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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

31 /JULY/2001

MEMORANDUM

Subject: EPA Reg.No./File Symbol: 7969-RIT Cabrio EG Fungicide
DP Barcode: D275787
Case No: 68821
PC Code: 099100

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	20.0%
Inert Ingredient(s):	80.0%
Total:	100.0%

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-RIA; Headline EC Fungicide is as follows:

Guideline No.	Study Type	MRIDs#	Results	Toxicity Category
81-1	Acute Oral	45118304	LD_{50}>2000 mg/kg	III
81-2	Acute Dermal	45118307	LD_{50}>2000 mg/kg	III
81-3	Acute Inhalation	45118310	LC_{50}= 4.7 mg/L	IV
81-4	Primary Eye Irritation	45118313	Moderate irritation	III
81-5	Primary Skin Irritation	45118316	Slight irritation	IV
81-6	Dermal Sensitization	45118319	Not a sensitizer	Not Applicable

LABELING:
ID #: 007969-00187 Cabrio EG Fungicide

AGRICULTURAL USE REQUIREMENTS:

DIRECTIONS FOR USE:

For early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, wear: coveralls over long-sleeved shirt and long pants, socks and chemical resistant footwear and chemical resistant gloves (such as Nitrile, Butyl, Neoprene, and/or Barrier Laminate).

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed or absorbed through skin. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Wear long-sleeved shirt and long pants, socks and shoes. and chemical resistant gloves (such as Nitrile, Butyl, Neoprene, and/or Barrier Laminate).

STATEMENT OF PRACTICAL TREATMENT (SOPT):

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 by mouth to an unconscious person.

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 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.

USER SAFETY RECOMMENDATION: Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

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

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

TEST MATERIAL (PURITY): BAS 500 002 F (21.0 % a.i.)

SYNONYMS: Cabrio EG (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1999) "BAS 500 02 F Acute Oral Toxicity in Rats." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.18A0236/991082, December 22, 1999. MRID # 54118304. 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 Cabrio EG (21.0 % pyraclostrobin) in aqua bidest at doses of 500 and 2000 mg/kg bw and observed for 14 days.

Oral LD_{50} for males, females, and combined > 2000 mg/kg bw (95% C.I. if available)

Formulation is of **LOW Toxicity** based on the LD_{50} of greater than 2000 mg/kg bw. No label comments are required. **Note from EPA Reviewer: LD_{50} indicates Toxicity Category III. The signal word is CAUTION.**

One male and one female died at 2000 mg/kg bw. Most animals at 2000 mg/kg bw exhibited impaired and poor general states, dyspnea, apathy, piloerection, and diarrhea. High dose females also showed staggering, salivation, and shaking. Diarrhea was also present in one male and all females of the low dose. Surviving animals were normal and healthy by day 9.

There were no necropsy findings or significant variations in body weight.

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 02 F
	Description:	Solid (granular powder, beige/brown), store at room temp.
	Lot/Batch #:	99-3
	Purity:	21.0% a.i.

2. **Vehicle**: Aqua bidest

3. **Test animals:**

Species:	Rat	
Strain:	Wistar CHBB: THOM (SPF)	
Age/weight at dosing:	8-9 weeks / 200 to 330 g, ± 20% of the mean weight	
Source:	Elevage Janvier, Route des Chenes Secs, B.P. 5, F-53940 Le Genest St Isle	
Housing:	Individually, stainless steel wire mesh, type DK-III, no bedding	
Diet:	Kliba rat/mouse/hamster laboratory diet, 10mm, Provimi Kliba SA *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: October 13, 1999 (low dose), October 19, 1999 (high dose)
End: October 27, 1999 (low dose), November 2, 1999 (high dose)

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 Cabrio EG 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)	Males	Females	Combined
500	0/5	0/5	0/10
2000	1/5 (Day 3)	1/5 (1 Hour)	2/10

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

II. RESULTS AND DISCUSSION:

A. **Mortality** is given in Table 1.

The oral LD_{50} for males, females, and combined is > 2000 mg/kg bw.

