UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

24/AUG/2004

MEMORANDUM

Subject:	Name of Pesticide Product:	Pristine Fungicide
	EPA Reg. No.:	7969-199
	DP Barcode:	D304472
	Decision No.:	217976
	PC Code:	099100 Pyraclostrobin
		128008 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro (1,1'-biphenyl)-2-yl)

From: Rick J. Whiting, Biologist
Technical Review Branch
Registration Division (7505C)

To: Robert Westin, RM Team 22
Fungicide Branch
Registration Division (7505C)

Applicant: BASF Corporation
Agricultural Products
P.O. Box 13528
Research Triangle Park, NC 27709-3528

FORMULATION FROM LABEL:

	Active Ingredient(s):	% by wt.
128008	3-pyridinecarboxamide, 2-chloro-N-(4'-chloro (1,1'-biphenyl)-2-yl) (CAS No. 188425-85-6)	25.2
099100	Pyraclostrobin (CAS No. 175013-18-0)	12.8
	Inert Ingredient(s):	62.0
	Total:	100.0%

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ACTION REQUESTED: The Risk Manager requests:

"Registrant submitted MRID 46210601 as an upgrade of MRID 45405314 that was accepted as a potentially upgradeable supplemental Acute Oral Toxicity study in D278285 dated 1/31/02.

Is MRID 46210601 acceptable?

BACKGROUND: BASF previously submitted an acute six pack (MRID Nos. 454053-14 to -19) to support the registration of EPA File Symbol 7969-ROO, BAS 516 02 F Crop Fungicide. These six studies were reviewed by TRB (McAndrew, D27825, 31/JAN/02) and the following recommendations were made:

"The six studies have been reviewed. The primary eye irritation study is classified as acceptable. The acute oral, acute dermal, acute inhalation and primary skin irritation studies are classified as supplementary due to the following deviations from the OPPTS guidelines:

1. The age of the female animals used in the acute oral, acute dermal and acute inhalation toxicity studies was 14-18 weeks rather than the 8-12 weeks as specified in the guideline.

2. Only three animals/sex were used in the acute oral study. The guideline specifies at least five animals/sex.

3. In the acute inhalation study, clinical examinations were not performed daily as specified in the guideline.

4. In the primary skin irritation study, the size of the area treated with the test substance was not reported. The guideline specifies that a 6 cm^2 area be tested.

The above studies are potentially upgradable depending on an adequate explanation of the deviations. The studies may be used to assign this formulation to toxicity categories by these exposure routes.

The dermal sensitization study is classified as unacceptable because the highest minimally irritating concentration of test substance was not established. A new study must be submitted to satisfy the requirements for registration. Please refer to p. 14 of this review for full explanation."

In its new submission, BASF has submitted a new acute oral toxicity study, MRID No. 46210601, as a replacement/upgrade of the previously reviewed acute oral toxicity study, MRID No. 45405314.

RECOMMENDATIONS: The acute oral toxicity study has been reviewed and is classified as Acceptable. Based on this study and the previously reviewed studies, the acute toxicity profile for Pristine Fungicide, EPA Reg. No. 7969-199, is as follows:

Acute oral toxicity	III	Acceptable	MRID 46210601
Acute dermal toxicity	III	Supplementary	MRID 45405316
Acute inhalation toxicity	IV	Supplementary	MRID 45406317
Primary eye irritation	III	Acceptable	MRID 45405316
Primary skin irritation	IV	Supplementary	MRID 45405318
Dermal sensitization	Negative	Unacceptable	MRID 45405319

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System:

PRODUCT ID #: 007969-00199

PRODUCT NAME: PRISTINE FUNGICIDE

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. Wear long-sleeved shirt and long pants, socks, shoes, and gloves. Avoid contact with eyes or clothing. Wear protective eyewear.

First Aid:

If on skin: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything to an unconscious person.

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

User Safety Recommendations:

Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

Reviewer: Rick J. Whiting **Date: August 24, 2004**
Risk Manager (EPA): Robert Westin, RM Team 22

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: BAS 516 02 F (Purity: PS 300355 (BAS 510 F): 25%; PS 304428 (BAS 500 F): 12.5%; Batch No. 2001-1; sold grey granules)

SYNONYMS: 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro-1,1'-biphenyl)-2-yl) and Pyraclostrobin

CITATION: Gamer, A.; Hellwig, J. (2004) BAS 516 02F - Acute Oral Toxicity Study in Wister Rats - UDP Method: Final Report. Project Number: 2003/1007136, 10A0657/001152. Unpublished study prepared by BASF Aktiengesellschaft. March 10, 2003. MRID No. 46210601

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC 27709-3528

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID No. 46210601), five young adult female Wistar CrlGlxBrlHan:WI rats (Age: 14-18 weeks; Weight: 195-215 g; Source: Charles River Deutschland GmbH, Sandhofer Weg 7, 97633 Sulzfeld, Germany) were given a single oral dose of BAS 516 02 F (Purity: PS 300355 (BAS 510 F): 25%; PS 304428 (BAS 500 F): 12.5%; Batch No. 2001-1; sold grey granules) using the Up and Down Procedure (OECD Guidelines for testing of Chemicals, Guideline No. 425: Acute Oral Toxicity – Up-and-Down Procedure, adopted December 17, 2001).

