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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

24 /JULY/2001

MEMORANDUM

Subject: EPA Reg. No. /File Symbol: 7969-RIL; BAS 500-F Manufacturing Use Product
DP Barcode: D275781
Case No: 068824
PC Code: 99100

From: John C. Redden, Team Leader
Technical Review Branch
Registration Division (7505C)

To: John Bazuin, PM 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.
pyraclostrobin	98.0%
Inert Ingredient(s):	2.0%
Total:	100.00%

(1)

ACTION REQUESTED:

The PM's instructions are as follows:

> "Please peer review the reviews of the Acute Toxicology data for this product that were performed by the Pest Management Regulatory Agency (PMRA) of Canada...Also attached are reviews of Pyraclostrobin Acute Tox. studies by California Department of Pesticide Regulation (CDPR) and BASF's response to questions CDPR raised in those reviews."

BACKGROUND:

The Canadian Pest Management Regulatory Agency (PMRA), and the United States Environmental Protection Agency (EPA) selected pyraclostrobin as a joint review chemical (reduced risk chemical pesticides). PMRA performed the primary review.

The Technical Review Branch (TRB) has done a secondary review of the PMRA primary reviews. In some cases minor changes, corrections or additions have been made to the PMRA reviews to allow EPA to use this data for regulatory purposes.

RECOMMENDATIONS:

The acute toxicity profile for EPA File Symbol 7969-RIL; BAS 500-F Manufacturing Use Product is as follows:

Guideline No.	Study Type	MRIDs#	Results	Toxicity Category
81-1	Acute Oral	45118302	LD50> 5000 mg/kg	IV
81-2	Acute Dermal	45118305	LD50> 2000 mg/kg	III
81-3	Acute Inhalation	45118308	LC50 < 1.07 mg/L; LC50 > 0.31 mg/kg	II
81-4	Primary Eye Irritation	45118311	Minimally irritating ; MAS 4.6/110	III

2

81-5	Primary Skin Irritation	45118314	Moderately irritating; MAS 2.2/8.0	III
81-6	Dermal Sensitization	45118317	Not a sensitizer	Not Applicable

LABELING:
ID #: 007969-00185 BAS 500-F Manufacturing Product Use

SIGNAL WORD: WARNING

PRECAUTIONARY STATEMENTS:

May be fatal if inhaled. Harmful if absorbed through skin. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Do not breathe dust. For handling activities, use dust/mist filtering respirator (MSHA/NIOSH approval number prefix TC-21C), or a NIOSH approved respirator with any N, P, R, or HE prefilter. Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove contaminated clothing and wash clothing before reuse.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF ON SKIN OR CLOTHING: 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 INHALED: Move person to fresh air. If person is not breathing, call 911 or ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. Call a poison control center or doctor for further treatment advice.

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 eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

Reviewer: Michael Honeyman , Date April 9, 2001

STUDY TYPE: Acute Oral Toxicity - Rats OPPTS 870.1100; OECD 401.

TEST MATERIAL (PURITY): BAS 500 .. F (98.5%)

SYNONYMS: Pyraclostrobin

CITATION: Wiemann, C., Hellwig, J. (1998) "BAS 500 .. F - Acute Oral Toxicity." Department of Toxicology of BASF Aktiengesellschaft. September 16, 1998. Lab report no. 10A0183/961058, MRID # 45118302. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In an acute oral toxicity study, groups of fasted, young adult Wistar rats (5/sex) were given a single oral dose of pyraclostrobin (98.5% a.i.) in 0.5% Tylose CB 30.000 at 2000 mg/kg bw and observed for 14 days. Based on interim results showing low toxicity one week after dosing, another set of 10 rats (5/sex) were exposed to 5000 mg/kg bw under the same conditions as above.

Oral LD_{50} Combined ≥5000 mg/kg bw, no mortality. The Toxicity Category is IV.

Pyraclostrobin **is of LOW toxicity** based on the LD_{50}.

Clinical effects noted in most animals included impaired or poor general states, dyspnea, apathy, staggering, piloerection, and diarrhea. These symptoms generally persisted up to three days following dosing. One high dose male exhibited smeared fur shortly after test article administration.

There were no body weight effects and no necropsy findings.

This acute oral study is classified acceptable. This study satisfies the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 401) in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1	**Test Material:**	BAS 500 .. F
	Description:	Solid (congealed melt), red-brown, store at room temp.
	Lot/Batch #:	CP 025 394
	Purity:	98.5 % a.i.
	CAS #:	175013-18-0

2. **Vehicle:** 0.5% Tylose CB 30.000 (Cleaned Natriumcarboxymethylcellulose from Hoechst AG) in aqua bidest.

3 **Test animals:**

Species:	Rat	
Strain:	Wistar CHBB: THOM (SPF)	
Age/weight at dosing:	Young adult / 150 to 300 g, ± 20% of the mean weight	
Source:	Dr. K. Thomae GMBH, Biberach, FRG	
Housing:	Individually, stainless steel wire mesh, type DK-III, no bedding	
Diet:	Kliba-Labordiaet 343, Klingentalmuehle AG *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Not provided, full air-conditioning
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least 1 week	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: 07/05/1996 End:29/05/1996 (Test article administration dates for the two dose levels did not coincide.)

2. Animal assignment and treatment - Animals were assigned to the test groups noted in Table 1. Following an overnight fast, rats were given a single dose of pyraclostrobin by gavage then observed daily and weighed weekly for 14 days. Survivors were sacrificed and a necropsy was performed.

TABLE 1. Doses, mortality/animals treated

Dose (mg/kg bw)	Concentration (g/100ml)	Administration Volume (ml/kg)	Males	Females	Combined
2000	20.00	10.00	0/5	0/5	0/10
5000	25.00	20.00	0/5	0/5	0/10

3. Statistics - The oral LD_{50} was calculated by the binomial test (Snedecor G.W., Cochran W.G., 1989).

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. The acute oral LD_{50} for males, females, and combined is greater than 5000 mg/kg bw.

B. Clinical observations - Observations included impaired or poor general state, dyspnea, apathy, staggering, piloerection, and diarrhea. The majority of animals exposed to pyraclostrobin exhibited these symptoms. One high dose male had smeared fur on the first day (location of smear not specified in study.)

Table 2. Symptoms Observed, Duration (# Affected)

Sex	Males		Females	
Dose (mg/kg bw)	2000	5000	2000	5000
Impaired general state	H4-D3 (5)	H0-D1 (5)	H4-D3 (5)	H0-D1 (5)

6

Poor general state	D2-D3 (3)	H1-H5 (1)	D2 (4)	H2-H5 (3)
Dyspnea	H4-D3 (5)	H0-D1 (5)	H4-D3 (5)	H0-D1 (5)
Apathy	D2-D3 (3)	H1-H5 (1)	D2 (4)	H2-H5 (3)
Staggering	H4-H5, D2-D3 (5)	H0-H5 (5)	H4-H5, D2-D3 (5)	H0-H5 (5)
Piloerection	H4-D3 (5)	H1-D1 (5)	H4-D3 (5)	H1-D1 (5)
Smeared fur		H3-H5 (1)		
Diarrhea	H2-H5 (5)	H1-H3 (5)	H2-H4 (5)	H1-H5 (5)

H: Hour, D: Day

C. Body Weight - Determined shortly before application (day 0), then again on day 7 and day 13 or 14 just prior to final fasting. Both the final body weight and body weight gains were comparable between low and high doses, no obvious effects.

Table 3. Mean Body Weights (g)

Sex	Males		Females	
Dose (mg/kg bw)	2000	5000	2000	5000
Day 0	175	180	180	179
Day 7	230	229	206	202
Day 13	272		224	
Day 14		279		219

D. Necropsy - Food was withdrawn at least 16 hours before CO_2 euthanasia. No pathologic findings noted.

E. Author's Conclusions: Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of BAS 500 .. F was found to be greater than 5000 mg/kg body weight for the male and female animals.

F. Reviewer's Conclusions: This reviewer agrees with the conclusions of the study authors.

G. Deficiencies - No deficiencies.

Reviewer: Michael Honeyman , **Date** April 10, 2001

STUDY TYPE: Acute Dermal Toxicity - Rats; OPPTS 870.1200; OECD 402.

TEST MATERIAL (PURITY): BAS 500 .. F (98.2%)

SYNONYMS: Pyraclostrobin

CITATION: Wiemann, C., (1998) "Study on the Acute Dermal Toxicity of BAS 500 .. F in Rats." Department of Toxicology of BASF Aktiengesellschaft. September 15, 1998. Lab report no.11A0308/961120, MRID #45118305. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In an acute dermal toxicity study, groups of young adult Wistar rats (5/sex) were dermally exposed to pyraclostrobin (98.2% a.i) in 0.5% Tylose CB 30.000 for 24 hours under semi-occlusive wrap to 10% of body surface area at a dose of 2000 mg/kg bw under semi-occlusive wrap. Animals then were observed for 14 days.

Dermal LD_{50} males & females both > 2000 mg/kg bw. The Toxicity Category is III.

Pyraclostrobin **is of LOW Toxicity** based on the LD_{50} for either sex.

There were no treatment related clinical signs, necropsy findings or changes in body weight. Mild skin irritation was observed on the first day after dosing. The test material was adhesive and left mechanical skin lesions upon removal.

This acute dermal study is classified as acceptable. This study satisfies the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BAS 500 .. F
   Description: Solid (congealed melt), red-brown, stored in freezer
   Lot/Batch #: CP 026063
   Purity: 98.2 % a.i.
   CAS #: 175013-18-0

2. **Vehicle:** 0.5% Tylose CB 30.000 (Cleaned Natriumcarboxymethylcellulose from Hoechst AG) in aqua bidest

3. **Test animals:**

Species:	Rat	
Strain:	Wistar CHBB: THOM (SPF)	
Age/weight at dosing:	Young adult / 200 to 300 g, ± 20% of the mean weight	
Source:	Dr. K. Thomae GMBH, Biberach, FRG	
Housing:	Individually, stainless steel wire mesh, type DK-III, no bedding	
Diet:	Kliba-Labordiaet 343, Klingentalmuehle AG *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Not provided, full air-conditioning
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least 1 week	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: Nov 21, 1996 End: Dec 5, 1996

2. **Animal assignment and treatment** - Animals were assigned to the test groups noted in Table 1. Animals were given a single dose of pyraclostrobin dermally as a single application to the clipped skin (dorsal and dorsolateral trunk, 50cm^2.) The application site was covered for 24 hours after dosing with a semi-occlusive dressing. The site was washed with warm water after the removal of the dressing. Animals were observed 30 to 60 minutes after removal of the dressing (day 1) and daily thereafter for 14 days. Skin irritation scores were recorded weekly. Body weights were measured before application (day 0) and weekly thereafter for two weeks including just prior to final fasting. Survivors were sacrificed and a necropsy was performed. Dermal irritation observation methodology was according to Draize.