B. **Clinical observations** - Males and females in the high dose group exhibited impaired and poor general states, dyspnea, apathy, piloerection, and diarrhea. Also noted in high dose females was staggering, salivation, and shaking. The only clinical observation in low dose animals was diarrhea in one male and all females. All clinical signs were cleared by day 9. See table 2 for the frequency and

duration of observations.

Table 2. Symptoms Observed, Duration (# Affected)

Sex	Males		Females	
Dose (mg/kg bw)	500	2000	500	2000
Impaired general state		H0, D3-D8 (3)		H0-H1, D1-D8 (4)
Poor general state		H0-H5 (5)		H0-H5, D3 (4)
Dyspnea		H0-H5, D3-D7 (5)		H0-H7 (4)
Apathy		H0-H5 (5)		H0-H5, D3 (4)
Staggering				H1- H5, D3 (2)
Piloerection		H1-H5, D3-D8 (5)		H1-H5, D3-D8 (4)
Diarrhea	H3 (1)	H1-H5 (5)	H3 (5)	H1-H5, D3-D8 (4)
Salivation				H1-H2 (1)
Shaking				H0-H5 (1)

H: Hour
D: Day

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

D. Necropsy - No significant findings upon necropsy.

E. Authors' Conclusions: Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of BAS 500 02 F was found to be greater than 2000 mg/kg bw for the male and female animals.

F. Reviewer's Conclusions: This reviewer agrees with the conclusions of the study authors. Based on the LD_{50} of > 2000 mg/kg bw, no label comments are required.

G. Deficiencies - No deficiencies.

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

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

TEST MATERIAL (PURITY): BAS 500 002 F (21.0 % a.i.)

SYNONYMS: Cabrio EG (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1999) "BAS 500 02 F Acute Dermal Toxicity in Rats." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.11A0236/991081, December 22, 1999. MRID # 54118307. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In an acute dermal toxicity study, groups of young adult Wistar rats (5/sex) were dermally exposed to 3.33 ml/kg Cabrio EG (21.0 % pyraclostrobin) in aqua bidest under a semi-occlusive wrap for 24 hours to 10% of body surface area at a dose of 2000 mg/kg bw. Animals were then observed for 14 days.

Dermal LD_{50} for males, females, and combined > 2000 mg/kg bw
This was a limit test, there was no mortality.

Cabrio EG is of **LOW Toxicity** based on the LD_{50} of greater than 2000 mg/kg bw. No label comments are necessary. **Note from EPA Reviewer: Toxicity Category III; signal word = CAUTION.**

There were no treatment related clinical signs or necropsy findings. On day one, four males and three females had very slight erythema while one female showed well-defined erythema. This condition cleared promptly.

Body weight gain was poor in females over the first week, but all animals had gained weight by the end of the study.

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 02 F

Description:	Solid (granular powder, beige/brown), store at room temp.
Lot/Batch #:	99-3
Purity:	21.0% a.i.
CAS # TGAI:	
	Concentration/homogeneity verified by analysis

2. **Vehicle:** 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:	Boehringer Ingelheim Pharma KG	
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: October 21, 1999 End: November 4, 1999

2. **Animal assignment and treatment** - Animals were assigned to the test groups noted in Table 1. Animals were given a single dose of Cabrio EG (3.33 ml/kg) dermally using a semi-occlusive wrap over clipped skin, 10% coverage, for 24 hours then rinsed with water. The animals were observed daily and weighed weekly for 14 days after dosing. Survivors were sacrificed and a necropsy was performed.

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 males, females, and combined is greater than 2000 mg/kg bw

B. **Clinical observations** - There were no clinical reactions. There were 4 cases of very slight erythema

in the males on day 1. In the females, there were 3 cases of very slight erythema and one of well-defined erythema, also on day 1.

