DATA EVALUATION RECORD

6/28/2001

PYRACLOSTROBIN (BAS 500F)

Study Type: §83-2 (b) Oncogenicity Study in Mice

Work Assignment No. 3-01-113E (MRID 45118330)

Prepared for
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U.S. Environmental Protection Agency
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DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Study in Mice
OPPTS Number: 870.4200 OPP Guideline Number: §83-2[b]

DP BARCODE: D269669, D267732 SUBMISSION CODE: S583112
P.C. CODE: 099100 TOX. CHEM. NO.: None

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

SYNONYMS: BAS 500F

CITATION: Mellert, W., Deckardt, K., Küttler, et.al. (1999) BAS 500F - Carcinogenicity Study in B6C3F1 Mice Administration in the Diet for 18 Months. BASF Aktiengesellschaft, Department of Toxicology, Ludwigshafen, Germany. Laboratory Project Id.: 76C0494/96101, November 22, 1999. MRID 45118330. Unpublished.

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

EXECUTIVE SUMMARY: In a mouse oncogenicity study (MRID 45118330), pyraclostrobin (97.09% a.i., Lot/Batch # J.-Nr. 27882/191/c) was administered in the diet to B6C3F1/CrlBR mice (50/sex/group) for up to 80 weeks at nominal doses of 0, 10, 30 or 120 ppm in males and 0, 10, 30, 120, or 180 ppm infemales, equivalent to 0/0, 1.4/1.6, 4.1/4.8, 17.2/20.5, and 32.8 (females only) mg/kg/day [M/F], respectively).

Mortality, clinical signs, body weight, body weight gain, food consumption, food efficiency, hematology, organ weights, and gross and microscopic findings for both sexes at all doses were unaffected by treatment.

Among all treated male and female groups, there were statistically significant decreased mean body weights (↓4-13%) and body weight gains (4-28%, excluding week 1). However, the magnitude of these effects was not clearly dose-related despite the fact that, during the study period, these effects were more consistently observed among the high dose animals than among the mid- or low dose mice. Nonetheless, in the analysis of the body weight and body weight gain

data, one should compare the results obtained in the high dose groups (120 ppm-M; 180 ppm-F) with the results obtained in the lowest dose group (10 ppm). Since no adverse effects are expected in the 10 ppm group, the 10 ppm group could serve as a second control group to which comparisons could be made. [It is noted that the 10 ppm group in the mouse oncogenicity group is 5X lower than the NOAEL obtained for mice in the 90-day subchronic study-MRID 45118320.] When the comparisons are made between body weight and body weight gain data obtained for both sexes in the high dose groups and the body weight and body weight gain data obtained for both sexes in the low dose (10 ppm) group, the overall differerences become biologically insignificant.

The LOAEL is >120 ppm for males (equivalent to >17.2 mg/kg/day) and >180 ppm for females (equivalent to >32.8 mg/kg/day). The NOAEL is ≥120 ppm for males (equivalent to ≥17.2 mg/kg/day) and ≥180 ppm for females (equivalent to ≥32.8 mg/kg/day).

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

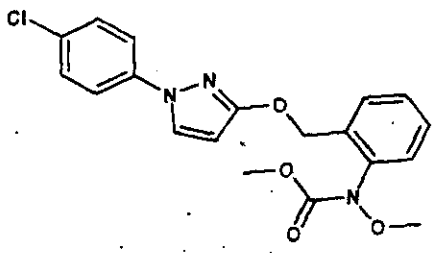
The submitted study is classified as **Unacceptable/guideline (§83-2[b])** and does not satisfy the requirements for a carcinogenicity study in mice. Dose levels were too low.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Pyraclostrobin, BAS 500
   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 stored at room temperature for up to 43 days
   CAS #: 175013-18-0
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Mouse
   Strain: B6C3F1/CrlBR
   Age and mean weight at start of dosing: Age 47-51 days; 20.5-27.8g (males) and 17.8-21.9 g (females)
   Source: Charles River Lab., USA
   Housing: Singly in type MI Makrolon cages with mesh wire tops.
   Diet: Kliba maintenance diet rat/mouse/hamster meal (KlingentalmühleAG, Kaiseraugst, Switzerland), ad libitum, except for 16-20 hours prior to termination
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 20-24°C
   Humidity: 30-70%
   Air changes: Information not provided
   Photoperiod: 12 hours light/12 hours dark
   Acclimation period: 6-7 days

