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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

30 /JULY/2001

MEMORANDUM

Subject: EPA Reg. No. /File Symbol: 7969-RIA Headline EC Fungicide
DP Barcode: D275784
Case No: 68823
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	23.6%
Inert Ingredient(s):	76.4%
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	45118303	LD_{50} ♂ is between 500 and 2000 mg/kg; LD_{50} ♀ = 260 mg/kg; LD_{50} (♀&♂) = 500 mg/kg	II
81-2	Acute Dermal	45118306	LD_{50} (♀&♂) > 4000 mg/kg	III
81-3	Acute Inhalation	45118309	LC_{50} (♀&♂) = 3.51 mg/L	IV
81-4	Primary Eye Irritation	45118312	Moderately irritating	I

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81-5	Primary Skin Irritation	45118315	Severely irritating	II
81-6	Dermal Sensitization	45118318	Not a sensitizer	Not applicable

LABELING:

ID #: 007969-00186 Headline EC Fungicide

RESTRICTED USE CLASSIFICATION RECOMMENDED:

Due to eye irritation toxicity category.

The PM Team should decide if restricted use classification is necessary or if alternative labeling will allay the requirement for restricted use classification.

SIGNAL WORD: DANGER PELIGRO

PRECAUTIONARY STATEMENTS:

Corrosive. Causes irreversible eye damage. May be fatal if swallowed. Causes skin irritation. Harmful if absorbed through skin. Do not get in eyes, on skin or on clothing. Wear coveralls worn over short-sleeved shirt and short pants, socks and chemical resistant footwear., goggles or face shield and chemical resistant gloves (such as Nitrile, Butyl, Neoprene, and/or Barrier Laminate). Overhead Exposure: Wear chemical resistant headgear. For Cleaning Equipment: Add a chemical resistant apron.

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 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.

The following "Note to Physician" statement is required for the subject product:

NOTE TO PHYSICIAN; Probable mucosal damage may contraindicate the use of gastric lavage.

USER SAFETY RECOMMENDATION:

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove contaminated clothing and wash clothing before reuse.

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

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

TEST MATERIAL (PURITY): BAS 500 00 F (23.4% a.i.)

SYNONYMS: Headline EC (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1998) "BAS 500 00 F - Acute Oral Toxicity in Rats." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.10A0185/971108, July 15, 1998. MRID # 54118303. Unpublished. **Note from EPA Secondary Reviewer: The MRID should read 45118303.**

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 Headline EC (247.83 g/L a.i.) in aqua bidest at 2000 mg/kg bw and observed for 14 days. Because all animals died from test article toxicity, another set of rats were dosed at 500 mg/kg bw. No males died, but four females did, so more rats were dosed at 200 mg/kg bw. In that test, one male and two females died. A final test was performed at 50 mg/kg bw resulting in zero mortalities.

Oral LD_{50} for males is between 500 and 2000 mg/kg bw
Oral LD_{50} for females = 260 mg/kg bw
Oral LD_{50} for combined sexes = 500 mg/kg bw

Headline EC is of HIGH toxicity based on the female LD_{50}. Label comments on the primary display panel should read DANGER - POISON. **Note from EPA Secondary Reviewer: The LD_{50} for females of 260 mg/kg indicates Toxicity Category II. The appropriate signal word for Toxicity Category II is WARNING. The signal word POISON would be inappropriate for this product.**

Clinical effects noted in most animals included impaired or poor general state, dyspnea, gasping, apathy, lateral position, staggering, ataxia, paresis, twitching, saltatory spasm, rolling convulsions, flexion spasm, opisthotonus, extension spasm, spasm of the jaws, exophthalmos, piloerection, diarrhea, and eyelid closure. These symptoms did not persist past the day of dosing.

Mean body weight and mean body weight gain were reduced in a dose-dependent manner. The females were affected more than the males. Tests for statistical significance were not performed.

Necropsy findings were negative in rats euthanized at study termination. All premature deaths yielded findings including dark red discolouration in lungs; white, watery stomach and intestinal contents; and congestive hyperaemia;

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 00 F
Description: Liquid brown, store at room temp.
Lot/Batch #: 97-2
Purity: 247.83 g/L a.i.
CAS #:

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 / 150 to 300 g, ± 20% of the mean weight	
Source:	Dr. K. Thomae GMBH, Biberach, FRG (high dose); Boehringer Ingelheim Pharma KG (all except high dose)	
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: 16/12/1997 End: 25/03/1998 (Test article administration dates for the separate 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 Headline EC 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
50	0.5	10	0/5	0/5	0/10
200	2	10	1/5	2/5	3/10
500	5	10	0/5	4/5	4/10
2000	20	10	5/5	5/5	10/10

3. Statistics - The oral LD_{50} for males was calculated by the binomial test (Snedecor G.W., Cochran W.G., 1989). For the female oral LD_{50}, a probit analysis was performed.