C. Body Weight - All animals gained weight over the observation period. However, the females did not gain much over the first week. One female lost four grams between day 0 and day 7. See table 2.

Table 2. Body weights (g)

Sex	Males					Females				
Animal No.	486	487	488	489	490	491	492	493	494	495
Day 0	250	253	253	266	268	226	228	227	234	226
Day 7	265	270	274	286	283	233	232	228	230	233
Day 13	299	293	301	315	313	244	251	241	250	274

D. Necropsy - No significant findings upon necropsy.

E. Authors' Conclusions: Under the conditions of this study, the acute dermal median lethal dose (LD_{50}) of BAS 500 02 F was found to be greater than 2000 mg/kg bw for the male and females animals.

F. Reviewer's Conclusions: This reviewer agrees with the conclusions of the study authors. Based on the LD_{50} of > 2000 mg/kg bw, no label comments are required.

G. Deficiencies - No deficiencies.

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

STUDY TYPE: Acute Inhalation Toxicity - Rat; OPPTS 870.1300; OECD 403.

TEST MATERIAL (PURITY): BAS 500 002 F (21.0 % a.i.)

SYNONYMS: Cabrio EG (Pyraclostrobin a.i.)

CITATION: Gamer, A.O., Kittel, B., Hoffmann, H.D. (1999) "BAS 500 02 F - Acute Inhalation Toxicity Study in Wistar Rats." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.1310236/997009, December 16, 1999. MRID # 54118310. 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 Cabrio EG (21.0 % pyraclostrobin) in Aerosil for 4 hours to head-nose only at concentrations of 1.00, 2.79, or 5.3 mg/L. Animals then were observed for 14 days.

LC_{50} Males = 4.5 mg/L
Females = 5.30 mg/L
Combined = 4.7 mg/L

Cabrio EG is classified as being of **LOW Toxicity** based on the LC_{50} of 4.5 mg/L in males. No label comments are required. **Note from EPA Secondary Reviewer: Toxicity Category IV; signal word = Caution.**

Four males and three females died at 5.3 mg/L. Clinical findings were similar between males and females. Accelerated respiration was ubiquitous from the start of dosing. Other observations included respiratory sounds, crust formation on nose, eyelid closure, squatting posture, piloerection, and reduced general state. In most cases, clinical symptoms increased in both incidence and duration with increasing dose levels. Duration of observed effects were varied, but all animals were normal following observation on day 11.

This acute inhalation study is classified as acceptable. It 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:

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1. **Test Material:** BAS 500 02 F

Description:	Extruded granulate beige/brown, store at room temp.
Lot/Batch #:	99-3
Purity:	21.0% a.i.
CAS # TGAI:	

2. **Vehicle and/or positive control:** Aerosil

3. **Test animals:**

Species:	Rat	
Strain:	SPF Wistar Rj:WI (SPF Han)	
Age/weight at dosing:	8-9 weeks / 200 to 330 g, ± 20% of the mean weight	
Source:	Elevage Janvier, Route des Chenes Secs, B.P. 5, F-53940 Le Genest St Isle	
Housing:	Individually, stainless steel wire mesh, type DK-III, no bedding	
Diet:	Kliba rat/mouse/hamster laboratory diet, 10mm, Provimi Kliba SA *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: October 28, 1999 End: November 18, 1999

2. **Exposure conditions** - Head-nose exposure to homogenous aerosol, 55 L, glass-steel construction. The technical equipment included a dosing wheel dust generator (Gericke/BASF). Aerosol was produced by compressed air. Air flow was set at positive internal air pressure to prevent dilution with lab air. The test substance was broken up in a mixer under addition of 0.5% (w/w) of Aerosil before introduction into the dust generator in order to improve dust formation. Air change occurred approximately 27 times per hour. Temperature and humidity were measured at 1 hour intervals with a digital thermometer and a dielectric probe (Vaisala).

