Reviewer: Brenda MacDonald, D.V.M. , Date: June, 2001

PMRA Assessment of USEPA Data Evaluation Record

STUDY TYPE: Prenatal Developmental Study - Rat; OPPTS 870.3700 [§83-3]; OECD 414.

TEST MATERIAL (PURITY): BAS 500 F, purity 98.9%.

SYNONYMS: Pyraclostrobin; Reg. No. 304 428

CITATION: Schilling, K., Hellwig, J., Hildebrand, B. (1999): BAS 500 F - Prenatal Developmental Toxicity Study in Wistar Rats Oral Administration (Gavage); Department of Toxicology of BASF Aktiengesellschaft for BASF Corporation Agricultural Products; Laboratory Project Identification No. 30R0494/96168, BASF Registration Document No. 1999/11511; October 25, 1999 (Unpublished); EPA MRID Number 4511832.

SPONSOR: BASF Canada Inc., Agricultural Products, Toronto, Ontario

REVIEWING AGENCY: Registration Action Branch 3/HED (7509C)
US EPA
MRID #45118325
EPA Submission No. S583112
Primary Reviewer: Stephen C. Dapson, Ph.D., 3/HED
Peer Reviewer: William B. Greear, M.P.H., D.A.B.T., 3/HED

PMRA SUMMARY: In a developmental toxicity study (MRID #45118325), BAS 500 F (purity 98.9%) in doubly distilled water, was administered to pregnant Chbb:THOM (SPF) Wistar rats by gavage at dose levels of 0, 10, 25 or 50 mg/kg bw/day, 25 females per group, from days 6 through 19 of gestation. There was no mortality, treatment-related clinical signs or gross pathological findings. Final maternal body weight was lower in the 25 and 50 mg/kg bw/day groups due to decreased body weight gain throughout the dosing and post-dosing periods. These findings were reflected in the corrected final body weight and body weight gain values. In addition, slightly decreased food consumption was noted during the dosing and post-dosing periods in the 25 and 50 mg/kg bw/day groups. **The maternal LOAEL is 25 mg/kg bw/day based on lower body weight and body weight gain and decreased food consumption. The maternal NOAEL is 10 mg/kg bw/day.**

There were no treatment-related developmental or teratogenic effects noted at any dose level tested. Hence, **the developmental LOAEL could not be determined. The developmental NOAEL is 50 mg/kg bw/day.**

STUDY AUTHOR'S CONCLUSIONS: BAS 500 F was administered to pregnant Wistar rats daily by stomach tube from implantation to one day prior to the expected day of parturition (days 6 - 19 post coitum [P.C.]).

50 mg BAS 500 F/kg body weight/day revealed overt signs of maternal toxicity. The high dose dams' food consumption was statistically significantly reduced on several days of the treatment period; if calculated for days 6 - 19 p.c. it was about 11% below the concurrent control value. The mean body weight of the high dose rats was statistically significantly lower than that of the concurrent controls on day 20 p.c. (about 5% below the corresponding control value) and body weight gain was statistically significantly impaired (16% below the mean weight gain of the concurrent control group) if calculated for the entire treatment period (days 6 - 19 p.c.). Moreover, carcass weight and corrected body weight gain were statistically significantly lower at 50 mg/kg body weight/day (carcass weight: about 6%, corrected body weight gain: about 45% below the concurrent control value), which demonstrate treatment-related, direct signs of maternal toxicity in line with the decrements in food uptake and/or body weight gain. Similar, but less pronounced substance-induced signs of maternal toxicity occurred in the mid dose (25 mg/kg body weight/day) group in the form of reduced food consumption (about 7% below controls if calculated for days 6 - 19 p.i.) and clearly reduced corrected body weight gain (about 22% below the concurrent cont-ml value).

No signs of substance-induced maternal toxicity occurred at the low dose level (10 mg/kg body weight/day).

The oral administration of BAS 500 F to the dams at all 3 dose levels (10, 25 and 50 mg/kg body weight/day) had no influence on the gestational parameters and induced no signs of developmental toxicity; especially, no indications for substance -induced teratogenicity were seen up to and including the highest dose level. Several malformations and variations were observed scattered throughout the dose levels, which showed either no dose dependency or occurred at incidences consistent with the historical background data for the rat strain used in the present study.

Based on these results, the no observed adverse effect level (NOAEL) for maternal toxicity is 10 mg/kg body weight/day, while it is 50 mg/kg body weight/day for developmental toxicity.

