5/24/01

DATA EVALUATION RECORD

PYRACLOSTROBIN (BAS 500F)

Study Type: §83-2(a); Oncogenicity Study in Rats

Work Assignment No. 3-02-140B (formerly 3-01-113F) (MRID 45118331)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Study in Rats
OPPTS Number: 870.4200

OPP Guideline Number: §83-2[a]

DP BARCODE: D269669
P.C. CODE: 099100

SUBMISSION CODE: S583112
TOX. CHEM. NO.: None

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

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

CITATION: Mellert, W., Deckardt, K., Gembardt, Chr., et.al (1999) BAS 500 F - Carcinogenicity Study in Wistar Rats Administration in Diet for 24 Months. BASF Aktiengesellschaft, Department of Toxicology, Ludwigshafen, Germany.. Laboratory Project Id.: 82S0494/96086, November 22, 1999. MRID 45118331. Unpublished.

SPONSOR: BASF Corporation Agricultural Products, P.O. Box 13528, Research Triangle Park, NC, 27769-3528

EXECUTIVE SUMMARY: In a rat oncogenicity study (MRID 45118331), pyraclostrobin (97.09% a.i., Lot/Batch # J.-Nr. 27882/191/c) was administered in the diet to Wistar rats (50/sex/group) for up to 104 weeks at nominal doses of 0, 25, 75, or 200 ppm, equivalent to 0/0, 1.2/1.5, 3.4/4.7, and 9.2/12.6 mg/kg/day [M/F], respectively.

Mortality, clinical signs, food efficiency, and hematology findings for both sexes at all doses were unaffected by treatment. No treatment-related findings were observed in the 25 or 75 ppm dose groups.

In the 200 ppm group, decreased ($p \leq 0.05$ or 0.01) body weights were observed in the males (↓3-7%) at weeks 1 through 81 and in the females (↓4-14%) at weeks 21 through 104; body weights in the males at 104 weeks was decreased (↓4%; not statistically significant [NS]). Decreased ($p \leq 0.05$ or 0.01) body weight gains were observed in the males (↓6-10%) at weeks 1 through 81

and in the females (↓7-22%) at weeks 21 through 104; cumulative body weight gain in the males at week 104 was decreased (↓5%; NS). Decreased ($p \leq 0.05$ or 0.01) food consumption was observed in the males (↓3-7%) sporadically during weeks 1 to 13. Increased ($p \leq 0.05$) relative kidney weights were observed in the males (↑9%) and females (↑19%). In addition, increased incidences of kidney tubular casts in the males (15/50 treated vs 5/50) and females (14/50 treated vs 10/50 controls) and kidney tubular atrophy in the males (16/50 treated vs 5/50 controls) and females (19/50 treated vs 12/50 controls) were observed. In the males, an increased incidence of necrosis of the liver was observed microscopically (10/50 treated vs 1/50 control). Additionally, erosion/ulcer of the glandular stomach was observed grossly (12/50 treated vs 7/50 controls) in the males. Microscopically, an increased incidence of acanthosis (6/50 treated vs 0/50 controls) and ulcers (4/50 treated vs 2/50 controls) of the forestomach and ulcers (7/50 treated vs 2/50 controls) and erosion of the glandular stomach (10/50 treated vs 2/50 controls) were also observed in the males.

The LOAEL is 200 ppm for males and females (equivalent to 9.2/12.6 mg/kg/day [M/F]) based on differences in body weight and body weight gains, increased incidences of kidney tubular casts and atrophy in males and females, and in males, an increased incidence of necrosis of the liver, gross and microscopic evidence of erosion/ulcer of the glandular stomach and an increased incidence of acanthosis and ulcers of the forestomach. The NOAEL is 75 ppm (equivalent to 3.4/4.7 mg/kg/day [M/F]).