3. **Animal assignment and treatment** - Animals were assigned to the test groups noted in Table 1. Rats were exposed to Cabrio EG by head-nose exposure for 4 hours. They were observed daily and weighed weekly for 14 days after dosing. Survivors were sacrificed with CO_2 and a necropsy was performed.

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

Nominal Conc. (mg/L)	Analytical Conc. (mg/L)	MMAD µm	GSD	Mortality (# dead/total)		
				Males	Females	Combined
12.4	1.00	3.5	3.8	0/5	0/5	0/10
38.5	2.79	3.9	3.8	0/5	0/5	0/10

85.6	5.3	3.0 / 3.0*	3.5 / 3.8*	4/5	3/5	7/10

* Two samples were taken for this group.

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

Test atmosphere concentration - Sampling equipment included a vacuum pump (Millipore), filtration equipment with probe (d = 4 mm), and an MN 85/90 BF (d = 4.7 cm) filter. Samples were taken immediately adjacent to the animals' noses. Flow of 1 L/min, velocity of 1.25 m/s, 4 samples per group approximately every hour.

Particle size determination - 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, and two balances, a Sartorius M3P and a Sartorius LC 1201S. Before sampling, impactor was assembled with preweighed glass-fiber collecting discs and a backup particle filter. The impactor was connected to the vacuum pump and samples according to the following table 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. The results can be seen in Table 1 above; they were not corrected for the Aerosil additive.

5. Statistics - The LC_{50} was calculated using the probit model.

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. All deaths occurred at high dose. Two males and two females were found dead on day 0. Two males and one female were euthanized on day 1 in a moribund state.

The LC_{50} (C.I.) for males is 4.5 mg/L

females is 5.30 mg/L
combined is 4.7 mg/L

B. Clinical observations - Findings were similar between males and females. Accelerated respiration was ubiquitous from the start of dosing. In most cases, clinical symptoms increased in both incidence and duration with increasing dose levels. Duration of observed effects were varied, but all animals were normal following observation on day 11. See Table 2.

Table 2a. Clinical Findings and Duration in the Males

Test group	1	2	3
Accelerated respiration	5 (<1 h - Day 6)	5 (<1 h - Day 11)	5 (<1 h - Day 11)
Respiratory sounds	n.d.	n.d.	3 (Day 1)
Crust formation on nose	n.d.	n.d.	3 (Days 0 -5)
Eyelid closure	n.d.	2 (Day 0)	3 (Days 0 - 1)
Attempts to escape	n.d.	n.d.	5 (<1 h)

Squatting posture	5 (Days 0 - 2)	5 (Day 0)	3 (Days 0-1)
Piloerection	n.d.	5 (Days 1 - 5)	3 (Days 1 - 8)
Smeared fur	5 (Days 0 - 1)	3 (Days 0 - 1)	3 (Days 0 - 1)
Reduced general state	n.d.	n.d.	3 (Day 1)

Table 2b. Clinical Findings and Duration in the Females

Test group	1	2	3
Accelerated respiration	5 (<1 h - Day 6)	5 (<1 h - Day 11)	5 (<1 h - Day 11)
Respiratory sounds	n.d.	n.d.	3 (Day 1)
Colourless discharge from nose	n.d.	n.d.	3 (Day 0)
Crust formation on nose	n.d.	n.d.	4 (Days 0 - 5)
Eyelid closure	n.d.	4 (Day 0)	2 (Days 0 - 1)
Attempts to escape	n.d.	n.d.	5 (<1 h)
Squatting posture	5 (Day 0 - 2)	5 (Day 0)	4 (Day 0 - 1)
Piloerection	n.d.	5 (Days 1 - 5)	3 (Days 1 - 8)
Smeared fur	5 (Days 0 - 1)	5 (Days 0 - 1)	4 (Days 0 - 1)
Reduced general state	n.d.	n.d.	3 (Day 1)

C. **Body Weight** - Body weight gain decreased with increasing dose levels . The surviving high-dose male experienced weight loss from day 0 to day 7.