TABLE 1. Doses, mortality/animals treated

Dose (mg/kg bw)	Males	Females	Combined
2000	0/5	0/5	0/10

3. **Statistics** - The dermal LD_{50} was not calculated.

II. RESULTS AND DISCUSSION:

A. Mortality - There were no mortalities

The dermal LD_{50} for either sex is greater than 2000 mg/kg bw

B. Clinical observations - No clinical signs of toxicity were noted. Irritation was limited to very slight erythema in all rats except one male that had well-defined erythema. Mechanical skin lesions occurred in all rats due to the adhesiveness of the test substance. All animals returned to normal after the first observation period.

Table 2. Observations

	Males		Females	
	Occurrences	Persistence	Occurrences	Persistence
Very slight erythema	4	Day 1	5	Day 1
Well-defined erythema	1	Day 1		
Remaining test substance	5	Day 1	5	Day 1
Mechanical skin lesion due to adhesive test substance	5	Day 1	5	Day 1

C. Body Weight - All animals gained weight during the observation period.

D. Necropsy - Food was withdrawn at least 16 hours before CO_2 euthanasia. No pathologic findings noted.

E. Author's Conclusions: Under the conditions of this study, the acute dermal median lethal dose (LD_{50}) of BAS 500 .. F was found to be greater than 20000 mg/kg bw for the male and female animals.

F. Reviewer's Conclusions: This reviewer agrees with the conclusions of the study authors.

G. Deficiencies - No deficiencies.

Reviewer: Michael Honeyman , Date April 10, 2001

STUDY TYPE: Acute Inhalation Toxicity - (species); OPPTS 870.1300; OECD 403.

TEST MATERIAL (PURITY): BAS 500 .. F (98.2%)

SYNONYMS: Pyraclostrobin

CITATION: Gamer, A. (December 10, 1999) "BAS 500 .. F - Acute inhalation toxicity study in Wistar rats." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.13I0308/967028. MRID # 45118308. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study, groups of young adult Wistar rats (5/sex) were exposed by inhalation route to pyraclostrobin (98.2% a.i.) in acetone for 4 hours head only at concentrations of 0, 0.31, 1.07, or 5.3 mg/L. Animals then were observed for 14 days.

The LC_{50} for males is $0.31 < LC_{50} < 1.07$ mg/L.
The LC_{50} for females is $0.31 < LC_{50} < 1.07$ mg/L.
The LC_{50} for combined sexes is $0.31 < LC_{50} < 1.07$ mg/L.
The Acute inhalation Toxicity Category is II.

Pyraclostrobin is classified as being of MODERATE Toxicity based on the combined LC_{50} of greater than 0.31 and less than 1.07 mg/L.

Clinical signs included irregular, accelerated, and/or intermittent breathing, bloody discharge from the nose, piloerection, and smeared fur. All animals except those in the mid-dose group attempted escape. Mortalities came quickly in the top two dose groups where all animals died within thirty minutes of dosing commencement except for one mid-dose female which died by the 1 ¼ hour mark. Piloerection, bloody nasal discharge, and accelerated breathing were the only symptoms that persisted beyond the day of exposure.

The only necropsy findings were in both mid-dose groups where all animals had agonal congestive hyperaemia.

This acute inhalation study is classified as acceptable. This study satisfies the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1 **Test Material:** BAS 500 .. F

Description:	Viscous melt, red-brown, stored at room temperature
Lot/Batch #:	CP 026063
Purity:	98.2 % a.i.
CAS #:	175013-18-0

2. **Vehicle and/or positive control: Acetone was used as both a solvent and as a vehicle control**

3 **Test animals:**

Species:	Rat	
Strain:	Wistar CHBB: THOM (SPF)	
Age/weight at dosing:	Approx 8-9 weeks / 261 g ± 22.7 (S.D.)♂, 202 g ± 6.7 (S.D.) ♀	
Source:	Dr. K. Thomae GMBH, Biberach, FRG	
Housing:	Individually, stainless steel wire mesh, type DK-III, no bedding	
Diet:	Kliba-Labordiaet 24-343-4, Klingentalmuehle AG ***ad libitum***	
Water:	**Tap water *ad libitum***	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Not provided, full air-conditioning
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	Not provided	

B. STUDY DESIGN and METHODS:

1. **In life dates - Start:** February 20, 1997 End: March 24, 1997

2. **Exposure conditions** - Head-nose exposure to homogenous aerosol, 55 L, glass-steel construction. The test substance was diluted 1:2 (w/w) with acetone. The technical equipment included a continuous infusion pump Perfusor VII for test article groups, a piston metering pump KP 2000 for the vehicle control group, and a two-component atomizer Mod. 970. Aerosol was produced by compressed air. Supply air flow was 1500 L/h and exhaust air flows were 1350 L/h (the difference ensured positive internal air pressure.) Air change occurred approximately 27 times per hour. Temperature and humidity were measured at 30 minute intervals.