REVIEWING AGENCY CONCLUSIONS:

a. **Maternal Toxicity**: No deaths, clinical signs of toxicity or gross pathological observations were noted in this study. The 25 and 50 mg/kg/day dose groups had lower overall body weights at gestation days 19/20 and gained less weight than the control during the dosing period (gestation days 6-19), for the post dosing period (19-20), for the overall gestation period (0-20) and for the calculated period of gestation days 6-20, also for corrected body weight gains from gestation days 6-20. As seen with the body weights and body weight gains, the 25 and 50 mg/kg/day dose groups had reduced food consumption during the dosing period (gestation days 6-19), for the post dosing period (19-20) and for the overall gestation period (0-20). There was reduced food efficiency in the 50 mg/kg/day dose group during the dosing period (gestation days 6-19) and in the 25 and 50 mg/kg/day dose groups for the post dosing period (19-20), for the overall gestation period (0-20) and for the calculated period of gestation days 6-20.

b. Developmental Toxicity:

i. Deaths/Resorptions: No treatment related effects were noted.

ii. Altered Growth: No treatment related effects were noted.

iii. Developmental Anomalies: There was an increase the fetal and litter incidence of dilated renal pelvis and increased incidence of cervical ribs with cartilage not present in the high dose group.

iv. Malformations: No treatment related effects were noted.

c. Conclusions:

Maternal Toxicity NOAEL = 10 mg/kg/day
Maternal Toxicity LOAEL = 25 mg/kg/day
Developmental Toxicity NOAEL = 25 mg/kg/day
Developmental Toxicity LOAEL = 50 mg/kg/day

PMRA HEALTH EVALUATION DIVISION (HED) COMMENTS AND CONCLUSION:
The USEPA's review was complete, and contained most of the required data in sufficient detail to support their conclusions. However, certain developmental data and historical control data were not included in the study review. Hence, the PMRA reviewer extracted these data from the actual study submitted by the sponsor and included it in the comments, as required.
Specific comments are as follows:

1. Preimplantation loss and postimplantation loss data in the reviewer's report were calculated by the reviewer from the mean data. However, these data, calculated from the individual data (including standard deviations), were included on page 57 of the study report, i.e.,

	Dose (mg/kg bw/day)			
	0	10	25	50
Preimplantation loss (%)	6.5±10.61	3.0±12.04	7.5±19.61	9.4±20.08
Postimplantation loss (%)	6.2±6.23	7.4±6.75	9.3±7.74	5.7±7.35

Historical control data provided by the sponsor (from page 259 of the study report) indicated a mean value of 7.9%±16.38% (range of 2.9% to 13.6%) for preimplantation loss, and a mean value of 7.9%±9.50% (range of 4.4% to 11.5%) for postimplantation loss. Based on these data, it is concluded that there is no treatment-related effect on postimplantation loss at any dose level tested.

2. Gravid uterus weights were not addressed in the reviewer's report. Data are as follows:

	Dose (mg/kg bw/day)			
	0	10	25	50
Gravid uterus weight, g	79.4±12.47	83.0±13.45	77.4±17.01	78.0±20.16

Data extracted from page 54 of the study report

Based on these data, it can be concluded that there was no treatment-related effect on gravid uterus weight.

3. The reviewer did not categorize the noted developmental findings, and so it is unknown which findings are malformations, variations or unclassified when reviewing to the reviewer's report only. The PMRA reviewer had to refer back to the study for this information. This differentiation is considered important by PMRA with respect to risk assessment of possible teratogenic effects.

4. Developmental toxicity data provided in the reviewer's report did not include data indicating the number of malformations, variations and unclassified findings observed in each group. These data have been extracted from the study, as follows:

a) External Observations

	Dose (mg/kg bw/day)			
	0	10	25	50
Malformations				
Fetal incidence	1/306 (0.3%)	1/291 (0.3%)	0/283 (0.0%)	2/343(0.6%)
Litter incidence	1/22 (4.5%)	1/20 (5.0%)	0/21 (0.0%)	2/25 (8.0%)
Variations				
Fetal incidence	0/306 (0.0%)	0/291 (0.0%)	0/283 (0.0%)	1/343 (0.3%)
Litter incidence	0/22 (0.0%)	0/20 (0.0%)	0/21 (0.0%)	1/25 (4.0%)
Unclassified				
Fetal incidence	0/306 (0.0%)	0/291 (0.0%)	2/283 (0.7%)	1/343 (0.3%)
Litter incidence	0/22 (0.0%)	0/20 (0.0%)	2/21 (9.5%)	1/25 (0.3%)

Data extracted from pages 60 and 64 of the study report

b) Soft Tissue Observations

	Dose (mg/kg bw/day)			
	0	10	25	50
Malformations				
Fetal incidence	2/148 (1.4%)	0/140 (0.0%)	0/136 (0.0%)	1/165 (0.6%)
Litter incidence	2/22 (9.1%)	0/20 (0.0%)	0/21 (0.0%)	1/24 (4.2%)

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	Dose (mg/kg bw/day)			
Variations				
Fetal incidence	8/148 (5.4%)	18/140 (13%)	21/136 (15%)	31/165 (19%)
Litter incidence	6/22 (27%)	12/20* (60%)	9/21 (43%)	15/24* (63%)
Unclassified				
Fetal incidence	0/148 (0.0%)	0/140 (0.0%)	0/136 (0.0%)	0/165 (0.0%)
Litter incidence	0/22 (0.0%)	0/20 (0.0%)	0/21 (0.0%)	0/24 (0.0%)