Histiocytic sarcoma and lymphoma of the hemolymphoreticular system was observed in males at 25 (2/9 vs 1/50 controls), 75 (2/10 vs 1/50 controls), and 200 (6/50 [12%] vs 1/50 [2%]) ppm. Historical data were submitted on 6/14/2001. The incidence of hemolympohreticular tumors in male wistar rats from 4/95- 7/00 at the testing laboratory is 4% (mean) and 0-10% (range). There was also an increased incidence of mammary gland adenocarcinoma in the females at 200 ppm (16% vs 4% controls). Historical data showed an incidence of female mammary gland adenocarcinoma in wistar rats from 4/95- 7/00 to be 6% (mean) and 0-14% (range). Testicular leydig cell tumor were observed in all male groups but were slightly higher in each of the three treated groups (48-50%) than the control group (38%). Historical control data were not submitted for this tumor. Neoplasms were not analyzed for statistical significance.

Under the conditions of this study the carcinogenic potential of pyraclostrobin appears to be positive.

The submitted study is classified as **Acceptable/guideline(§83-2[a])** and satisfies the requirements for a carcinogenicity study in rats.

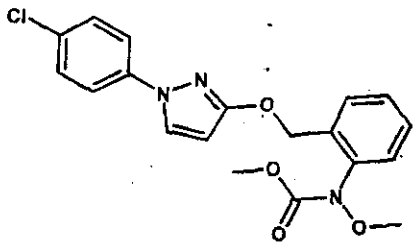
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Pyraclostrobin
   Description: Viscous melting, red-brown, clear
   Lot/Batch #: J.-Nr. 27882/191/c (Tox. III/Part 1)
   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: Rat
   Strain: Wistar Chbb:THOM (SPF)
   Age and mean weight at start of dosing: Age 42-44 days; 168.5-208.2g (males) and 142.3-178.9 g (females)
   Source: Dr. Karl Thomae GmbH, Biberach/Riss, FRG
   Housing: Singly in type DK III stainless steel wire mesh cages.
   Diet: Ground Kliba maintenance diet rat/mouse/hamster meal (KLIBA MHÜLEN AG, 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: 7-8 days

B. STUDY DESIGN:

1. In life dates: start: 1/27/97 (M); 2/11/97 (F) end: 2/2/99 (M); 2/18/99 (F)

2. Animal assignment: The rats 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] (Males/Females)	Number of Animals	
			Males	Females
Control	0	0	50	50
Low	25	1.2/1.5	50	50
Mid	75	3.4/4.7	50	50
High	200	9.2/12.6	50	50

a Data obtained from the study report, page 23.
b Achieved doses obtained from the study report, page 36.

3. Dose selection rationale - In this subchronic oral study, (MRIDs 45118321 & 45118322) pyraclostrobin (BAS 500F; 98.5% a.i.; Lot/Batch # CP 025394) was administered in the diet to 10 Wistar rats/sex/group at doses of 0, 50, 150, 500, 1000, or 1500 ppm (equivalent to 0, 3.5/4.2, 10.7/12.6, 34.7/40.8, 68.8/79.7, and 105.8/118.9 mg/kg/day for males/females) for 3 months.

There were no mortalities. No treatment-related differences were observed in clinical signs, ophthalmology, or urinalysis at any dose level. There were no treatment-related findings at 50 ppm, and the only findings noted at 150 ppm was extramedullary hematopoiesis in the spleen of females (3/10 vs 0/10 controls). However, because the finding in the spleen was not corroborated by hematology changes at the same dose, they are not considered to be of toxicological relevance.

Terminal body weights (↓7%) and overall (day 91) body weight gains (↓11%) were decreased in males in the 500 ppm group. At 1000 and 1500 ppm, body weights (↓12-26%) and body weight gains (↓23-75%) were decreased throughout treatment in males. Additionally at 1500 ppm, body weights (↓8-9%) and body weight gains (↓16-65%) were decreased in females. Body weights were decreased in the 1500 ppm females (↓8-9%) on study days 7, 14, and 91. Food consumption was decreased intermittently throughout treatment in both sexes (↓6-17%) in the 500 ppm group. In the 1000 and 1500 ppm groups, food consumption was decreased (↓9-46%) in both sexes throughout the study. Several clinical chemistry parameters differed from controls and reflected the continual catabolic state associated with the reduced nutritional status in these animals. For example, in the 500 ppm group cholesterol was decreased in males (↓19%), and alkaline phosphatase was decreased in females (↓14%). In the 1000 and 1500 ppm groups, alkaline phosphatase (↓14-23%) and globulins (↓8-13%) were decreased in both sexes. Triglycerides (↓50-61%) and cholesterol (↓26-29%) were decreased in males and total

bilirubin (↑58-95%) was increased in males. Serum cholinesterase was decreased in the 1000 (↓41%) and 1500 (↓49%) females. [In addition, at 1500 ppm total bilirubin (↑35%) was increased in females.]