3. **Animal assignment and treatment** - Animals were assigned to the test groups noted in Table 1. Rats were exposed to pyraclostrobin by head-nose only exposure for 4 hours. This exposure was stopped at 1 ¼ hours in group 3 and at 30 minutes in group 4 due to high lethality. Animals were observed daily (except days 5, 6, 12, and 13) and were weighed weekly (first measurement just prior to exposure) for 14 days after dosing. Survivors were sacrificed and a necropsy was performed.

TABLE 1. Concentrations, exposure conditions, mortality/animals treated

Group	Flow Rate (active ingr.), (ml/h)	Nominal Conc. (mg/L)	Analytical Conc. (mg/L)	MMAD µm	GSD	Mortality (# dead/total)		
						♂	♀	♂ & ♀
0	55.0 (0.00)	29.0 (acetone)	n/a	n/a	n/a	0/5	0/5	0/10
1	1.9 (0.63)	0.42	0.31	1	2.5	0/5	0/5	0/10
2	9.0 (3.0)	2	1.07	1.2	2.7	5/5	5/5	10/10
3	55.0 (18.3)	12.2	5.3	2.9	3	5/5	5/5	10/10

4. Generation of the test atmosphere - Time to equilibrium was 10 minutes.

Test atmosphere concentration - Concentration was calculated from the amount of test substance consumed and the air flow. Sampling equipment included a vacuum compressed air pump (Millipore), filtration equipment with probe, internal diameter of 4 mm, and MN 85/90 Bf (d = 4.7 cm) filters. Samples were taken immediately adjacent to the animals' noses. Air flow was 1 L/min, velocity was 1.25 m/s, 4 samples per group were taken approximately every hour. Samples were not taken for groups 3 and 4 once the tests were halted. Results are in table 1 above.

Particle size determination - Gravimetric determination was performed with a Mettler AT 250 balance and preweighed filters. Metered volumes of the aerosol were drawn through the filter by vacuum pump. For particle size analysis, the equipment included a Stack Sampler Mark III, a Vacuum Compressed Air Pump (Millipore), a Sampling probe (internal d = 6.9 mm), a limiting orifice at 3 L/min, glass-fiber collecting discs, and a Sartorius M3P and Mettler AE 240 Balance. Before sampling, the impactor was assembled with preweighed glass-fiber collecting discs and a backup particle filter. The impactor was connected to the vacuum pump and samples were taken from the breathing zone of the animals starting not earlier than 30 minutes after the beginning of the exposure. After sampling, the collecting discs and backup particle filter were re-weighed. Wall losses were determined quantitatively. Results are in table 1 above.

5. Statistics - The LC_{50} for males is $0.31 < LC_{50} < 1.07$ mg/L.
The LC_{50} for females is $0.31 < LC_{50} < 1.07$ mg/L.
The LC_{50} for combined sexes is $0.31 < LC_{50} < 1.07$ mg/L.

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. All dose-related deaths occurred within the first ½ hour of exposure except for one mid-dose female which died between ½ and 1 ¼ hours of exposure.

The LC_{50} for males, females, and combined is $0.31 < LC_{50} < 1.07$ mg/l.

B. Clinical observations - Findings were similar between males and females. Irregular and/or intermittent breathing, bloody discharge from the nose, piloerection, and smeared fur were noted in a dose-response manner. Accelerated breathing was seen in all groups, but persisted the longest in the low-dose animals. Piloerection, bloody nasal discharge, and accelerated breathing were the only

symptoms that persisted beyond the day of exposure. See Table 2.

Table 2a. Clinical Findings and Duration in the Males

Test group	0	1	2	3
Irregular respiration	n.d.	2 (¼ h)	n.d.	n.d.
Accelerated respiration	5 (½ h - Day 0)	5 (¼ h - Day 3)	5 (¼ - ½ h)	4 (¼ h)
Intermittent respiration	n.d.	n.d.	n.d.	5 (½ h)
Bloody nasal discharge	n.d.	2 (Days 0 - 1)	n.d.	n.d.
Eyelid closure	5 (½ - 4 h)	n.d.	n.d.	n.d.
Apathy	5 (3 h - Day 0)	n.d.	n.d.	n.d.
Attempts to escape	5 (¼ h)	5 (<¼ h)	n.d.	5 (<¼ h)
Piloerection	n.d.	5 (Days 0-4)	n.d.	n.d.
Smeared fur	n.d.	5 (Day 0)	n.d.	n.d.

Table 2b. Clinical Findings and Duration in the Females

Test group	0	1	2	3
Irregular respiration	n.d.	4 (¼ h)	n.d.	n.d.
Accelerated respiration	5 (½ h - Day 0)	5 (¼ h - Day 2)	5 (¼ - 1 ¼ h)	5 (¼ h)
Intermittent respiration	n.d.	n.d.	n.d.	5 (½ h)
Eyelid closure	5 (½ - 4 h)	n.d.	n.d.	n.d.
Apathy	5 (3 h - Day 0)	n.d.	n.d.	n.d.
Attempts to escape	5 (¼ h)	5 (<¼ h)	n.d.	5 (<¼ h)
Piloerection	n.d.	5 (Days 0-4)	n.d.	n.d.
Smeared fur	n.d.	5 (Day 0)	n.d.	n.d.