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. The acute oral LD_{50} for males was greater than 500 mg/kg bw but less than 2000 mg/kg bw. The LD_{50} for females was found to be 260 mg/kg bw. The combined sexes figure is approximately 500 mg/kg bw.

B. Clinical observations - Observations included impaired or poor general state, dyspnea, gasping, apathy, lateral position, staggering, ataxia, paresis, twitching, saltatory spasm, rolling convulsions, flexion spasm, opisthotonus, extension spasm, spasm of the jaws, exophthalmos, piloerection, diarrhea, and eyelid closure. These conditions were completely absent by the second day.

Table 2. Symptoms Observed, Duration (# Affected)

Sex	Males				Females			
Dose (mg/kg bw)	50	200	500	2000	50	200	500	2000
Impaired general state		H2-H5 (4)	H0,H4-H5 (5)	H0 (1)		H4-H5 (1)	H0 (2)	H0 (1)
Poor general state			H0-H5 (5)	H0-H3 (1)		H0-H5 (5)	H0-H5 (4)	H0-H3 (5)
Dyspnea		H2-H5 (4)	H0-H5 (5)	H0-H3 (5)		H0-H5 (5)	H0-H5 (5)	H0-H3 (5)
Gasping							H0 (1)	
Apathy			H0-H5 (5)	H0-H3 (5)		H0-H5 (5)	H0-H5 (4)	H0-H3 (5)
Lateral position							H0 (2)	H3 (1)
Staggering		H3-H5 (1)	H0-H5 (5)	H0,H2-H3 (5)		H0-H5 (2)	H0-H5 (3)	H0, H2 (2)
Ataxia				H1 (3)				H0-H1 (5)
Paresis								H0 (3)
Twitching			H1 (1)					H3 (1)
Saltatory spasm				H1 (5)				H1 (5)

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Rolling convulsions				H1 (4)				H1 (5)
Flexion spasm				H1 (5)				H1 (5)
Opisthotonus				H1 (4)				H1 (4)
Extension spasm				H1 (4)				H1 (5)
Spasm of the jaws				H1 (4)				H1 (5)
Piloerection		H3-H5 (4)	H1-H5 (5)	H2-H3 (1)		H1-H5 (4)	H1-H5 (1)	H2-H3 (1)
Diarrhea		H2-H4 (2)	H2-H5 (4)		H1-H4 (4)	H1-H5 (4)	H1-H4 (1)	H2-H3 (1)
Salivation							H0 (2)	H1 (5)
Eyelid closure						H3-H5 (2)		
Exophthalmos			H0 (1)					

H: Hour

C. Body Weight - Mean body weight and mean body weight gain were reduced in a dose-dependent manner (more notably in the females), but no tests for statistical significance were performed.

Table 3. Mean Body Weights (g)

Sex	Males				Females			
Dose (mg/kg bw)	50	200	500	2000	50	200	500	2000
Day 0	190	180	184	181	189	183	183	181
Day 7	263	247	254	--	225	212	198	--
Day 13	301	283	294	--	233	227	205	--

D. Necropsy - Food was withdrawn at least 16 hours before CO_2 euthanasia. Significant findings were observed in all animals that died during the study. All terminal sacrifice rats were healthy.

Table 4. Necropsy Findings

Dose	# Males	# Females	Findings
200	1	2	Dark red discolouration in all lobes of lungs
	0	2	White, watery stomach contents
500	0	4	Congestive hyperaemia
2000	1	5	White, liquid stomach contents; White discolouration of intestinal contents; Dark red discolouration in all lobes of lungs

E. Author's Conclusions: Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of BAS 500 00 F was found to be about 500 mg/kg body weight for the male and female animals. (LD_{50} for the male animals was found to be greater than 500 mg/kg bw and less or equal to 2000 mg/kg bw; LD_{50} for the female animals was found to be 260 mg/kg bw.)

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 00 F (23.4% a.i.)

SYNONYMS: Headline EC (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1998) "BAS 500 00 F - Acute Dermal Toxicity in Rats." Department of Toxicology of BASF Aktiengesellschaft. Lab report no. 11A0185/971109, July 15, 1998. MRID # 45118306. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In an acute dermal toxicity study, groups of young adult Wistar rats (5/sex) were dermally exposed to Headline EC, 247.83 % pyraclostrobin for 24 hours to 10 % of body surface area at a dose of 4000 mg/kg bw under semi-occlusive wrap. Animals then were observed for 14 days.