The liver, spleen, and duodenum were the target organs of toxicity. Absolute (↑16-58%) and relative (↑22-74%) spleen weights were increased) in the females and/or males at doses of 500 ppm and greater. Relative liver weight was increased in the females 1000 and 1500 ppm groups (↑14-34%). Absolute weights of the liver in females in the 1500 ppm group were increased (↑22%).

Several hematological findings corroborated these effects on the spleen. Mild hemolytic anemia was evidenced by increased reticulocytes in the 1000 ppm males and in the 1500 ppm animals (↑41-94%), decreased erythrocytes in the 1000 and 1500 ppm females (↓7-11%), and increased prothombin time in males (↑11-13%). Likewise, gross and microscopic spleen changes, including spleen discoloration (2-11/20 vs 0/20 controls), sinus distension (18/20 vs 0/20 controls), extramedullary hematopoiesis (9/10 females vs 0/10 controls), and histiocytosis (13-17/20 vs 0/20 controls) corroborated a toxic effect on the spleen, consistent with the hematology.

Dose-related increases in minimal to slight hepatocyte hypertrophy, predominantly in zone 3, were observed in the 500 (3/10 vs 0/10 controls) and 1000 ppm males (6/10 vs 0/10 controls) and in the 1500 ppm animals (4-10/20 vs 0/20 controls). Dose-related thickening of the duodenal wall was observed macroscopically in the 1000 ppm females (2/10 vs 0/10 controls) and in the 1500 ppm animals (20/20 vs 0/20 controls). Microscopically, dose-related increases were observed in the incidences of hyperplasia in the duodenal mucosa in the 500 (4/10 vs 2/10 controls) and 1000 ppm males (5/10 vs 2/10 controls) and in the 1500 ppm animals (20/20 vs 4/20 controls).

The LOAEL is 500 ppm (equivalent to 34.7/40.8 mg/kg/day for males/females) based on decreased body weights/body weight gains (males), decreased food consumption, increased relative liver weight and absolute and relative spleen weight in females, and histopathology of the duodenum, spleen and liver. The NOAEL for this study is 150 ppm (equivalent to 10.7/12.6 mg/kg/day for males/females).

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

4. Dose preparation, administration, and analysis - The test substance was frozen and mechanically crushed. Acetonic solutions of the test substance were sprayed on aliquots (about 3 kg each) of diet in a rotation vaporizer under partial vacuum to form premixes. After removal of the acetone (by heating at up to 40°C for 30 minutes), the premixes were diluted with additional diet to obtain the appropriate doses. With the exception of the first two weeks, diets were prepared at weekly 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 was determined for the 25 and 200 ppm formulations. 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 (mean as % of day 0): 104%

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

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 one-way analysis of variance (ANOVA), and if resulting p values were ≤0.05, each group was compared with the control group using Dunnett's test. According to the data tables, mortality data were analyzed using two-sided Fisher's exact test. A one-way Kruskal-Wallis test was applied to the terminal body weight and organ weight data; 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 made weekly.

2. Body weight - All animals were weighed at the start of dosing (day 0), weekly for the first 13 weeks, then at 4-week intervals until study termination. Body weights were also recorded at scheduled termination. Mean cumulative body weight gains were calculated for each weighing day.

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. Hematology - Blood smears were obtained after decapitation of animals at study termination and from animals killed *in extremis*; differential counts were determined in the control and high-dose animals only.

5. 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	X	Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	XX	Testes	X	Parathyroids/thyroid
XX	Liver	X	Epididymis		
X	Pancreas	X	Prostate		OTHER
		X	Seminal vesicles	X	Bone (femur and knee joint)
	RESPIRATORY	XX	Ovaries	X	Skeletal Muscle
X	Trachea	X	Oviducts	X	Skin and subcutis
X	Lungs	X	Uterus	X	All gross lesions
	Pharynx	X	Vagina		Head
	Larynx				Harderian gland
	Diaphragm				Preputial Gland

A complete complement of tissues was examined microscopically for 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. All gross lesions, thymus, lungs, liver, spleen, kidneys, adrenal glands, testes, ovaries, stomach, duodenum and female mammary glands from animals of all dose groups were examined microscopically.

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. At 12 months, survival in all dose groups was 100%. Survival in all dose groups at 24 months was 68-84% for males and 78-90% for females.

B. Body weight/body weight gain:

Mean body weights and body weight gains are presented in Tables 2a and 2b. In the 200 ppm group, decreased ($p \leq 0.05$ or 0.01) body weights were observed in the males (↓3-7%) at weeks 1 through 81 and in the females (↓4-14%) at weeks 21 through 104; body weights in the males at 104 weeks were decreased (↓4%; not statistically significant [NS]). Body weights in the 75 and 25 ppm groups were similar to controls throughout the study.

Decreased ($p \leq 0.05$ or 0.01) cumulative body weight gains were observed in the 200 ppm males (↓6-10%) at weeks 1 through 81 and in the females (↓7-22%) at weeks 21 through 104; cumulative body weight gain in the males at week 104 was decreased (↓5%; NS). Body weight gains in the 75 and 25 ppm groups were similar to controls throughout the study.

Table 2a. Mean (± SD) body weights at selected intervals in rats fed pyraclostrobin for up to 104 weeks.[a]

Study Week	Dose (ppm)			
	0	25	75	200
Males				
-1 (Start of Dosing)	187.5±7.4	185.1±7.8	185.6±7.9	185.2±7.7
1	242.4±14.1	237.6±10.6	237.1±14.6	234.4**±11.5(↓3)
13	497.1±36.9	487.3±33.6	494.3±35.8	466.0**±30.8(↓6)
53	658.6±65.1	650.8±65.8	662.8±73.9	610.8**±50.5(↓7)
81	714.8±90.8	712.5±74.0	709.8±102.5	665.5*±70.4(↓7)
104	684.0±94.0	689.4±89.8	699.7±110.7	656.8±87.9
Females				
-1	159.2±6.6	159.1±6.7	157.4±6.7	157.1±7.9
1	180.6±9.5	182.3±10.2	180.3±9.1	179.8±12.1
13	285.7±21.4	294.4±21.2	290.8±23.6	279.2±22.7
21	305.3±21.0	311.6±23.3	309.1±25.2	293.2*±25.3(↓4)
53	353.7±32.2	347.7±30.6	346.7±35.3	324.1**±31.9(↓8)
81	389.5±57.2	376.6±37.9	377.7±49.1	351.2**±52.9(↓10)
104	417.4±73.3	396.1±68.4	390.2±61.5	360.2**±60.7(↓14)

a These data were extracted from the study report, Tables IA-017 through IA-026, pages 68-77. Numbers listed parenthetically represent the percent difference from controls.

Table 2b. Mean (± SD) body weight gains at selected intervals in rats fed pyraclostrobin for up to 104 weeks.[a]

Study Week	Dose (ppm)			
	0	25	75	200
Males				
1	54.9±8.6	52.5±4.9	51.6±12.1	49.2**±7.5(↓10)
2	100.1±9.2	100.0±8.6	101.4±10.5	93.7**±7.8(↓6)
13	309.6±33.0	302.3±31.2	308.7±32.9	280.9**±27.3(↓9)
53	471.1±62.4	465.7±64.2	477.2±71.7	425.6**±47.3(↓10)
81	527.3±88.9	527.1±72.3	524.7±101.6	480.5*±67.4(↓9)
104	496.8±92.9	503.9±88.6	514.7±109.3	472.5±85.1
Females				
1	21.4±7.3	23.2±6.0	23.0±5.5	22.7±6.4
13	126.5±19.4	135.3±18.1	133.5±20.3	122.1±18.6
21	146.1±18.6	152.4±20.4	151.7±21.8	136.1*±21.3(↓7)
53	194.5±30.5	188.6±29.1	189.3±32.0	167.0**±28.2(↓14)
81	230.4±56.3	217.7±37.1	220.3±46.1	194.0**±50.0(↓16)
104	258.6±73.3	237.3±67.8	232.8±60.0	202.6**±58.8(↓22)

a These data were extracted from the study report, Tables IA-027 through 1A-034, pages 78-85. Numbers listed parenthetically represent the percent difference from controls.