C. Body Weight - All surviving animals gained weight during the study. There were no treatment-related body weight effects. Weight gain in females of both the control and low-dose groups was low.

Table 3. Mean Body Weights (g)

	Males			Females		
Test Group	Day 0	Day 7	Day 13	Day 0	Day 7	Day 13
0	267.8 (8.2)	300.5 (9.4)	328.3 (10.0)	197.3 (5.4)	205.1 (10.2)	212.8 (9.5)
1	225.6 (8.3)	283.5 (13.3)	322.8 (21.6)	200.1 (2.8)	213.3 (5.9)	220.1 (10.3)
2	268.8 (5.2)	n/a	n/a	210.6 (5.7)	n/a	n/a
3	281.0 (8.7)	n/a	n/a	202.0 (5.9)	n/a	n/a

D. Necropsy - All animals in the mid-dose group had agonal congestive hyperaemia. No other animals had any particular macroscopic findings.

E. Reviewer's Conclusions: The authors present a valid study. For males, females, and both sexes combined, $0.31 < LC_{50} < 1.07$ mg/l. Label comments on primary display panel should contain the words "WARNING - POISON". **NOTE FROM EPA SECONDARY REVIEWER: EPA uses the word "POISON" as the signal word for Toxicity Category I. As this is a Toxicity Category III study the appropriate signal word is "WARNING."**

F. Deficiencies - Acclimation period was not given.

Humidity during exposure was below OECD guidelines due to the use of compressed air for generating the aerosol. This should not compromise the validity of this study.

Table 4. Humidity and Temperature

Test Group	Supply air (l/h)	Exhaust air (l/h)	Temperature (°C)	Humidity
0	1500	1350	20.6	19.3
1	1500	1350	22.3	4.6
2	1500	1350	21.9	10.3
3	1500	1350	22.2	18

Reviewer: Michael Honeyman , Date April 9, 2001

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405.

TEST MATERIAL (PURITY): BAS 500 .. F (98.2%)

SYNONYMS: Pyraclostrobin

CITATION: Wiemann, C. (1998) "BAS 500 .. F - Acute Eye Irritation in Rabbits." Department of Toxicology of BASF Aktiengesellschaft. Lab report no. 13H0308/962191, September 15, 1998. MRID # 45118311. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a primary eye irritation study, 0.1 ml (33 mg) of pyraclostrobin (98.2 % a.i.) was instilled into the conjunctival sac of the right eye of young adult NZW rabbits (1 male and 5 females) for 24 hours before washing with tap water. Animals then were observed for 8 days. Irritation was scored by the method of Draize.

Conjunctival redness was seen to a moderate extent through 24 hours, improving to three rabbits with slight and three with moderate scores from 48 to 72 hours. Mild chemosis was present in most animals through 24 hours, and in two animals through 72 hours. The male had a mild case of conjunctival discharge at 1 hour. No irritation was seen at day 8 so the study was ended. Hair loss was seen at the margins of the eyelids from 24 hours through 8 days.

In this study, pyraclostrobin is minimally irritating to the eye based on an maximum average score of 4.6/110 and the 24 h maximum irritation score of 6.3/110. **The Toxicity Category for this Primary Eye Irritation study is III.**

This study is classified as acceptable. This study satisfies the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1	**Test Material:**	BAS 500 .. F
	Description:	Solid (congealed melt), red-brown, store in freezer
	Lot/Batch #:	CP 026063
	Purity:	98.2 % a.i.
	CAS #:	175013-18-0

Content and homogeneity confirmed by analysis

2. **Vehicle and/or positive control:** None

3 **Test animals:**

Species:	Rabbit	
Strain:	New Zealand White	
Age/weight at dosing:	Young adult / 3.08 - 3.87 g, one male, five females	
Source:	Dr. K. Thomae GmbH, Biberach, FRG	
Housing:	Stainless steel wire mesh cages with grating	
Diet:	Kliba-Labordiaet, Klingentalmuehle AG, 130 g/animal/d	
Water:	Tap water, 250 ml/animal/d	
Environmental conditions:	**Temperature:**	20 - 24°C
	Humidity:	30 - 70%
	Air changes:	Not provided, full air-conditioning
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least one week	

B. STUDY DESIGN and METHODS:

1. **In life dates** - **Start:** October 22, 1996 and October 28, 1996 **End:** November 5, 1996

2. **Animal assignment and treatment** - The test substance was applied undiluted in a single 0.1 ml (33 mg) comminuted dose to the conjunctival sac of the right eyelid. The substance was washed out with tap water about 24 hours after application. One male and five female NZW rabbits were used. Readings were taken at 1 hour, just after the rinsing of the eye at 24 h, and then at 48 h, 72 h, and 8 days post-dosing. Scoring was performed according to Draize methodology.