Data extracted from pages 65 and 69 of the study report

c) Skeletal Observations

	Dose (mg/kg bw/day)			
	0	**10**	**25**	**50**
Malformations				
Fetal incidence	4/158 (2.5%)	2/151 (1.3%)	0/147 (0.0%)	4/178 (2.2%)
Litter incidence	3/22 (14%)	2.20 (10%)	0/21 (0.0%)	3/25 (12%)
Variations				
Fetal incidence	129/158 (82%)	135/151 (89%)	121/147 (82%)	162/178 (91%)
Litter incidence	22/22 (100%)	20/20 (100%)	21/21 (100%)	25/25(100%)
Unclassified				
Fetal incidence	49/158 (31%)	39/151 (26%)	57/147 (39%)	49/178 (28%)
Litter incidence	20/22 (91%)	17/20 (85%)	18/21 (86%)	21/25 (84%)

Data extracted from pages 70 and 90 of the study report

Based on the above data, an increased litter incidence of soft tissue variations was noted in the 10 and 50 mg/kg bw/day groups. However, the incidence fell well within the historical control range of values provided by the sponsor, (from page 266 of the study report) i.e., mean litter incidence of 56.2%, range 30.4% to 79.2%; and mean fetal incidence 16.8%, range 9.4% to 28.8%, there was no dose response relationship, and the concurrent control values were exceptionally low. The increased incidence of soft tissue variations in the 10 and 50 mg/kg bw/day groups was therefore not considered to be treatment-related.

5. There was an increased fetal and litter incidence of dilated renal pelvis (classified as a variation) in the 50 mg/kg bw/day group, i.e.,

	Dose (mg/kg bw/day)			
	0	**10**	**25**	**50**
Dilated renal pelvis				
Fetal incidence	8/148 (5.4%)	16/140 (11.4%)	20/136 (14.7%)	31/165 (18.8%)
Litter incxidence	6/22 (27.3%)	10/20 (50.0%)	9/21 (42.8%)	15/24* (62.5%)

Data extracted from page 67 of the study report

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The reviewer considered this to be treatment-related. However, the incidence fell within the historical control range of values provided by the sponsor, (from page 266 of the study report) i.e., mean fetal incidence of 16.7%, range of 8.8% to 28.8%, mean litter incidence of 55.9%, range of values 30.4% to 79.2%, and there was no dose-response relationship. In addition, according to WOO and HOAR (Woo and Hoar, 1972, "Apparent hydronephrosis" as a Normal Aspect of Renal Development in Late Gestation of Rats: The Effect of Methyl Salicylate, Teratology 6, 191-196 (1972)) the normal pattern of renal development on gestation days 18-20 in rats involves transient variation in the growth rates of the renal papilla and the renal parenchyma. This difference in growth rate can result in an apparently enlarged renal pelvis. This transitory condition is considered a normal aspect of renal development. The difference in growth rate, which leads to an enlarged renal pelvis, can also result in blockade of tubules and consequently lead to distended ureters, a condition which was also observed in this study at a low incidence, but within historical control values. Hence, the PMRA reviewer concurs with the study author and does not consider the increased incidence of dilated renal pelvis to be a treatment-related finding.

6. There was an increased incidence of cervical ribs with no cartilage (classified as a variation) at 50 mg/kg bw/day, i.e.,

	Dose (mg/kg bw/day)			
	0	10	25	50
Cervical ribs, cartilage not present				
Fetal incidence	1/158 (0.63%)	2/151 (1.3%)	2/147 (1.4%)	9/178 (5.1%)
Litter incxidence	1/22 (4.5%)	2/20 (10.0%)	2/21 (9.5%)	8/25* (32.0%)

Data extracted from page 84 of the study report

The reviewer considered this finding to be treatment-related. However, the incidence fell within the historical control range of values provided by the sponsor, (from pages 41 and 270 of the study report) i.e., mean fetal incidence of 2.0%, range of 0.5% to 6.6%, mean litter incidence of 11.3%, range of values 4.0% to 27.3%, and there was no dose-response relationship. Hence, the PMRA reviewer concurs with the study author and does not consider the increased incidence of cervical ribs without cartilage in the 50 mg/kg bw/day group to be treatment-related.

6. The reviewer set the developmental NOAEL at 25 mg/kg bw/day (LOAEL at 50 mg/kg bw/day) based on the increased incidence of dilated renal pelvis and cervical ribs without cartilage in the 50 mg/kg bw/day group. However, the PMRA reviewer does not consider these findings to be treatment-related, and therefore sets the developmental NOAEL at 50 mg/kg bw/day. The LOAEL cannot be determined in the absence of any treatment-related effects.

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Approved by:

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Date