Dermal LD_{50} males & females both > 4000 mg/kg bw.

Headline EC is of LOW Toxicity based on the LD_{50} for either sex. No label comments are applicable. **Note from EPA Secondary Reviewer: This dermal LD_{50} places this product in Toxicity Category III. The signal word for Toxicity Category III is CAUTION.**

Dyspnea, apathy and poor general state were seen in rats shortly after exposure, but not after day 2. Skin irritation responses included very slight, well defined, and moderate-to-severe erythema. Very slight to slight edema was also observed in 3/5 males and 2/5 females. More severe reactions included petechia, severe scaling, and bleeding both at and beyond the area of exposure. The were no irritation symptoms recorded on day 14

Body weight gain in four of the five females over the first week was poor. One of the females was still underweight by study end. No tests for statistical significance were performed.

There were no notable findings during necropsy.

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 00 F
	Description:	Liquid brown, store at room temp.
	Lot/Batch #:	97-2
	Purity:	247.83 g/L a.i.
	CAS # TGAI:	

2. **Vehicle:** None

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: November 21, 1996 End: December 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 Headline EC dermally using 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. 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.

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TABLE 1. Doses, mortality/animals treated.

Dose (mg/kg bw)	Males	Females	Combined
4000	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 4000 mg/kg bw.

B. Clinical observations - Rats were apathetic and in poor general state shortly after exposure, but improved by day 3. Similarly, dyspnea was noted shortly after exposure and was gone by day 3. Skin irritation responses included very slight, well defined, and moderate-to-severe erythema. Some instances of edema were slight or very slight. More severe reactions included petechia, severe scaling, and bleeding both at and beyond the area of exposure. The were no irritation symptoms recorded on day 14.

Table 2. Observations

	Males		Females	
	Occurrences	Persistence	Occurrences	Persistence
Impaired general state	3	Days 1-2	2	Days 1-2
Poor general state	5	Hour 4	5	Hour 4
Dyspnea	5	Hour 4 - Day 2	5	Hour 4 - Day 2
Apathy	5	Hour 4	5	Hour 4
Very slight erythema	1	Day 7	3	Days 1-7
Well-defined erythema	1	Day 1	3	Days 1-7
Moderate to severe erythema	4	Day 1	1	Day 1
Very slight edema	3	Day 1	2	Day 1
Slight edema	3	Day 1	2	Days 1-7
Scaling	1	Day 7		
Petechia extending beyond area of exposure	2	Day 1		
Petechia at area of exposure	1	Day 1	1	Day 1

Severe scaling extending beyond the area of exposure			2	Day 7
Superficial scabbing extending beyond the area of exposure			2	Day 7
Bleeding extending beyond the area of exposure			1	Day 7
Bleeding			1	Day 1

C. Body Weight - All males gained weight during the observation period. However, four females experienced either zero or negative body weight gain during the first week. By day 14, only one of those females did not have a significant body weight gain. There are no obvious corresponding clinical symptoms to explain the meagre body weight gain. No statistical tests were performed on this data.

Table 3. Body Weights (g)

	Day 0	Day 7	Day 14
550 M	271	294	324
551 M	273	293	315
552 M	267	289	315
553 M	265	283	307
554 M	271	297	322
Mean males	269	291	317
555 F	238	273	310
556 F	247	250	271
557 F	249	246	270
558 F	245	245	254
559 F	249	246	277
Mean females	246	252	276

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 00 F was found to be greater than 4000 mg/kg bw for the male and female animals.

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

F. Deficiencies - No deficiencies

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

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

TEST MATERIAL (PURITY): BAS 500 00 F (Formulation strength; other studies using the same test substance batch state 23.4% a.i. as the purity)

SYNONYMS: Headline EC (Pyraclostrobin a.i.)

CITATION: Gamer, A., Leibold, E., Hoffmann, H. (1998) "BAS 500 00 F - Acute Inhalation Study in Wistar Rats." Department of Toxicology of BASF Aktiengesellschaft. October 14, 1998. Lab report no. 13I0185/977014, MRID # 45118309. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study, groups of young adult Wistar rats (5/sex) were exposed by the inhalation route to Headline EC (Pyraclostrobin, 24.1%) for 4 hours to head/nose only at concentrations of 1.06, 2.72, or 5.2 mg/L. Animals then were observed for 14 days.