B. STUDY DESIGN:

1. In life dates: start: 3/27/97 end: 10/23/98

2. Animal assignment: The mice were randomly assigned (stratified by weight) to the test groups shown in Table 1.

Table 1. Study design [a]

Test Group	Dietary Concentration (ppm)	Mean Achieved Dose (mg/kg/day)[b] (M/F)	Number of Animals	
			Males	Females
Control	0	0	50	50
Low	10	1.4/1.6	50	50
Mid	30	4.1/4.8	50	50
High/mid-high	120	17.2/20.5	50	50
High	180	32.8 (F)	-	50

a Data obtained from the study report, page 21
b Achieved doses obtained from the study report, page 35.

3. Dose selection rationale - The doses chosen for the current study were based on the results of a 3-month study (MRID 45118320) in which pyraclostrobin was administered in the diet to 10 B6C3F1 Crl BR mice/sex/group at nominal doses of 0, 50, 150, 500, 1000, or 1500 (equivalent to 0, 9.2/12.9, 30.4/40.4, 119.4/162.0, 274.4/374.1, 475.5/634.8 mg/kg/day for the males/females) for 3 months. No treatment-related differences were observed in mortality, clinical signs, or organ weight data. At 150 ppm, body weights and body weight gains were decreased ($p \leq 0.05$ or 0.01) in the males throughout treatment. Body weights gains were decreased in the females at study day 77. Urea was increased ($p \leq 0.02$ or 0.002) and triglycerides were decreased ($p \leq 0.05$ or 0.02) in both males and females. Ulcer/erosion of the glandular stomach was observed in the males and females. Increased apoptosis was observed in the mesenteric lymph nodes in the females (2/10 treated vs 0/10 controls). At doses ≥500 ppm, body weights and body weight gains were decreased ($p \leq 0.05$ or 0.01) throughout treatment. Food efficiency was decreased ($p \leq 0.01$) throughout treatment in the males and during the first three weeks in the females. Decreases ($p \leq 0.05$) were observed in mean corpuscular volume in the males and mean corpuscular hemoglobin in the females. Increased urea ($p \leq 0.002$) and decreased triglycerides ($p \leq 0.002$) were observed in both sexes. Decreased globulin ($p \leq 0.02$ or 0.002) and increased cholesterol ($p \leq 0.02$) were observed in the females. Ulcer/erosion of the glandular stomach was observed both macroscopically in the males and microscopically in the males and females. Thickening of the duodenal wall was observed both macroscopically and microscopically in the males and females. Increased apoptosis was observed in the mesenteric lymph nodes in the males and females (5-16/20 treated vs 0/20 controls). Atrophy of the thymus was observed in the males (3-8/10 treated vs 0/10 controls). At doses ≥1000, food consumption was intermittently increased ($p \leq 0.05$ or 0.01) throughout treatment in the males and females. Leukocytes and mean corpuscular hemoglobin were decreased ($p \leq 0.05$ or 0.002) in the males, and creatinine and hemoglobin were decreased ($p \leq 0.05$ or 0.02) in the females. At 1500 ppm, hemoglobin

was decreased ($p \leq 0.002$) in the males, and platelets were increased ($p \leq 0.02$) in both sexes. Discoloration of the jejunum (2/10 treated) and colon (1/10 treated) were observed in the males (vs 0/10 controls each), and focal necrosis of the liver was observed in the females (1/10 treated vs 0/10 controls). The LOAEL for this study was 150 ppm for both sexes and the NOAEL was 50 ppm.

Based upon the results of this 3-month study, the doses summarized in Table 1 were selected for the oncogenicity study.

4. Dose preparation, administration, and analysis - The appropriate amount of test substance was mixed with the diet to obtain a premix which was then serially diluted with additional food to obtain the appropriate dose. Diets were prepared at 4-week intervals. Stability was determined in a 20 ppm formulation stored at room temperature for 43 days. Concentration was analyzed for all dietary formulations at the beginning of the study and at 3-month intervals. Homogeneity analysis (top, middle, bottom) was determined on two samples each of the 25 and 200 ppm formulations prepared for a rat oncogenicity study running concurrently with this mouse oncogenicity study; both studies were using the same mixing procedure. The homogeneity and concentration samples were stored frozen prior to analysis.