Table 3. Mean Body Weights (g)

	Males			Females		
Test Group	Day 0	Day 7	Day 14	Day 0	Day 7	Day 14
1	310.9 (5.8)	359.8 (10.8)	404.5 (10.6)	213.5 (4.5)	226.8 (5.1)	242.5 (6.2)
2	319.4 (8.3)	360.0 (10.9)	408.6 (9.7)	217.1 (10.9)	232.5 (11.2)	249.1 (9.7)
3	316.6 (4.8)	265.2 (0.0)	385.0 (0.0)	212.0 (4.5)	229.8 (10.7)	240.4 (1.5)

D. **Necropsy** - In animals found dead or killed in a moribund state, the authors found dark red discolouration of all lobes of the lungs (some multi-focal) and edema in all lobes of the lungs. All early death animals had contamination of the fur around the snouts and in the abdominal region.

Observations among the survivors included multi-focal dark red discolouration of all lobes of the lungs and grey foci in the lungs. One high dose male had moderate multi-focal perivascular lympho-histiocytic infiltrates and slight multi-focal alveolar histiocytosis.

E. **Reviewer's Conclusions:** Note if in agreement with study authors.

KL

F. Deficiencies - The calculations for the female LC_{50} is approximate, but due to the low toxicity seen at mid-dose, this deficiency does not affect our regulatory decision.

Reviewer: Michael Honeyman , Date April 10, 2001

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

TEST MATERIAL (PURITY): BAS 500 002 F (21.0 % a.i.)

SYNONYMS: Cabrio EG (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1999) "BAS 500 02 F Acute Eye Irritation in Rabbits." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.13H0236/992152, December 22, 1999. MRID # 54118313. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a primary eye irritation study, 0.5 mL of Cabrio EG (21.0 % pyraclostrobin) was instilled into the conjunctival sac of the right eye of young adult New Zealand White rabbits (4 males, 2 females) for 24 hours. Eyes were washed with tap water following exposure. Animals then were observed for 7 days. Irritation was scored by the method of Draize.

Normal to moderate reactions were seen in the conjunctivae, mostly redness and swelling with little discharge. Based on the MAS of 4.4/110 and the 24 h MIS of 9/110, Headline EC is minimally irritating to rabbit eyes. Label comments are not required. **Note from EPA Secondary Reviewer: Toxicity Category III; signal word = CAUTION.**

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.

A. MATERIALS:

1.	**Test Material:**	BAS 500 02 F
	Description:	Solid (granular powder, beige/brown), store at room temp.
	Lot/Batch #:	99-3
	Purity:	21.0% a.i. Content and homogeneity confirmed by analysis

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

3. **Test animals:**

Species:	Rabbit	
Strain:	Chbb: NZW (SPF)	
Age/weight at dosing:	Young adult, 2.47 - 2.68 kg	
Source:	Boehringer Ingelheim Pharma KG	
Housing:	Stainless steel wire mesh cages with grating	
Diet:	Kliba-Labordiaet, Provimi Kliba SA *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: November 2, 1999 (one male), November 8, 1999 (others)
End: November 9, 1999 and November 15, 1999 respectively.

2. **Animal assignment and treatment** - Six animals received 0.1 ml bulk volume (approx. 40 mg) of comminuted Cabrio EG to the conjunctival sac of the right eye. This material was washed out at 24 hours with tap water. Observations were made at 1, 24, 48, and 72 hours as well as at 7 days after application. Scoring method is Draize.

II. RESULTS AND DISCUSSION:

A. Irritation was limited to the conjunctivae. Redness ranged from "normal" to "diffuse, crimson colour, individual vessels not easily discernible." Chemosis ranged from "no swelling" to "Obvious swelling with partial eversion of lids." Discharge was minimal except for one animal at 24 hours which had moistening of the lids and hairs adjacent to the lids. No effects were seen at 7 days and the study was ended.