The LC_{50} (95% C.I.) for males is 3.76 mg/L
females is 3.27 mg/L (1.05 - 9.04)
combined is 3.51 mg/L (2.41 - 5.09 mg/l)

Headline EC is classified as being of **LOW Toxicity** based on the LC_{50} of females. No label comments are required. **Note from EPA Secondary Reviewer: A LC_{50} of 3.51 mg/L places this product in Toxicity Category IV. The signal word Caution is still required, by USEPA, on the Label.**

Clinical observations were similar between males and females. Accelerated and intermittent breathing were nearly ubiquitous from the start of dosing. All animals that survived dosing exhibited respiratory sounds, bloody crust formation on the nose, eyelid closure, high-stepping gait, squatting posture, piloerection, smeared fur, and reduced general state. Extended abdomens seen at high doses. Duration of clinical observations were varied, with most lasting a few days.

There was a dose-related effect on body weight gain, but all groups gained weight over the study period except for the surviving high dose females (net weight loss.)

Terminal sacrifice necropsies yielded no gross pathological abnormalities. Rats found deceased showed diffuse dark red discolouration of all lobes of the lungs; clear, liquid nasal discharge; and a "stinging" odour from the carcass. In addition, all mid-dose rats and 2 males and 1 female from the high-dose group had edema of all lobes of the lungs.

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:

1	**Test Material:**	BAS 500 00 F
	Description:	Liquid brown, store at room temp.
	Lot/Batch #:	97-2
	Purity:	Formulation (Spec sheet lists 24.1% a.i.)
	CAS # TGAI:	
		Confirmed homogenous and stable by analysis

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

3 **Test animals:**

Species:	Rat	
Strain:	Wistar CHBB: THOM (SPF)	
Age/weight at dosing:	8 - 10 weeks / 273.5 to 309.6 g ♂, 199.1 to 238.6 g ♀	
Source:	Boehringer Ingelheim Pharma KG, FRG	
Housing:	Individually, stainless steel wire mesh, type DK-III, no bedding	
Diet:	Kliba rat/mouse/hamster lab diet 10 mm pellets, 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: March 16, 1998 End: April 1, 1998

2. Exposure conditions - Head-nose exposure to homogenous aerosol, 55 L, glass-steel construction. The technical equipment included a glass cyclonic separator, a glass aerosol mixing vessel, a stainless steel piston metering pump KP 2000, 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 about 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 Headline EC by head-nose only exposure for 4 hours. They were observed daily (except days 4, 5,11, and 12) 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)		
						♂	♀	♂ & ♀
1	4	2.8	1.06	0.9	3.8	0/5	0/5	0/10
2	12	8.5	2.72	1	3.7	1/5	2/5	3/10
3	35	24.7	5.2	1.3	3.4	4/5	4/5	8/10

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

Test atmosphere concentration - Sampling equipment included a probe (d = 7 mm) with quartz wool, 3 impingers connected in series and filled with sorption solvent. The solvent used was acetonitrile. A BASF sampling station with vacuum pump, gas meter, impulse counter, and automatic pump switch was also used. Samples were taken immediately adjacent to the animals' noses. Flow was 3 L/min and velocity was 1.25 m/s, 4 samples per group were taken approximately every hour.

HPLC (Hewlett Packard HP 1050) description: Column was metal 250 mm x 4 mm, polygosil-60-5-C_{18} The photometric detector with variable wavelength (274 nm) had an injection volume of 10 µL, the mobile phase was 62.5% acetonitrile + 5 mL 0.5 M H_2SO_4,37.5% bid. Water + 5 mL 0.5 M H_2SO_4. Flow rate was 1.2 mL/min. Concentrations were calculated in mg/L from the mean analytically determined mass values of the test substance derived from the measurements of the active ingredients and the sample volumes of the inhalation atmospheres. Results are in table 1 above.

Particle size determination - Equipment included a Stack Sampler Mark III, a Vacuum Compressed Air Pump (Millipore), a Sampling probe (internal d = 6.9 mm), and a limiting orifice at 3 L/min. 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 impactor stages and backup particle filter were eluted with acetonitrile and analyzed by HPLC as described above. Wall losses were determined quantitatively. Results are in Table 1 above.

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

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1.
Time of Death from Start of Dosing

Group	Low	Mid	High
Male	n/a	4 Hours	½ - 2 Hours; End of first day
Female	n/a	½ - 1 Hour	½ - 1 Hour; End of first day

The LC_{50} (95% C.I.) for males is 3.76 mg/l
females is 3.27 mg/l (1.05 - 9.04)
combined is 3.51 mg/l (2.41 - 5.09 mg/l)

B. Clinical observations - Findings were similar between males and females. Accelerated and intermittent breathing were ubiquitous from the start of dosing except for one mid-dose female that lacked the latter condition. Effects seen in all animals that survived dosing were respiratory sounds, bloody crust formation on the nose, eyelid closure, high-stepping gait, squatting posture, piloerection, smeared fur, and reduced general state. The surviving high-dose male and female showed extended abdomens during days 1 and 2. Duration of clinical observations were varied and except for squatting posture in females, none were completely resolved by the end of the day of exposure. See Table 2.