   Results:

   Homogeneity (range as mean % of nominal±SD): 92.9±2.0-93.9±1.5%

   Stability (% of day 0): 104%

   Concentration (range as % of nominal): 92.0-114%

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

5. Statistics - Food consumption, food efficiency, body weight and body weight gain data were analyzed by two-sided analysis of variance (ANOVA), and if resulting p values were ≤ 0.05, each group was compared with the control group using Dunnett's test. The two-sided Kruskal-Wallis test was applied to the organ weight data and if resulting p values were ≤ 0.05, the Wilcoxon test was applied.

C. METHODS:

1. Observations - All animals were inspected for clinical signs and behavior twice daily on weekdays and once daily on weekends and holidays. Detailed clinical observations, including palpation for masses, were performed weekly.

2. Body weight - All animals were weighed at the start of dosing, weekly for the first 13

weeks, then at 4-week intervals until study termination. Body weights were also recorded at scheduled termination. Group mean cumulative body weight gains were also reported.

3. Food consumption/efficiency and compound intake - Food consumption for each animal (reported as g/animal/day) was measured at weekly intervals through week 13, then every fourth week thereafter until study termination. Mean food efficiency was calculated for the first 13 weeks using individual body weight and food consumption data. Compound intake values (mg/kg/day) were calculated from the nominal dietary test material concentration, food consumption, and body weight data.

4. Water consumption - Water bottles were checked daily for overt changes in volume.

5. Hematology - Blood smears were obtained via tail venipuncture from all surviving animals at 12 months and after decapitation of animals at 18 months; differential counts were determined on the control and high-dose animals only. In addition, a blood smear was obtained from the animal killed *in extremis* during the study.

6. Sacrifice and pathology - All animals were subjected to a gross pathological examination. The following checked (X) tissues were collected from all animals sacrificed at scheduled termination, animals that died prematurely, and animals sacrificed *in extremis*. Additionally at termination, the (XX) organs were weighed.

	DIGESTIVE		CARDIOVASC./HEMAT		NEUROLOGIC
	Tongue	X	Aorta	XX	Brain
X	Salivary glands	X	Heart	X	Peripheral nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes with optic nerve
X	Jejunum	X	Thymus		GLANDULAR
X	Ileum		UROGENITAL	XX	Adrenal glands
X	Cecum	XX	Kidneys		Harderian gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	XX	Testes	X	Parathyroids/thyroid
XX	Liver	X	Epididymis		
X	Gall bladder	X	Prostate		OTHER
X	Pancreas	X	Seminal vesicles	X	Bone (femur and knee joint)
	RESPIRATORY	XX	Ovaries	X	Muscle
X	Trachea	X	Oviducts	X	Skin
X	Lungs	X	Uterus	X	Lacrimal gland
	Diaphragm	X	Vagina		Head
			Preputial gland	X	All gross lesions and masses

A complete complement of tissues was examined microscopically from all control and high-dose animals that were sacrificed on schedule and from any animal that died or was killed during the course of the study. Gross lesions and masses, lungs, liver, kidneys, and stomach from all animals in all groups were subjected to microscopic examination.

II. RESULTS

A. Observations:

1. Toxicity - No treatment-related clinical signs or palpable masses were observed.

2. Mortality - No differences in mortalities were observed in either sex of the treated groups throughout the study when compared to the respective control groups. Percentage survival in all dose groups of mice after 18 months was 92-100%.

B. Body weight/body weight gain: Selected mean body weight and body weight gain data are presented in Tables 2a and 2b. Decreased ($p \leq 0.05$ or 0.01) mean body weights were observed in the following dose groups: (i) the 120 ppm males (↓4-13%) at weeks 8 to 80; (ii) the 30 ppm males (↓5-8%) and the 10 ppm males (↓6-10%) at weeks 65 to 80; (iii) the 180 ppm females (↓6-13%) at weeks 21, 29 to 53, and 65 to 80; and (iv) the 120 ppm females (↓9-10%) at weeks 65 to 80. Only minor, sporadic and/or incidental differences ($p \leq 0.05$) from controls were observed in the 10 (↓4-8%) and 30 ppm (↓4%) females.