Table 1. Mean Eye Irritation Scores

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	2	1.33	1.17
24 h	0	0	0	2	1.33	0
48 h	0	0	0	1.83	0.17	0.17
72 h	0	0	0	1	0.17	0
7 d	0	0	0	0	0	0
Mean (24 - 72h)	0	0	0	1.61	0.56	0.06

B. Authors' Conclusions: Under the test conditions chosen and considering the described findings, BAS 500 02 F does not give indication of an irritant property to the eye.

C. Reviewer's Conclusions: The authors present a valid study. Based on the 24/48/72 h MAS of 4.4/110 and the 24 h MIS of 9/110, Headline EC is minimally irritating to rabbit eyes. No label comments are required.
D. Deficiencies - No deficiencies.

Reviewer: Michael Honeyman , Date April 10, 2001

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

TEST MATERIAL (PURITY): BAS 500 002 F (21.0 % a.i.)

SYNONYMS: Cabrio EG (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1999) "BAS 500 02 F Acute Dermal Irritation/Corrosion in Rabbits." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.14H0236/992151, December 22, 1999. MRID # 54118316. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a primary dermal irritation study, young adult Himalayan rabbits (6 males) were dermally exposed to 0.5 g of Cabrio EG (21.0 % pyraclostrobin) in distilled water for 4 hours to 6.25 cm^2 under semi-occlusive dressing. Animals then were observed for 7 days. Irritation was scored by the method of Draize.

Mild to well-defined erythema was noted in all animals through 48 hours. Mild erythema was seen at 72 hours. There was no edema and no effects were observed at 7 days so the study was ended. In this study, Cabrio EG is slightly irritating to the skin based on the 24/48/72 h MAS of 1.2/8.0 and the 24 h MIS of 1.7/8.0. No label comments are required. **Note from EPA Secondary Reviewer: Toxicity Category IV; signal word = CAUTION.**

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 02 F

Description:	Solid (granular powder, beige/brown), store at room temp.
Lot/Batch #:	99-3
Purity:	21.0% a.i.
	Content and homogeneity confirmed by analysis

2. **Vehicle and/or positive control:** Distilled water.

3. **Test animals:**

Species:	Rabbit	
Strain:	Chbb: HM (outbred strain)	
Age/weight at treatment:	Young adult, 2.33 - 2.68	
Source:	Boehringer Ingelheim Pharma KG	
Housing:	Stainless steel wire mesh cages with grating	
Diet:	Kliba-Labordiaet, Provimi Kliba SA *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: October 25, 1999 End: November 1, 1999

2. **Animal assignment and treatment** - Six male Himalayan rabbits were given a single 0.5 g dose of Cabrio EG 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 day 7. Irritation scoring method was Draize.

II. RESULTS AND DISCUSSION:

A. Mild to well-defined erythema was seen in all rabbits through 48 hours. Four animals had mild erythema at 72 hours. There was no edema observed. There were no lasting reactions at 7 days so the study was ended. Two animals had mechanical skin lesions due to the adhesiveness of the test substance. Both of these animals had well-defined erythema through 48 hours and mild erythema at 72 hours.

Table 1. Mean Irritation Scores

Time	Erythema	Edema
1 h	1.5	0
24 h	1.67	0
48 h	1.33	0
72 h	0.67	0

7 d	0	0
Mean (24 - 72h)	1.22	0

Total erythema and edema are scored out of 8

B. Author's Conclusions: Under the test conditions chosen and considering the described findings, BAS 500 02 F gives indication of an irritant property to the skin.

C. Reviewer's Conclusions: This reviewer agrees with the conclusions of the study authors. Based on the 24/48/72 h MAS of 1.2/8.0 and the 24 h MIS of 1.7/8.0, Cabrio EG is slightly irritating to rabbit skin. No label comments are required.