Table 2a. Clinical Findings and Duration in the Males

Test group	1	2	3
Dragging respiration	n.d.	4 (Days 0 - 2)	3 (1 h - Day 0)
Accelerated respiration	5 (¼ - 4 h, Days 1 - 3)	5 (¼ h, Day 2)	5 (<¼ h, Days 3 - 4)
Intermittent respiration	5 (Day 0)	5 (½ - 4 h)	5 (¼ - 1 h)
Gasping	n.d.	1 (Day 1)	1 (Days 1 - 2)
Respiratory sounds	5 (Day 0)	4 (Days 0 - 5)	1 (Days 0 - 2)
Bloody crust formation on nose	5 (Days 0 - 1)	4 (Days 0 - 2)	1 (Days 0 - 3)
Eyelid closure	5 (Day 0)	4 (Day 0)	1 (Days 0 - 1)
Attempts to escape	5 (<¼ h)	5 (<¼ h)	5 (<¼ h)
High-stepping gait	5 (Day 0)	4 (Days 0 - 1)	1 (Days 0 - 2)
Squatting posture	5 (Day 0)	4 (Days 0 - 1)	1 (Day 0)
Piloerection	5 (Days 0 - 1)	4 (Days 0 - 6)	1 (Days 0 - 8)
Smeared fur (urine)	5 (Day 0)	4 (Days 0 - 6)	1 (Days 0 - 4)
Abdomen extended	n.d.	n.d.	1 (Days 1 - 2)

Reduced general state	5 (Day 0)	4 (Days 0 - 1)	1 (Days 0 - 1)

Table 2b. Clinical Findings and Duration in the Females

Test group	1	2	3
Dragging respiration	n.d.	3 (Days 0 - 1)	2 (1 h - Day 0)
Accelerated respiration	5 (¼ - 4 h, Days 1 - 3)	5 (¼ h, Days 2 - 6)	5 (<¼ h, Days 3 - 4)
Intermittent respiration	5 (Day 0)	4 (½ - 4 h)	5 (¼ - ½ h)
Gasping	n.d.	n.d.	1 (Days 1 - 2)
Respiratory sounds	5 (Day 0)	3 (Day 0)	1 (Days 0 - 2)
Bloody crust formation on nose	5 (Days 0)	3 (Days 0 - 1)	1 (Days 0 - 3)
Eyelid closure	5 (Day 0)	3 (Day 0)	1 (Days 0 - 1)
Attempts to escape	5 (<¼ h)	5 (<¼ h)	5 (<¼ h)
High-stepping gait	5 (Day 0)	3 (Day 0)	1 (Days 0 - 2)
Squatting posture	5 (Day 0)	3 (Day 0)	1 (Day 0)
Piloerection	5 (Days 0 - 1)	3 (Days 0 - 6)	1 (Days 0 - 8)
Smeared fur (urine)	5 (Day 0)	3 (Days 0 - 6)	1 (Days 0 - 4)
Abdomen extended	n.d.	n.d.	1 (Days 1 - 2)
Reduced general state	5 (Day 0)	3 (Day 0)	1 (Days 0 - 1)

C. **Body Weight** - On average, all animals in the low and mid dose groups gained weight during the study, though one male from each of those groups lost weight during the first week. The females' gains were poor, especially in the first week, but overall they were positive. The one surviving high dose male lost some weight during the first week, but recovered to have a body weight comparable to the other groups by study end. The high dose female that survived did not recover and experienced two consecutive weeks of weight loss.

Table 3. Mean Body Weights (g)

	Males			Females		
Test Group	Day 0	Day 7	Day 13	Day 0	Day 7	Day 13
1	303 (9.2)	316 (12.2)	341 (16.2)	218 (2.3)	222 (4.5)	234 (6.2)
2	282 (7.6)	291 (6.3)	332 (6.8)	202 (4.3)	210 (2.5)	222 (4.3)
3	295 (14.5)	296 (0.0)	343 (0.0)	230 (7.1)	212 (0.0)	208 (0.0)

D. **Necropsy** - No gross pathological abnormalities were detected in the animals that survived to terminal sacrifice.

In all rats found deceased, researchers found diffuse dark red discolouration of all lobes of the lungs; clear, liquid nasal discharge; and a "stinging" odour from the carcass. In addition, all mid-dose rats and 2 males and 1 female from the high-dose group had edema of all lobes of the lungs.

Table 4. Necropsy Results

Findings	Test group 2		Test group 3	
Number of animals	1 Male	2 Females	4 Males	4 Females
Lung: - Diffuse dark red discolouration of all lobes - Edema of all lobes	11	22	42	41
Nose: Clear liquid discharge	1	2	4	4
Carcass: "Stinging" odour	1	2	4	4

E. <u>Reviewer's Conclusions</u>: The authors present a valid study. For males, LC_{50} = 3.76 mg/l; females, LC_{50} = 3.27 mg/l; and both sexes combined, LC_{50} = 3.51 mg/l. No label comments are required.

F. <u>Deficiencies</u> - No deficiencies

Reviewer: Michael Honeyman , Date April 10, 2001

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

TEST MATERIAL (PURITY): BAS 500 00 F (23.4% a.i.)

SYNONYMS: Headline EC (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1998) "BAS 500 00 F - Acute Eye Irritation in Rabbits." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.13H0185/972189, July 15, 1998. MRID # 45118312. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a primary eye irritation study, 0.1 mL of Headline EC (24.1 % pyraclostrobin) was instilled into the conjunctival sac of the right eye of young adult NZW rabbits (2 males, 4 females) for 24 hours. Eyes were washed with tap water. Animals then were observed for 14 days. Irritation was scored by the method of Draize.

Mild corneal opacity was present across varying areas of the eyes at 24, 48, and 72 hours. Moderate effects on the iris were noted for the same time period. Conjunctivae showed redness, chemosis, and discharge to different degrees (no effect to severe), from 1 hour to 7 days port-dosing. The worst effects were recorded at 24 hours.

At 24/48/72 hours post-dosing, the following non-irritation effects were seen in some or all animals: Suppuration, pupil contracted, discharge of blood, small retractions in the eyelids, and loss of corneal tissue.

In this study, Headline EC is moderately irritating to the eye based on the MAS of 35.3/110 and the 24 h MIS of 39/110. Due to the presence of severe effects not included in the irritation calculations such as loss of corneal tissue and bloody discharge, signal words on the primary display panel should read "DANGER - EYE IRRITANT".

Note from the EPA Reviewer: Although, the corneal involvement and irritation cleared within 7 days, the other effects noted by the primary reviewer place this product in

Toxicity Category I. Toxicity Category I results in the signal word DANGER.

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 00 F
	Description:	Liquid brown, store at room temp.
	Lot/Batch #:	97-2
	Purity:	247.83 g/L a.i.
	CAS # TGAI:	
		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 / 3.05 - 3.64 g, two males, four 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: December 8, 1997 End: December 22, 1997

2. Animal assignment and treatment - Two males and four females received 0.1 ml of Headline EC to the conjunctival sac of the right eye. This was washed out with tap water at 24 hours. Readings were made at 1, 24, 48, and 72 hours, 7 and 14 days post-dosing. Scoring method was Draize.

II. RESULTS AND DISCUSSION:

A. Corneal effects were present at 24, 48, and 72 hours, opacity was mild, but the area involved ranged from ¼ to the whole eye. Observation of the irises showed moderate change lasting from 24 to 72 hours

with one animal still showing effects at 7 days post-dosing. The conjunctivae were significantly affected right from 1 hour through to 7 days. The scores ranged from no effect to severe with the highest totals occurring at 24 hours. On day 7, the highest score in any category was 1.

At 24/48/72 hours post-dosing, several non-irritation effects were seen: Suppuration (5/4/4), pupil contracted (6/6/4), discharge of blood (6/6/4), small retractions in the eyelids (0/1/1), and loss of corneal tissue (0/0/2).

Table 1. Individual Animal Observations

Time	Animal	Cornea		Iris (0 to 2)	Conjunctivae			Other
		Opacity (0 to 4)	Area (0 to 4)		Redness (0 to 3)	Chemosis (0 to 4)	Discharge (0 to 3)	
1 H	1	0	0	0	2	1	3	
	2	0	0	0	2	2	3	
	3	0	0	0	2	2	3	
	4	0	0	0	2	1	3	
	5	0	0	0	2	2	3	
	6	0	0	0	2	2	3	
24 H	1	1	3	1	2	4	2	P, D
	2	1	4	1	3	3	3	S, P, D
	3	1	♧	1	3	4	3	S, P, D
	4	1	3	1	3	4	3	S, P, D
	5	1	3	1	2	4	3	S, P, D
	6	1	3	1	2	4	3	S, P, D
48 H	1	1	3	1	2	2	1	P, D
	2	1	4	1	3	3	2	S, P, D
	3	1	4	1	3	3	2	S, P, D
	4	1	4	1	3	3	2	S, P, D
	5	1	3	1	2	2	2	S, P, D, R
	6	1	3	1	3	3	2	S, P, D
72 H	1	1	3	0	2	2	0	S, P, D, L
	2	2	2	1	2	2	1	S, P, D

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	3	1	3	1	3	3	1	S, P, D
	4	1	4	1	3	2	1	S, R
	5	1	2	0	2	2	1	S, P, D, L
	6	2	2	0	3	2	1	
7 D	1	0	0	0	1	0	0	
	2	0	0	0	1	1	0	
	3	0	0	0	1	1	0	
	4	0	0	1	1	1	0	
	5	0	0	0	1	1	0	
	6	0	0	0	1	1	0	
14 D	1	0	0	0	0	0	0	
	2	0	0	0	0	0	0	
	3	0	0	0	0	0	0	
	4	0	0	0	0	0	0	
	5	0	0	0	0	0	0	
	6	0	0	0	0	0	0	

♔ - Area index could not be established due to severe edema
S - Suppuration
P - Pupil contracted
D - Discharge of blood
L - Loss of corneal tissue
R - Small retractions in the eyelids

Table 2. 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	2	1.67	3
24 h	1	3.2	1	2.5	3.83	2.83
48 h	1	3.5	1	2.67	2.67	1.83
72 h	1.33	2.67	0.5	2.5	2.17	0.83
7 d	0	0	0.17	1	0.17	0
14 d	0	0	0	0	0	0
Mean (24 - 72h)	1.11	3.12	0.83	2.56	2.89	1.83

B. Author's Conclusions: Under the test conditions chosen and considering the described findings, BAS 500 00 F gives indication of an irritant property to the eye.

C. Reviewer's Conclusions: The authors present a valid study. Although the MAS of 35.3/110 and the 24 h MIS of 39/110 indicate moderate irritation, the presence of severe effects not included in the irritation calculations such as loss of corneal tissue and bloody discharge justify a categorization as severely irritating. Signal words on the primary display panel should read "DANGER - EYE IRRITANT".

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 00 F (23.4% a.i.)

SYNONYMS: Headline EC (Pyraclostrobin a.i.)

CITATION: Wiemann, C., Hellwig, J. (1998) "BAS 500 00 F - Acute Dermal Irritation/Corrosion in Rabbits." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.14H0185/972188, July 15, 1998. MRID # 45118315. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a primary dermal irritation study, young adult NZW rabbits (2 males, 4 females) were dermally exposed to 0.5 mL of Headline EC, (24.1 % pyraclostrobin) for 4 hours to 6.25 cm^2 of dorsal body surface area under semi-occlusive wrap. Animals then were observed for 14 days. Irritation was scored by the method of Draize.

Erythema patterns were mostly in the moderate range through 72 hours and improved to well-defined for days 7 through 14. Edema was mild or non-existent at 1 hour and again for 72 hours through 14 days. Mild or well-defined edema was noted at 24 and 48 hours. Mild edema was observed in 4 animals at 72 hours and 2 animals at 7 and 14 days.

All animals had erythema and edema extending beyond the area of exposure. Either scaling or severe scaling were observed in all animals on days 7 and 14.

In this study, Headline EC is severely irritating to the skin based on the 24/48/72 h MAS of 4.0/8.0, the 24 h MIS of 4.33/8.0, severe scaling, and persisting irritation beyond 14 days. Signal words on the primary display panel should read "DANGER - SKIN IRRITANT." **Note from EPA Reviewer: The results from this reviewer indicate that this product is in Toxicity Category II. The USEPA signal word for Toxicity Category II is WARNING.**

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 00 F
Description: Liquid brown, store at room temp.
Lot/Batch #: 97-2
Purity: 247.83 g/L a.i.
CAS # TGAI:

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 / 3.92 - 3.99 g, two males, four 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: December 8, 1997 End: December 22, 1997

2. **Animal assignment and treatment** - Animals (2 males, 4 females) 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 7 and 14. Irritation scoring method was Draize.

II. RESULTS AND DISCUSSION:

A. Erythema patterns were mostly in the moderate range through 72 hours and improved to well-defined for days 7 through 14. Edema was mild or non-existent at 1 hour and again for 72 hours through 14

days. Mild or well-defined edema was noted at 24 and 48 hours. Mild edema was observed in 4 animals at 72 hours and 2 animals at 7 and 14 days.

All animals had erythema extending beyond the area of exposure until day 14 when only four had this condition. Likewise, edema extended beyond the test site in most cases when edema was present. Either scaling or severe scaling were observed in all animals on days 7 and 14.

Table 1. Individual Animal Observations

Time	Animal	Erythema	Edema	Other	Time	Animal	Erythema	Edema	Other
1 H	1	2	0	Er	72 H	1	3	1	Er, Ed
	2	3	1	Er, Ed		2	3	0	Er
	3	3	1	Er, Ed		3	3	1	Er, Ed
	4	3	1	Er, Ed		4	3	0	Er
	5	3	1	Er, Ed		5	2	1	Er
	6	3	1	Er, Ed		6	3	1	Er, Ed
24 H	1	2	1	Er, Ed	7 D	1	2	1	Er, s
	2	3	1	Er, Ed		2	2	0	Er, S
	3	3	2	Er, Ed		3	2	1	Er, Ed, S
	4	3	1	Er, Ed		4	2	0	Er, S
	5	3	2	Er, Ed		5	2	0	Er, S
	6	3	2	Er, Ed		6	2	0	Er, s
48 H	1	3	1	Er, Ed	14 D	1	1	1	Er, s
	2	3	1	Er		2	2	0	Er, s
	3	3	2	Er, Ed		3	2	1	Er, s
	4	3	0	Er		4	2	0	Er, S
	5	3	2	Er, Ed		5	2	0	S
	6	3	1	Er, Ed		6	2	0	S

Total erythema and edema are scored out of 8.
s - Scaling
S - Severe scaling
Er - Erythema extending beyond test site
Ed - Edema extending beyond test site

Table 2. Mean Irritation Scores

Time	Erythema	Edema

27

1 h	2.83	0.83
24 h	2.83	1.5
48 h	3	1.17
72 h	2.83	0.67
7 d	2	0.33
14 d	1.83	0.33
Mean (24 - 72h)	2.89	1.11

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 00 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 4.0/8.0 and the 24 h MIS of 4.33/8.0 indicate moderate irritation, the persistent nature of the irritation and the spread to non-treated areas justify a categorization as severely irritating. Signal words on the primary display panel should read "DANGER - SKIN IRRITANT".

D. Deficiencies - No deficiencies.

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

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

TEST MATERIAL (PURITY): BAS 500 00 F (23.4% a.i.)

SYNONYMS: Headline EC (Pyraclostrobin a.i.)

CITATION: Wiemann, C. (1998) "BAS 500 00 F - BUEHLER Test in Guinea Pigs." Department of Toxicology of BASF Aktiengesellschaft. Lab report no.32H0185/972201. October 1, 1998, MRID # 54118318. Unpublished.

SPONSOR: BASF Corporation.

EXECUTIVE SUMMARY: In a dermal sensitization study with Headline EC (pyraclostrobin, 24.1 %) in aqua bidest, young adult Pirbright White, Dunkin Hartley guinea pigs (20 females) were tested using the method of Buehler. The experiment involved three induction exposures at 25% test formulation and one challenge exposure at 5%. The formulation was applied at 0.5 mL/animal under occlusive wrap.

At 24 hours after the second and third inductions, 2 and 7 animals respectively exhibited scaling of the skin. No irritation or skin sensitization responses were seen following challenge exposure. In this study, **Headline EC 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 00 F

Description:	Liquid brown, clear, store at room temp.
Lot/Batch #:	97-2
Purity:	247.83 g/L a.i.
CAS # TGAI:	
	Concentration/homogeneity verified by HPLC

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

3 **Test animals:**

Species:	Guinea Pigs	
Strain:	Pirbright White, Dunkin Hartley Crl:(HA)BR [SPF]	
Age/weight at treatment initiation:	Young adult / 336 - 385 g	
Source:	Charles River GmbH - WIGA, Kisslegg, FRG	
Housing:	Stainless steel wire mesh cages with plastic-coated grating	
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: March 10, 1998 End: April 9, 1998

2. **Animal assignment and treatment** - Buehler test method. As pretest, two 6-hour occlusive percutaneous applications were performed. The minimum irritant concentration was found to be 10% Headline EC in aqua bidest, however, similar results were seen at 25% so that concentration was used for the inductions. The maximum non-irritant concentration was 5% Headline EC 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 for 6 hours to the anterior left flank, once a week on days 0, 7, and 14. Observations were recorded 24 hours after patch removal.

Challenge was carried out 14 days after the third 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 - No irritation responses were observed in any animals at 25% Headline EC. However, scaling was seen in 2 test group animals after the second induction and in 7 test group animals following the third induction. Persistence of scaling was not provided, but was less than 14 days in all cases because there was no evidence at challenge. One of the animals with scaling after the second induction exposure was clear following the third induction.

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.) Eleven of nineteen guinea pigs had a positive result during the first challenge and 16 of the 19 were positive at second challenge.

D. Author's Conclusions: Based on the evaluation criteria cited under 3.4, the results of this study show that BAS 500 00 F does not have a sensitizing effect on the skin of the guinea pig in the Buehler test under the test conditions chosen.

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

F. Deficiencies - No deficiencies.