II. RESULTS AND DISCUSSION:

A. The authors did not provide text description of the irritation patterns seen. The cornea and iris were free of irritation effects throughout the study. Conjunctival redness was seen to a moderate extent through 24 hours (except the male at 1 hour), improving to three rabbits with slight and three with moderate scores from 48 to 72 hours. Mild chemosis was present in all females at 1 hour, in all animals through 24 hours, and in two animals through 72 hours. The male had a mild case of conjunctival discharge at 1 hour. No irritation patterns were seen at day 8 so the study was ended. MIS was 6.3 at 24 h and MAS for 24, 48, 72 h was 4.6.

Hair loss was seen at the margins of the eyelids from 24 hours through 8 days.

Table 1. Mean Eye Irritation Ratings

Time	Cornea		Iris (0 to 2)	Conjunctivae		
	Opacity (0 to 4)	Area (0 to 4)		Redness (0 to 3)	Chemosis (0 to 4)	Discharge (0 to 3)
1 h	0	0	0	1.83	0.83	0.17
24 h	0	0	0	2	1.17	0

48 h	0	0	0	1.5	0.33	0
72 h	0	0	0	1.5	0.33	0
8 d	0	0	0	0	0	0
Mean (24 - 72h)	0	0	0	1.67	0.61	0

B. Author's Conclusions: Under the test conditions chosen and considering the described findings, BAS 500 .. F does not give indication of an irritant property to the eye.

C. Reviewer's Conclusions: This reviewer agrees with the conclusions of the study authors. Based on the MAS of 4.6/110 and the 24 h MIS of 6.3/110, pyraclostrobin is minimally irritating to rabbit eyes.

D. Deficiencies - No deficiencies.

Reviewer: Michael Honeyman , Date April 9, 2001

STUDY TYPE: Primary Dermal Irritation - Rabbits; OPPTS 870.2500: OECD 404.

TEST MATERIAL (PURITY): BAS 500 .. F (98.2%)

SYNONYMS: Pyraclostrobin

CITATION: Wiemann, C. (1998) "BAS 500 .. F - Acute Dermal Irritation / Corrosion in Rabbits." Department of Toxicology of BASF Aktiengesellschaft. Lab report no. 13H0308/962190. September 15, 1998. MRID # 45118314. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a primary dermal irritation study, young adult NZW rabbits (3/sex) were dermally exposed to 0.5 g of pyraclostrobin (98.2% a.i.) for 4 hours to 6.25 cm^2 of body surface area. Animals then were observed for 15 days. Irritation was scored by the method of Draize.

Erythema was largely well-defined until 72 hours when clearing began, one case worsened at day 8. Mild edema was observed in 4 rabbits at 24 hours. Two animals still showed irritation effects at study end. Other findings included residual test substance, mechanical damage to the skin, scaling, and irritation extending beyond the test site.

In this study, pyraclostrobin is moderately irritating to the skin based on the MAS of 2.2/8.0, the 24 h MIS of 2.7/8.0, the persistent irritation through 15 days, the erythema and edema extending beyond the exposure site, and the difficulty in removing the substance from the skin. **This dermal irritation study is a Toxicity Category III.**

This study is classified as acceptable. This study satisfies the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1	**Test Material:**	BAS 500 .. F
	Description:	Solid (congealed melt), red-brown, store in freezer
	Lot/Batch #:	CP 026063

Purity:	98.2 % a.i.
CAS #:	175013-18-0
	Content and homogeneity confirmed by analysis

2. **Vehicle and/or positive control:** None

3 **Test animals:**

Species:	Rabbit	
Strain:	New Zealand White	
Age/weight at treatment:	Young adult / 3.50 - 3.88 g	
Source:	Dr. K. Thomae GmbH, Biberach, FRG	
Housing:	Stainless steel wire mesh cages with grating	
Diet:	Kliba-Labordiaet, Klingentalmuehle AG, 130 g/animal/d	
Water:	Tap water, 250 ml/animal/d	
Environmental conditions:	**Temperature:**	20 - 24°C
	Humidity:	30 - 70%
	Air changes:	Not provided, full air-conditioning
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least one week	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: October 22, 1996 End: November 6, 1996

2. **Animal assignment and treatment** - Animals (3/sex) were given a single dose of undiluted pyraclostrobin dermally using a semi-occlusive patch over 6.25 cm^2 of dorsal, clipped skin for 4 hours. Washing was performed with both Lutrol E400 (PEG DAB) and Lutrol/water (1:1). Observations were made at 1, 24, 47, 72 hours and days 8 and 15. Irritation scoring method was Draize.

II. RESULTS AND DISCUSSION:

A. Erythema patterns were consistently well-defined for the first 48 hours. At 72 hours, one animal was cleared of irritation altogether and another improved to mild erythema. Moderate erythema was seen in one animal at 72 hours while another improved to mild. At study termination, single cases of both well-defined and mild erythema were still present in two of the six test animals.

No case worse than mild edema was recorded for any of the animals. Edema was first noted at 24 hours in four animals. This improved to two animals by 48 hours and only one by 72 hours, the latter persisting to 8 days. The rabbit with the moderate erythema at 8 days also developed mild edema which persisted through to study termination.

Also noted were mechanical skin lesions due to test substance at 1 and 24 hours and scaling at 15 days in the rabbit with the moderate erythema. Residual test substance in all animals through 8 days and two at 15 days. Erythema extended beyond the test site in 5 animals at 24 and 48 hours, in 4 animals at 72 hours and 8 days, and in 2 animals at 15 days. Likewise, edema extended beyond the test site in 3 animals at 24 hours, 2 at 48 hours, and the rabbit with moderate erythema at days 8 through 15.

Table 1. Individual Animal Observations

Time	Animal	Erythema	Edema	Other	Time	Animal	Erythema	Edema	Other
1 H	1	2	0	R	72 H	1	0	0	R
	2	2	0	R		2	2	0	R
	3	2	0	R, M		3	2	0	R, Er
	4	2	0	R		4	1	0	R, Er
	5	2	0	R		5	2	1	R, Er
	6	1	0	R		6	2	0	R, Er
24 H	1	2	1	R	8 D	1	0	0	R
	2	2	1	R, Er, Ed		2	1	0	R
	3	2	0	R, M, Er		3	3	1	R, Er, Ed
	4	2	0	R, Er		4	1	0	R, Er
	5	2	1	R, Er, Ed		5	2	1	R, Er
	6	2	1	R, Er, Ed		6	2	0	R, Er
48 H	1	2	0	R	15 D	1	0	0	
	2	2	1	R, Er, Ed		2	0	0	
	3	2	0	R, Er		3	2	1	R, S, Er, Ed
	4	2	0	R, Er		4	1	0	R, Er
	5	2	1	R, Er, Ed		5	0	0	
	6	2	0	R, Er		6	0	0	

Total erythema and edema are scored out of 8
R - Residual test substance
M - Mechanical skin lesion due to adhesive test substance
S - Scaling
Er - Erythema extending beyond test site
Ed - Edema extending beyond test site

Table 2. Mean Irritation Scores

Time	Erythema	Edema
1 h	1.83	0
24 h	2	0.67
48 h	2	0.33
72 h	1.5	0.17
8 d	1.5	0.33
15 d	0.5	0.17
Mean (24-72h)	1.83	0.39

Total erythema and edema are scored out of 8.

21

B. Author's Conclusions: Under the test conditions chosen and considering the described findings, BAS 500 .. F gives indication of an irritant property to the skin.

C. Reviewer's Conclusions: This reviewer agrees with the conclusions of the study authors. Although the 24/48/72 h MAS of 2.2/8.0 and the 24 h MIS of 2.7/8.0 indicate mild irritation, the persistent irritation through 15 days, the erythema and edema extending beyond the exposure site, and the difficulty in removing the substance from the skin justify a categorization as moderately irritating to rabbit skin.

D. Deficiencies - No deficiencies

Reviewer: Michael Honeyman , **Date** April 9, 2001

STUDY TYPE: Dermal Sensitization - Guinea Pigs; OPPTS 870.2600; OECD 406.

TEST MATERIAL (PURITY): BAS 500 .. F (99.0%)

SYNONYMS: Pyraclostrobin

CITATION: Wiemann, C. (1998) "BAS 500 .. F - Maximization Test in Guinea Pigs." Department of Toxicology of BASF Aktiengesellschaft. Lab report no. 30H0494/962329. September 11, 1998. MRID # 45118317. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a dermal sensitization study with pyraclostrobin (99.0%) in 1% Tylose CB 30.000, young adult female Pirbright White, Dunkin Hartley guinea pigs were tested using the method of Maximization (Magnusson, B. and Kligman, A.M.: The Identification of Contact Allergens by Animal Assay. The guinea Pig Maximization Test. J. Invest. Dermatol. 52, 268-276, 1969).

Moderate and confluent erythema with swelling was seen in all animals (including controls) following the intradermal induction injections. This condition persisted in all animals with "incrustation, partially open" skin after the percutaneous induction. As for the challenges, there were no positive results in any animal in any group. In this study, pyraclostrobin is not a dermal sensitizer.

This study is classified as acceptable. This study satisfies the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pig.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1	**Test Material:**	BAS 500 .. F
	Description:	Solid (crystalline), yellowish, store in refrigerator
	Lot/Batch #:	CP 029053
	Purity:	99.0 % a.i.
	CAS #:	175013-18-0
		Content and homogeneity confirmed by analysis

2. **Vehicle:** 1% Tylose CB 30.000 (cleaned sodium carboxymethyl cellulose from Hoechst AG) in aqua bidest.

Positive Control: alpha-hexylcinnamaldehyde

3 **Test animals:**

Species:	Guinea Pigs	
Strain:	Pirbright White, Dunkin Hartley Crl:(HA)BR [SPF]	
Age/weight at start:	Young adult / 306 - 381 g	
Source:	Charles River GmbH - WIGA, Kisslegg, FRG	
Housing:	Makrolon, type IV	
Diet:	Kliba Labordiät ad libitum	
Water:	Tap water ad libitum	
Environmental conditions:	**Temperature:**	21 - 25°C
	Humidity:	30 - 70 %
	Air changes:	Not provided, full air-conditioning
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	7 days	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: October 28, 1997 **End:** November 28, 1997

2. Animal assignment and treatment - Maximization test (Magnusson and Kligman). Twenty female guinea pigs in the test group and 10 in each of the control groups. Suitable test substance concentrations were determined in a pretest. Two 24-hour percutaneous occlusive applications within 96 hours were performed. The minimum irritant concentration was found to be 2% a.i. in 1% Tylose CB 30.000 in aqua bidest. The maximum non-irritant concentration was 1% a.i. in 1% Tylose CB 30.000 in aqua bidest.

A 5% test substance preparation in 1% Tylose CB 30.000 in aqua bidest caused discrete to moderate erythema. It was chosen for the percutaneous induction.

For the intradermal induction stage of this experiment, three pairs of injections were made in the shoulder area of each animal in the *test group*:
A) Front row - 2 injections each of 0.1 ml Freund's adjuvant without test substance emulsified with 0.9% aqueous NaCl solution in a ratio of 1:1
B) Middle row - 2 injections each of 0.1 ml of test substance in vehicle
C) Back Row: 2 injections each of 0.1 ml of 0.1 mL Freund's adjuvant / 0.9% aqueous NaCl solution (1:1) with test substance

Induction injections for the *control groups*:
A) Front row - 2 injections each of 0.1 ml Freund's adjuvant without test substance emulsified with 0.9% aqueous NaCl solution in a ratio of 1:1
B) Middle row - 2 injections each of 0.1 ml of the undiluted vehicle
C) Back Row: 2 injections each of 0.1 ml of a 50% formulation of the vehicle without test substance emulsified with Freund's adjuvant / 0.9% aqueous NaCl solution (1:1)

Percutaneous induction was performed one week after intradermal induction. Application volume was 1 ml of test substance on the shoulder and under an 8 cm^2 occlusive gauze patch with rubberized linen patches. Patches were left on for 48 hours. Control groups were treated in the same manner, only with straight vehicle.

Two challenge applications were made; the first was 14 days after the percutaneous induction, the second occurred one week later. The test substance formulation was applied at 0.5 ml under 4 cm^2 occlusive gauze patches for 24 hours to the intact flank.

During the first challenge, the test group and control group 1 were treated with the test substance formulation. Additionally, 1% Tylose CB 30.000 in aqua bidest was applied as a vehicle control. Control group 2 only received Tylose CB 30.000 in aqua bidest.

During the second challenge, the test group and control groups 1 and 2 were treated with the test substance formulation. Again, 1% Tylose CB 30.000 in aqua bidest was applied as a vehicle control to all animals.

Positive controls were not performed with this study, however, the ability to illicit a positive response was tested twice annually at this lab with alpha-hexylcinnamaldehyde (85%)

Table 1. Induction and Challenge Treatments

Intradermal induction	**Pyraclostrobin 5% in 1% Tylose CB 30.000 in aqua bidest or in Freund's adjuvant / 0.9% aqueous NaCl-solution (1:1)**
Percutaneous induction	**Pyraclostrobin 5% in 1% Tylose CB 30.000 in aqua bidest**
1st challenge	**Pyraclostrobin 1% in 1% Tylose CB 30.000 in aqua bidest**
2nd challenge	**Pyraclostrobin 1% in 1% Tylose CB 30.000 in aqua bidest**

II. RESULTS AND DISCUSSION:

A. Intradermal induction reactions and duration - All observations were made 24 hours after injection. Moderate and confluent erythema along with swelling were observed at the Freund's/NaCl injection sites of all control and test group animals. Injections of 5% pyraclostrobin in 1% Tylose or Freund's/NaCl (1:1) caused moderate and confluent erythema and swelling in all test group animals. Injections of 1% Tylose CB 30.000 in aqua bidest showed no reaction. Finally, injections of a 50% preparation of 1% Tylose with Freund's/NaCl (1:1) caused moderate and confluent erythema in addition to swelling in all control group animals.

Table 2. Assessment of skin reactions

Score	Description
0	No visible changes
1	Discrete or patchy erythema
2	Moderate and confluent erythema
3	Intense erythema and swelling

B. Percutaneous induction reactions and duration - All observations were made after patch removal (48 hours.) All animals in all groups exhibited "incrustation, partially open" skin reactions. This was attributed to the previous induction injections by the study author. Moderate and confluent erythema and swelling was

also ubiquitous.

C. Challenge reactions and duration - First challenge - No skin reactions were seen at 24 and 48 hours after 1% pyraclostrobin patch removal in either the test group or control group 1. Vehicle control 1% Tylose was applied to all animals and did not cause any skin reactions.

Second challenge - No skin reactions were seen at 24 and 48 hours after 1% pyraclostrobin patch removal in either the test group or the control groups. Again, vehicle control 1% Tylose was applied to all animals and did not cause and skin reactions.

D. Positive control - This test showed that the lab is capable of producing a positive skin sensitization response to a known mild to moderate human sensitizer (alpha-hexylcinnamaldehyde.) All nineteen guinea pigs had a positive result during the first challenge and 17 of the 19 were positive at second challenge.

E. Author's Conclusions: Based on the evaluation criteria cited under 3.4, the results of this study show that BAS 500 .. F does not have a sensitizing effect on the skin of the guinea pig in the Maximization Test under the test conditions chosen.

F. Reviewer's Conclusions: This reviewer is in agreement with the study author. Pyraclostrobin shows no evidence of skin sensitization.

G. Deficiencies - No deficiencies.