D. Deficiencies: No deficiencies.

Reviewer: Michael Honeyman , Date April 10, 2001

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

TEST MATERIAL (PURITY): BAS 500 002 F (21.0 % a.i.)

SYNONYMS: Cabrio EG (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1999) "BAS 500 02 F Modified Buehler Test (9 Inductions) in Guinea Pigs." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.33H0236/992153, December 22, 1999. MRID # 54118319. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a dermal sensitization study with Cabrio EG (21.0% pyraclostrobin) in aqua bidest, young adult DH (SPF) guinea pigs (20 females) were tested using the method of modified Buehler.

At 24 hours after all but the fourth induction exposures, several animals exhibited discrete or patchy erythema. Two animals had moderate and confluent erythema 24 hours after the ninth induction exposure, one with swelling. No irritation or skin sensitization responses were seen following challenge exposure. In this study, **Cabrio EG is not a dermal sensitizer.** No label comments are required.

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 02 F

Description:	Solid (granular powder, beige/brown), store at room temp.
Lot/Batch #:	99-3
Purity:	21.0% a.i.
	Content and homogeneity confirmed by analysis

2. **Vehicle:** Aqua bidest
Positive Control: alpha-hexylcinnamaldehyde

3. **Test animals:**

Species:	Guinea Pig	
Strain:	Hsd Poc:DH (SPF)	
Age/weight at treatment initiation:	Young adult, 313-386 g	
Source:	Harlan Winkelmann GmbH, Borchen, FRG	
Housing:	Stainless steel wire mesh cages with plastic-coated grating	
Diet:	Kliba-Labordiaet (Kaninchen-Meerschweinchen-Haltungsdiät) *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:	Seven days	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: October 19, 1999 End: November 19, 1999

2. **Animal assignment and treatment** - Buehler test method. As pretest, six 6-hour occlusive percutaneous applications were performed. The minimum irritant concentration was found to be 60% Cabrio EG in aqua bidest. The maximum non-irritant concentration was 25% Cabrio EG in aqua bidest. This concentration was used as the challenge dose.

The main study was performed on 20 guinea pigs in the test group and 10 in each of the irritation control groups 1 and 2. The second irritation control group was precautionary in the event of borderline results at challenge necessitating a re-challenge. All animals were female. The occlusive patches were 4 cm^2 and contained 0.5 mL of the test substance formulation. Exposure was 6 hours to the anterior left flank, three times a week. Observations were recorded 24 hours after patch removal

Challenge was carried out 13 days after the ninth and final induction. Same type of patches were used, again with 0.5 mL of test substance for six hours to the right flank. Observations were recorded 24 and 48 hours after the patch removal.

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%)

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration - Throughout the first 8 inductions, animals showed either no reaction or discrete/patchy erythema with no apparent pattern. See Table 1. Following the final induction exposure, two guinea pigs had moderate and confluent erythema and one of those had swelling.

Table 1. Number affected per induction exposure

Induction	# With discrete or patchy erythema	Induction	# With discrete or patchy erythema
1	6	6	2
2	12	7	5
3	9	8	5
4	0	9	7*
5	3		

* Does not include the two animals with moderate and confluent erythema at this time point.

B. Challenge reactions and duration - The challenge did not cause any skin reactions in either the control group 1 animals or the test group animals at 24 and 48 hours after patch removal. Control group 2 was not utilized in a re-challenge because the results were not borderline.

C. 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.) Seven of twenty guinea pigs had a positive result during the first challenge and eleven of the twenty were positive at second challenge.

D. Authors' Conclusions: Based on the chosen evaluation criteria, the results of this study show that BAS 500 02 F does not have a sensitizing effect on the skin of the guinea pig in the modified Buehler test under the test conditions chosen.

E. Reviewer's Conclusions: This reviewer is in agreement with the study author. Cabrio EG shows no evidence of skin sensitization in the guinea pig

F. Deficiencies - No deficiencies.