C. Food consumption/efficiency and compound intake:

1. Food consumption - Decreased ($p \leq 0.05$ or 0.01) food consumption was observed in the 200 ppm males (↓3-7%) sporadically during weeks 1 to 13. Food consumption for the 75 and 25 ppm males and all of the females were similar to controls.

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. Hematology - Differential blood counts were similar to controls in all dose groups.

E. Sacrifice and pathology:

1. Organ weights - The Sponsor stated that the weight of some organs were excluded in determining mean organ weights. At the terminal sacrifice, mean body weight was decreased ((↓14%; p≤ 0.01) in the 200 ppm females (Table 3). The following differences (p≤0.05 or 0.01) from controls were observed: (i) increased relative kidney weights in the 200 ppm males (↑9%) and females (↑19%) and in the 75 ppm females (↑10%); (ii) decreased absolute liver weights (↓10%) in the 200 ppm females; and (iii) increased relative brain weights (↑16%) in the 200 ppm females.

Table 3. Selected mean (±SD) absolute and relative (to body) organ weights (g) in rats treated with pyraclostrobin for up to 104 weeks[a]

	Dose (ppm)			
	0	25	75	200
Males				
Kidney				
Absolute	4.006±0.423	4.169±0.548	4.041±0.469	4.163±0.521
Relative	0.621±0.11	0.643±0.109	0.613±0.074	0.675±0.133* (↑9)
Females				
Terminal body weight	393.90 ±72.04	378.39± 57.31	367.85±59.92	338.62**±57.68 (↓14)
Kidney				
Absolute	2.704±0.264	2.771±0.309	2.798±0.412	2.798±0.486
Relative	0.701±0.102	0.740±0.086	0.77±0.106* (↑10)	0.836±0.137** (↑19)
Liver				
Absolute	12.857±2.156	12.746±2.411	12.504±2.541	11.527±2.355** (↓10)
Relative	3.282±0.31	3.364±0.339	3.403±0.427	3.408±0.433
Brain				
Absolute	2.03±0.087	2.027±0.073	2.042±0.093	2.045±0.088
Relative	0.532±0.096	0.545±0.067	0.57±0.099	0.617±0.087** (↑16)

a Data were obtained from Tables IC 1 through IC 4, pages 112 through 115. Numbers listed parenthetically represent the percent difference from controls.

*; ** Significantly different from controls at (p≤0.05 or 0.01).

2. Gross pathology - Erosion/ulcer of the glandular stomach was observed in all the males (7, 8, 10, and 12, in control, 25, 75, and 200 ppm groups, respectively; n=50; Table 4).

The majority of these findings occurred in those found dead or sacrificed *in extremis* (5, 5, 7 and 11 in control, 25, 75, and 200 ppm groups, respectively).

When all animals were combined, including those sacrificed on schedule and those found dead or sacrificed *in extremis,* increased incidences (# animals/50) of the following were observed in the 200 ppm group: (i) brain compression in the females (23 treated vs 16 controls); (ii) mass in thymus (7 treated vs 2 controls) and mammary gland (17 treated vs 11 controls) in the females; (iii) heart calcification in the females (9 treated vs 3 controls); (iv) erosion/ulcer of glandular stomach in the females (9 treated vs 4 controls); (v) calcification and/or cystic degeneration of the testes (7-8 treated vs 2-4 controls); and (vi) reduced seminal vesicle size (7 treated vs 4 controls). In addition, focal lesions of the liver in the females were observed at 75 (35/50 treated vs 32/50 controls) and 200 (37/50 treated) ppm. With the possible exception of mammary gland tumors (see later), none of these findings were considered treatment-related because they were not dose-related and/or they lacked corroborating histopathological data.

Table 4. Erosion/ulcers observed in the glandular (mucosal) stomach of male rats treated with pyraclostrobin for up to 104 weeks[a]

	Dose (ppm)			
	0	25	75	200
Number of animals examined (Total)	50	50	50	50
Erosion/Ulcers (all animals)	7	8	10	12
Erosion/Ulcers (decedents)	5	5	7	11

a Data were obtained from Table IC 5, page 116.

3. Microscopic pathology:

a) Non-neoplastic: When all animals were combined, including those sacrificed on schedule and those found dead or sacrificed *in extremis,* increased incidences (# animals/50) of the following were observed: (i) vascular mineralization of the lungs in the 75 and 200 ppm females (11 and 13 treated, respectively vs 8 controls); (ii) in the kidney of the 200 ppm males, tubular casts (15 treated vs 5 controls) and tubular atrophy (16 treated vs 5 controls) and in the females tubular casts (10,13,14 and 14 in control, 25, 75, and 200 ppm groups, respectively) and tubular atrophy (19 in the 200 ppm group and 12 in control and other two treated groups); (iii) in the 200 ppm males, testicular tubular necrosis (2 treated vs 0 controls), tubular mineralization (13 treated vs 5 controls) and oligospermia in the epididymides (16 treated vs 8 controls); and (iv) in the 200 ppm females, sciatic nerve radiculoneuropathy (25 treated vs 18 controls).

When all animals were combined (n=50), an increased incidence of acanthosis (6 treated vs 0 controls) and ulcers (4 treated vs 2 controls) of the forestomach was observed in the 200 ppm males (Table 5). The majority of these findings occurred in those found dead or sacrificed *in extremis* (acanthosis; 5 treated vs 0 controls, ulcers; 3 treated vs 2 controls). Also observed in the 200 ppm males were erosion of the glandular stomach (10 treated vs 2 controls) and stomach ulcers (7 treated vs 2 controls). In the decedents, erosion (8 treated vs 1 control) and ulcers (6 treated vs 2 controls) were observed. Additionally, the following lesions were observed in the liver of the control, 25, 75 and 200 ppm males (n=50):(i) congestion (9, 5, 7, and 12, respectively); (ii) vacuolated foci (3,10, 10 and 9, respectively); (iii) clear cell foci (13, 20, 16 and 17, respectively); and (iv) necrosis (1, 2, 2 and 10 in control, 25, 75, and 200 ppm groups, respectively).

Table 5. Selected microscope findings observed in the forestomach and glandular (mucosal) stomach of male rats treated with pyraclostrobin for up to 104 weeks[a]

Finding	Dose (ppm)			
	0	25	75	200
Number of animals examined	50	50	50	50
Forestomach				
Acanthosis	0	1	1	6
Ulcers	2	1	0	4
Glandular stomach				
Erosions	2	5	7	10
Ulcers	2	2	2	7

a Data were obtained from Table IC 23, page 134.

b) Neoplastic: Histiocytic sarcoma and lymphoma of the hemolymphoreticular system was observed in males at 25 (2/9 vs 1/50 controls), 75 (2/10 vs 1/50 controls), and 200 (6/50 [12%] vs 1/50 [2%]) ppm (Table 6). Historical data were submitted on 6/14/2001. The incidence of hemolymphoreticular tumors in male wistar rats from 4/95- 7/00 at the testing laboratory is 4% (mean) and 0-10% (range). There was also an increased incidence of mammary gland adenocarcinoma in the females at 200 ppm (16% vs 4% controls). Historical data showed an incidence of female mammary gland adenocarcinoma in wistar rats from 4/95- 7/00 to be 6% (mean) and 0-14% (range). Testicular leydig cell tumor were observed in all male groups but were slightly higher in each of the three treated groups (48-50%) than the control group (38%). Historical

control data were not submitted for this tumor. Neoplasms were not analyzed for statistical significance.

Table 6. Selected neoplastic lesions observed in rats (# affected/# examined) fed pyraclostrobin for up to 104 weeks.[a]

Finding	Dose (ppm)			
	0	25	75	200
Males				
Hemolymophoretic system				
Histiocytic sarcoma	1/50 (2)	1/9 (11)	2/10 (20)	5/50 (10)
Lymphoma	0/50	1/9 (11)	0/10	1/50
Testes				
Leydig cell tumor	19/50 (38)	25/50 (50)	24/50 (48)	25/50 (50)
Mesothelioma	0/50 (0)	0/50 (0)	1/50 (2)	0/50 (0)
Females				
Mammary glands				
Adenoma	0/49 (0)	0/50 (0)	2/50 (4)	1/49 (2)
Adenocarcinoma	2/49 (4)	6/50 (12)	2/50 (4)	8/49 (16)

a Data obtained from study report, Tables IC 37 through IC 39, pages 148 through 150. Numbers listed parenthetically represent the percent incidence.

III. DISCUSSION

A. Investigator's conclusions - In the 200 ppm males, impairment of food consumption, body weights and body weight gains, and increased incidence of liver cell necrosis were observed. Impairment of body weights and body weight gains of the 200 ppm females also occurred. It was concluded that the test substance was not carcinogenic to Wistar rats and that the NOAEL was 75 ppm and the LOAEL was 200 ppm.

B. Reviewer's discussion/conclusion - In this rat oncogenicity study, pyraclostrobin was administered in the diet to Wistar rats (50/sex/group) for up to 104 weeks at nominal doses of 0, 25, 75, or 200 ppm, equivalent to 0/0, 1.2/1.5, 3.4/4.7, and 9.2/12.6 mg/kg/day [M/F], respectively. The analytical data indicated that the variation between nominal and actual dosage to the study animals was acceptable.

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

In the 200 ppm group, decreased ($p \leq 0.05$ or 0.01) body weights were observed in the males (↓3-7%) at weeks 1 through 81 and in the females (↓4-14%) at weeks 21 through 104; body

weights in the males at 104 weeks was decreased (↓4%; not statistically significant [NS]). Decreased ($p \leq 0.05$ or 0.01) body weight gains were observed in the males (↓6-10%) at weeks 1 through 81 and in the females (↓7-22%) at weeks 21 through 104; cumulative body weight gain in the males at week 104 was decreased (↓5%; NS). Decreased ($p \leq 0.05$ or 0.01) food consumption was observed in the males (↓3-7%) sporadically during weeks 1 to 13.

In the 200 ppm group, increased ($p \leq 0.05$) relative kidney weights were observed in the males (↑9%) and females (↑19%). In addition, increased incidences (# animals/50) of kidney tubular casts in the males (15 treated vs 5) and females (14 treated vs 10 controls) and kidney tubular atrophy in the males (16 treated vs 5 controls) and females (19 treated vs 12 controls) were observed. These findings in the 200 ppm animals were considered treatment-related. In the 75 ppm females, increased ($p \leq 0.05$) relative kidney weights (↑10%) and an increased incidence of kidney tubular casts (14 treated vs 10 controls) were also observed.

Grossly, erosion/ulcer of the glandular stomach was observed in all males (7, 8, 10, and 12, in control, 25, 75, and 200 ppm groups, respectively; n=50). The majority of these findings occurred in those found dead or sacrificed *in extremis* (5, 5, 7 and 11 in control, 25, 75, and 200 ppm groups, respectively). Microscopically, an increased incidence of acanthosis (6 treated vs 0 controls) and ulcers (4 treated vs 2 controls) of the forestomach was observed in the 200 ppm males; the majority of these findings occurred in those found dead or sacrificed *in extremis* (acanthosis, 5 treated vs 0 controls and ulcers, 3 treated vs 2 controls). Also observed microscopically in the 200 ppm males were erosion of the glandular stomach (10 treated vs 2 controls) and stomach ulcers (7 treated vs 2 controls). In the 200 ppm decedents, erosion (8 treated vs 1 control) and ulcers (6 treated vs 2 controls) were observed. The Sponsor stated that the erosion and ulcer findings were not treatment-related effects, but lesions that develop shortly prior to death. It was also stated that these findings were never the cause of death in the animals. The reviewers note that while these findings were mainly observed in the decedents, all of the unscheduled deaths in the 200 ppm males with these findings occurred after the first year of dosing (study days 465-736) and therefore consider these findings treatment-related in the high-dose males.