Body weight gains were decreased ($p \leq 0.05$ or 0.01) throughout the study (weeks 1-78) in the 120 ppm males (↓14-38%) and at weeks 65 to 78 in the 30 (↓12-18%) and 10 (↓14-23%) ppm males. Other decreases ($p \leq 0.05$ or 0.01) in body weight gains observed in the 30 (↓38%) and 10 (↓10-23%) ppm males were incidental, sporadic and/or not dose-related. Overall (weeks 1-80) body weight gains (calculated by the reviewers) were decreased in the 120 (↓26%), 30 (↓15%) and 10 ppm males (↓19%). In the 180 ppm females, body weight gains were decreased (↓15-50%; $p \leq 0.05$ or 0.01) throughout most of the study; only not dose-dependent, sporadic differences ($p \leq 0.05$ or 0.01) from controls were observed in the 120 (↓12-20%), 30 (↓16-18%) and 10 (↓17-18%) ppm females. Overall body weight gains (calculated by the reviewers) were decreased in the 180 (↓23%), 120 (↓21%), 30 (↓2%) and 10 (↓15%) ppm females.

In the analysis of the body weight and body weight gain data, one should compare the results obtained in the high dose groups (120 ppm-M; 180 ppm-F) with the results obtained in the lowest dose group (10 ppm). Since no adverse effects are expected in the 10 ppm group, the 10 ppm group could serve as a second control group to which comparisons could be made. [It is noted that the 10 ppm group in the mouse oncogenicity group is 5X lower than the NOAEL obtained for mice in the 90-day subchronic study-MRID 45118320.] When the comparisons

are made between body weight and body weight gain data obtained for both sexes in the high dose groups and the body weight and body weight gain data obtained for both sexes in the low dose (10 ppm) group, the overall differerences become biologically insignificant (see Tables 2a and 2b).

Table 2a. Mean (± SD) body weight and body weight gains at selected intervals in male mice fed pyraclostrobin for up to 80 weeks.[a]

Study Week	Dose (ppm)			
	0	10	30	120
Mean Body Weight (g)				
1	25.6±1.8	25.4±1.6	25.2±1.5	24.9±1.5
8	30.9±2.5	30.6±2.4	30.7±2.2	29.7*±2.2(↓4)
13	33.1±3.2	32.4±2.6	32.4±2.7	31.0**±2.7 (↓6)
53	43.1±4.1	41.6±4.2	42.5±3.5	40.3**±4.4(↓6)
65	43.4±4.2	40.9**±4.0(↓6)	41.2*±3.7(↓5)	39.1**±3.9(↓10)
78	43.1±4.7	38.9**±4.1(↓10)	39.7**±4.5(↓8)	37.6**±4.3(↓13)
Termination	39.3±4.0	36.5**±3.5(↓7)	36.9**±3.9(↓6)	35.1**±4.0(↓11)
Mean Body Weight Gain (g)				
1	1.3±0.6	1.0*±0.6(↓23)	0.8**±0.6(↓38)	0.8**±0.7(↓38)
13	9.9±3.0	9.0±2.3	8.9±2.7	7.9**±2.7(↓20)
29	17.3±3.5	15.6*±3.4(↓10)	16.0±3.5	13.5**±3.5(↓22)
53	18.8±3.5	17.2±3.6	18.2±3.2	16.2**±3.9(↓14)
65	19.1±3.5	16.5**±3.5(↓14)	16.9**±3.3(↓12)	15.0**±3.5(↓21)
78	18.8±4.0	14.5**±3.7(↓23)	15.4**±4.5(↓18)	13.5**±3.9(↓28)
Overall (weeks 1-80)[b]	13.7	11.1(↓19)	11.7(↓15)	10.2(↓26)

a These data were extracted from the study report, Tables IA 017 through 1A 020, IA 025 through 1A 028, and IC-1, pages 64-67, 72-75, and 108. Numbers listed parenthetically represent the percent difference from controls. Body weight at termination was rounded-off to the nearest tenth by the reviewers.

b Calculated by reviewers.

* or ** Significantly different from controls $p<0.05$ or <0.01, respectively.

Table 2b. Mean (± SD) body weight and body weight gains at selected intervals in female mice fed pyraclostrobin for up to 80 weeks.[a]

Study Week	Dose (ppm)				
	0	10	30	120	180
Mean Body Weight (g)					
1	20.9±1.0	20.7±1.0	20.8±0.9	20.7±0.8	20.5±1.0
6	24.9±1.2	24.0**±1.3(↓4)	24.0**±1.2(↓4)	24.0**±1.2(↓4)	23.9**±1.5(↓4)
13	27.3±2.4	26.9±2.3	28.4±3.0	27.1±2.2	26.8±2.3
21	32.4±4.0	31.5±4.0	33.3±4.7	31.4±3.3	30.4*±3.9(↓6)
29	35.7±4.4	34.5±4.5	35.9±5.4	33.7±3.8	32.5**±4.2(↓9)
53	38.7±4.9	38.2±5.6	39.9±6.7	38.1±4.6	35.8*±4.5(↓7)
65	37.9±5.4	35.6±5.3	36.2±6.4	34.5**±5.0(↓9)	33.6**±4.6(↓11)
78	39.0±6.1	35.7**±5.1(↓8)	36.7±5.8	35.2**±5.3(↓10)	34.0**±4.3(↓13)
Termination	35.0±5.8	32.7*±4.9(↓7)	34.6±6.0	31.9**±5.1(↓9)	31.4**±4.0(↓10)
Mean Body Weight Gain (g)					
1	1.0±0.6	0.9±0.6	1.0±0.7	0.9±0.5	0.5**±0.8(↓50)
6	5.1±0.7	4.2**±0.8(↓18)	4.2**±0.9(↓18)	4.2**±1.0(↓18)	3.9**±1.1(↓24)
7	5.0±0.9	4.8±0.9	4.7±1.0	4.4*±1.0(↓12)	4.1**±1.1(↓18)
13	7.5±2.0	7.1±1.8	8.6*±2.7(↑15)	7.3±2.0	6.8±1.9
53	18.9±4.5	18.4±5.1	20.0±6.5	18.3±4.6	15.8**±4.2(↓16)
65	18.1±5.0	15.7±4.9	16.4±6.2	14.7**±4.9(↓19)	13.6**±4.5(↓25)
78	19.2±5.7	15.9**±4.7(↓17)	16.8±5.7	15.4**±5.1(↓20)	14.1**±4.2(↓27)
Overall (weeks 1-80)	14.1	12.0(↓15)	13.8(↓2)	11.2(↓21)	10.9(↓23)

a These data were extracted from the study report, Tables IA 021 through IA 024, IA 029 through IA 032 and IC-2, pages 68-71, 76-79 and 109. Numbers listed parenthetically represent the percent difference from controls. Body weight at termination was rounded-off to the nearest tenth by the reviewers.

b Calculated by reviewers.

* or ** Significantly different from controls $p<0.05$ or <0.01, respectively.

C. Food consumption/efficiency and compound intake:

1. Food consumption - No treatment-related findings in food consumption were observed. In the males, decreased ($p \leq 0.05$ or 0.01) food consumption was observed towards the end of the study in the 120 (↓7-26% at weeks 61 to 78), 30 (↓7-16% at weeks 61 to 77) and 10 ppm groups (↓9-18% at weeks 61 to 81). In the females, decreased ($p \leq 0.05$ or 0.01) food consumption was also observed towards the end of the study in the180 (↓16-19% at weeks 65, 73 and 81), 120 (↓19-23% at weeks 65, 73 and 81), 30 (↓14-26% at weeks 61, 65, 73 and 81) and 10 ppm groups (↓12-26% at weeks 61, 65, 69, 73 and 81). These findings in the males and females were considered not treatment-related since they were not dose-dependent.

2. Food efficiency - Differences ($p \leq 0.05$ or 0.01) from controls in food efficiency were observed in males and females of all dose groups. These differences were sporadic and not dose-related and therefore considered not treatment-related.

