examined microscopically.
3. The following organs were not weighed: epididymides, heart, spleen, and uterus.

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