The following incidences (# animals/50) were observed microscopically in the liver of the males (i) vacuolated foci (3, 10, 10 and 9, in control, 25, 75, and 200 ppm groups, respectively); (ii) clear cell foci (13, 20, 16 and 17 in the respective dose groups); (iii) necrosis (1, 2, 2, 10 in the respective dose groups); and (iv) liver congestion (9, 5, 7 and 12 in the respective dose groups). Except for liver necrosis (which the Sponsor stated was slight to severe), none of the liver findings in the males were clearly dose-related. Low incidences of testicular tubular necrosis (2 treated vs 0 controls) and oligospermia of the epididymides were also observed (16 treated vs 8 controls) in the 200 ppm males; these findings were also not clearly dose-related.

The decrease ($p \leq 0.01$) in absolute liver weights observed in the 200 ppm females (↓10%) could be related to the decrease ($p \leq 0.01$) in terminal body weight observed in these animals

(↓14%). A slight increase in the incidence (# animals/50) of focal lesions of the liver in the females (32, 33, 35, 37, in control, 25, 75, and 200 ppm groups, respectively) was observed. In addition, a slight increase in liver adenoma (3, 3, 0, 5 in the respective dose groups) was observed at 200 ppm, but the increase was not dose-related and no carcinomas were observed in any control or treated females. An increase ($p \leq 0.051$) was observed in relative brain weights of the 200 ppm females (↑16%); an increased incidence (# animals/50) of brain compression in these animals was observed grossly (23 treated vs 16 controls) and microscopically (25 treated vs 21 controls), but the differences from controls were minor and not dose-related. The differences in brain relative weight were most likely related to the differences in terminal body weight in these animals. Additionally, an increased incidence of erosion/ulcer of glandular stomach was observed in the 200 ppm females (9 treated vs 4 controls), but this also was not dose-related. The increased incidence of masses observed grossly in the thymus of the 200 ppm females (7 treated vs 2 controls) could be related to the lymphoid hyperplasia and/or the benign thymomas observed in all treated and control females. Vascular mineralization of the lungs in the 75 (11/50 treated vs 8/50 controls) and 200 (13/50 treated) ppm females was also observed, however, there were no corroborating data such as dyspnea, wheezing, coughing, pulmonary edema, or fibrosis, indicating a toxic effect on the lungs.

The LOAEL is 200 ppm for males and females (equivalent to 9.2/12.6 mg/kg/day [M/F]) based on differences in body weight and body weight gains, increased incidences of kidney tubular casts and atrophy in males and females, and in males an increased incidence of necrosis of the liver, gross and microscopic evidence of erosion/ulcer of the glandular stomach and an increased incidence of acanthosis and ulcers of the forestomach. The NOAEL is 75 ppm (equivalent to 3.4/4.7 mg/kg/day [M/F]).

Histiocytic sarcoma and lymphoma of the hemolymphoreticular system was observed in males at 25 (2/9 vs 1/50 controls), 75 (2/10 vs 1/50 controls), and 200 (6/50 [12%] vs 1/50 [2%]) ppm (Table 6). Historical data were submitted on 6/14/2001. The incidence of hemolymphoreticular tumors in male wistar rats from 4/95- 7/00 at the testing laboratory is 4% (mean) and 0-10% (range). There was also an increased incidence of mammary gland adenocarcinoma in the females at 200 ppm (16% vs 4% controls). Historical data showed an incidence of female mammary gland adenocarcinoma in wistar rats from 4/95- 7/00 to be 6% (mean) and 0-14% (range). Testicular leydig cell tumor were observed in all male groups but were slightly higher in each of the three treated groups (48-50%) than the control group (38%). Historical control data were not submitted for this tumor. Neoplasms were not analyzed for statistical significance.

Under the conditions of this study the carcinogenic potential of pyraclostrobin appears to be positive.

The submitted study is classified as **Acceptable/guideline(§83-2[a])** and satisfies the requirements for a carcinogenicity study in rats.

C. Study deficiencies - Neoplasms were not analyzed for statistical significance.

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