3. Compound intake - Compound intake values (mg/kg/day) are presented in Table 1 of this DER.

D. Water consumption - It was stated that no obvious changes in volume were observed.

E. Hematology - No treatment-related differences from concurrent controls were observed in any of the differential blood counts.

F. Sacrifice and pathology:

1. Organ weights - At the terminal sacrifice, mean body weights were decreased (↓6-11%; $p \leq 0.05$ or 0.01) in the males and females of all dose groups, except the 30 ppm females. The following differences ($p \leq 0.05$ or 0.01) from controls were considered not treatment-related because they were minor, not dose-dependent, related to differences in body weights, and/or lacked corroborating histopathological or gross pathological data: (i) decreased absolute liver weights in the 120 (↓19%), 30 (↓11%) and 10 ppm males (↓16%) and relative (to body) liver weights in the 10 ppm males (↓9%) and increased relative liver weights in the 180 ppm females (↑7%); (ii) decreased absolute kidney weights in the 120 (↓5%), and 10 ppm (↓6%) males and increased relative kidney weights in the 120 ppm males (↑6%) and 180 ppm females (↑10%); (iii) increased relative testes weights in the 120 (↑11%), 30 (↑5%) and 10 ppm males (↑7%); and (iv) increased relative brain weights in the 120 (↑14%), 30 (↑8%) and 10 ppm males (↑8%) and the 180 ppm (↑11%), 120 (↑9%), and 10 ppm females (↑7%).

2. Gross pathology - No treatment-related gross pathology findings were observed.

3. Microscopic pathology:

a) Non-neoplastic: No treatment-related non-neoplastic findings were observed. Differences from controls, such as diffuse liver fatty infiltration in the males and focal adrenal hypertrophy in the females were minor, and/or not dose-related.

b) Neoplastic: No treatment-related neoplastic changes were observed.

III. DISCUSSION

A. Investigators conclusions - Treatment-related decreases in body weight and body weight gains were observed in the 180 ppm females and the 120 ppm males. It was concluded that there was no evidence of carcinogenicity in mice of both sexes; the NOAEL was 120 ppm in the females and 30 ppm in the males.

B. Reviewer's discussion/conclusions - In this mouse oncogenicity study, pyraclostrobin was administered in the diet to B6C3F1/CrlBR mice (50/sex/group) for up to 80 weeks at nominal doses of 0, 10, 30, 120, or 180 ppm (females only), equivalent to 0/0, 1.4/1.6, 4.1/4.8, 17.2/20.5, and 32.8 (females only) mg/kg/day [M/F], respectively). Dietary analyses confirmed that nominal diet concentrations were achieved.

Mortality, clinical signs, food consumption, food efficiency, hematology, organ weights, gross and microscopic findings for both sexes at all doses were unaffected by treatment.

Among all treated male and female groups, there were statistically significant decreased mean body weights (↓4-13%) and body weight gains (4-28%, excluding week 1). However, the magnitude of these effects was not clearly dose-related despite the fact that, during the study period, these effects were more consistently observed among the high dose animals than among the mid- or low dose mice. Nonetheless, in the analysis of the body weight and body weight gain data, one should compare the results obtained in the high dose groups (120 ppm-M; 180 ppm-F) with the results obtained in the lowest dose group (10 ppm). Since no adverse effects are expected in the 10 ppm group, the 10 ppm group could serve as a second control group to which comparisons could be made. [It is noted that the 10 ppm group in the mouse oncogenicity group is 5X lower than the NOAEL obtained for mice in the 90-day subchronic study-MRID 45118320.] When the comparisons are made between body weight and body weight gain data obtained for both sexes in the high dose groups and the body weight and body weight gain data obtained for both sexes in the low dose (10 ppm) group, the overall differerences become biologically insignificant (see Tables 2a and 2b).

The LOAEL is >120 ppm for males (equivalent to >17.2 mg/kg/day) and >180 ppm for females (equivalent to >32.8 mg/kg/day). The NOAEL is ≥120 ppm for males (equivalent to ≥17.2 mg/kg/day) and ≥180 ppm for females (equivalent to ≥32.8

mg/kg/day).

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

The submitted study is classified as **Unacceptable/guideline (§83-2[b])** and does not satisfy the requirements for a carcinogenicity study in mice.

C. Study deficiencies - None noted.