Based on the median lethal dose and the slope of the dose response curve estimated from a previous acute oral toxicity study (MRID No. 45405314), "a starting dose of 1,490 mg/kg body weight was suggested by the statistical software recommended in the test guideline and has been chosen in the first step with 1 female animal. As the animal survived, 2,100 mg/kg body weight were administered to another female animal in the second step. Because this animal died, 1,490 mg/kg body weight have been tested in a third step with another female animal. As this animal died, the dose for the next female animal was decreased to 1,050 mg/kg (fourth step). Because the animal survived, 1,490 mg/kg body weight have been tested in the fifth step. As no mortality occurred at this step, the study could be terminated and evaluated based on the stopping rules underlying the method."

Body weights were obtained just prior to dosing (day 0) and on days 7 and 14. Animals were observed for clinical signs of toxicity and mortality several times on the day of dosing and at least once daily thereafter for 14 days. A gross necropsy examination was performed on all animals at scheduled euthanasia.

Estimated Oral LD_{50} Females = 1490 mg/kg bw (95% PL Confidence interval is 0 to Greater than 20,000.)

Based on the estimated LD_{50}, BAS 516 02 F is classified as EPA Toxicity Category III.

1050 mg/kg bw: The one female animal dosed at this level survived and gained weight during the study. No clinical signs of toxicity were noted during the study. No significant gross abnormalities were noted a necropsy.

1490 mg/kg bw: One of the three animals tested at this dose died (found on hour 0). The two surviving animals gained weight during the study. Observed clinical signs included impaired general state, dyspnoea, smeared fur and diarrhea. Clinical signs were observed from 1-5 hours after dosing. No significant gross abnormalities were noted a necropsy.

2100 mg/kg bw: The one female animal dosed at this level was found dead on hour 0. Observed clinical signs included impaired general state, dyspnoea and staggering. No significant gross abnormalities were noted a necropsy.

This acute oral study is classified as Acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

Note: The guidelines for Test Guideline 425 state "At the commencement of its dosing, each animal should be between 8 and 12 weeks old and its weight should fall in an interval with ± 20% of the mean initial weight of any previously dosed animals."

The animals used in this study were between 14-18 weeks of age. Although this is a study deficiency, TRB does not believe it affected the results of this study. Therefore, the study will be classified as Acceptable.

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

RESULTS and DISCUSSION:

"Individual animals were dosed as follows:

Main Test

Dosing Sequence	Animal No.	Dose level (mg/kg)	24 hour Outcome	14 Day Outcome
1	1	1490	O	O
2	2	2100	X	X
3	3	1490	X	X
4	4	1050	O	O
5	5	1490	O	O

S = survival D = death

OT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Monday, August 23, 2004, 1:22:08 PM
Data file name: work.dat
Last modified: 8/23/2004 1:22:07 PM

Test/Substance: 7969-199
Test type: Main Test
Limit dose (mg/kg): 5000
Assumed LD50 (mg/kg): 2100
Assumed sigma (mg/kg): 0.15

Recommended dose progression: 5000, 4200, 3000, 2100, 1490, 1050, 750, 530, 370, 260, 187, 133, 94, 66, 47, 33, 23.6, 16.7, 11.8, 8.4, 5.9, 4.2, 3, 2.1, 1.49

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	1	1490	O	O
2	2	2100	X	X
3	3	1490	X	X
4	4	1050	O	O
5	5	1490	O	O

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: LR criterion.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
1050	1	0	1
1490	2	1	3
2100	0	1	1
All Doses	3	2	5

Statistical Estimate based on long term outcomes:

Estimated LD50 = 1490 (The one dose with partial response).
95% PL Confidence interval is 0 to Greater than 20,000.

Statistics - Acute Oral Toxicity (Guideline 425) Statistical Program (Westat, version 1.0, May 2001) was used for all data analyses including: dose progression selections, stopping criteria determinations and/or LD_{50} and confidence limit calculations.

A. Mortality - as noted in table.

B. Clinical observations: 1050 mg/kg bw: No clinical signs of toxicity were noted during the study.

1490 mg/kg bw: Observed clinical signs included impaired general state, dyspnoea, smeared fur and diarrhea. Clinical signs were observed from 1-5 hours after dosing.

2100 mg/kg bw: Observed clinical signs included impaired general state, dyspnoea and staggering.

C. Gross Necropsy: No significant gross abnormalities were noted a necropsy at any of the dose levels tested.

D. Reviewer's Conclusions: Agree with study author.

E. Deficiencies: The guidelines for Test Guideline 425 state "At the commencement of its dosing, each animal should be between 8 and 12 weeks old and its weight should fall in an interval with ± 20% of the mean initial weight of any previously dosed animals."

The animals used in this study were between 14-18 weeks of age. Although this is a minor deficiency, TRB does not believe it affected the results of this study. Therefore, the study will be classified as Acceptable.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D304472
2. **PC CODE:** 099100, 128008
3. **CURRENT DATE:** 24/AUG/2004
4. **TEST MATERIAL:** BAS 516 02 F (Purity: PS 300355 (BAS 510 F): 25%; PS 304428 (BAS 500 F): 12.5%; Batch No. 2001-1; sold grey granules)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Experimental Toxicology & Ecology Toxicology of BASF Aktiengesellschaft 2003/1007136, 10A0657/001152 03-10-03	46210601	LD_{50} = 1490 mg/kg (females)	III	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable