DATA EVALUATION RECORD

BAS 510 F

STUDY TYPE: 28-DAY DERMAL TOXICITY - RAT; OPPTS 870.3200 [§82-2]

MRID 45404824

7/24/2002

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task No. 02-01

Primary Reviewer:
Cheryl B. Bast, Ph.D., D.A.B.T

Signature: Cheryl B Bast
Date: DEC 13 2001

Secondary Reviewers:
Sylvia Talmage, Ph.D., D.A.B.T.

Signature: Sylvia S. Talmage
Date: DEC 13 2001

Robert H. Ross, M.S. Group Leader

Signature: Robert H. Ross
Date: DEC 13 2001

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: DEC 13 2001

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory is managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

(1)

EPA Reviewer: A. Levy, Ph.D. **Signature:** Alan C. Levy
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-24-2002
EPA Work Assignment Manager: G. Dannan, Ph.D. **Signature:** _____
Registration Action Branch 3, Health Effects Division (7509C) **Date** _____

DATA EVALUATION RECORD
TXR#: 0050193

STUDY TYPE: 28-Day Dermal Toxicity - rat; OPPTS 870.3200 [§82-2] (rodent); OECD 410.

PC CODE: 128008 **DP BARCODE:** D278384
SUBMISSION NO.: S604279

TEST MATERIAL (PURITY): BAS 510 F (96.3%)

SYNONYMS: None provided

CITATION: Mellert, W., K. Deckardt, W. Kaufmann, W., et al. (2000) BAS 510 F- Repeated dose dermal toxicity study in Wistar rats: Administration for 4 weeks. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, FRG. Laboratory Project Identification number 33C0179/97151, BASF Registration Document number 2000/1013240. June 16, 2000. MRID 45404824. Unpublished.

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

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 45404824), BAS 510 F (96.3% a.i., batch # N 46) was applied to the shaved skin of 10 Wistar rats/sex/dose at dose levels of 0, 100, 250, or 1000 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The solvent was an aqueous solution of 0.5% carboxymethyl cellulose and 0.5% Cremophor® EL.

There were no compound related dermal effects or effects on mortality, clinical signs, body weight, food consumption, hematology, or gross and histologic pathology. Toxicologically insignificant decreases ($p \leq 0.01$) in absolute and relative spleen weight were noted in males at 250 and 1000 mg/kg/day. Toxicologically insignificant decreases in bilirubin concentration were noted in high-dose males ($p \leq 0.05$) and females (N.S). **The systemic and dermal LOAELs are not identified, and the systemic and dermal NOAELs are the limit dose of 1000 mg/kg/day.**

This 28-day dermal toxicity study in the rat is **Acceptable/Guideline.** It satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in rats.

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

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: BAS 510 F

Description:	White solid
Lot/Batch #:	N 46
Purity:	96.3% a.i.
Compound Stability:	Stability proven by HPLC reanalysis after the in-life phase of the study
CAS #:	188425-85-6

2. Vehicle and/or positive control: Aqueous solution of 0.5% carboxymethyl cellulose for low- and mid-dose preparations. 0.5% Cremophor® EL was added to the high-dose preparation to obtain sufficient test material in the dosing preparation. Supplied by Hoechst AG, Frankfurt/Main.

3. Test animals:

Species:	Rat	
Strain:	Wistar Chbb:THOM (SPF)	
Age/weight at study initiation:	Males: 8-9 weeks/ 283-325 g Females: 8-9 weeks/ 177-217 g	
Source:	Boehringer Ingelheim, Pharma KG, FRG	
Housing:	Singly in Typr DK III stainless steel wire mesh cages	
Diet:	Ground Kliba maintenance diet rat/mouse/hamster, Provimi Kliba SA, Kaiseraugst, Switzerland, *ad libitum*	
Water:	Drinking water from water bottles, *ad libitum*	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	not stated
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	13-14 days	

B. STUDY DESIGN:

1. **In life dates**: Start: April 13, 1999; End: May 12, 1999

2. **Animal assignment**: Animals were assigned randomly by computer to the test groups noted in Table 1 so that mean group body weights would be normalized.

TABLE 1: Study design.

Test Group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Dosing Volume (mL)	No. Male	No. Female
Control	0	-	5	10	10
Low	100	2.0	5	10	10
Mid	250	5.0	5	10	10
High	1000	20.0	5	10	10

3. **Dose selection rationale:** The dose levels were selected based on the results from a preliminary study in which BAS 510 F was administered to groups of 3 male and 3 female Wistar rats by the dermal route at dose levels of 0 or 1000 mg/kg/day for 5 days. No treatment-related effects were noted regarding body weight, clinical signs, or macroscopic findings. The limit dose of 1000 mg/kg/day was selected for the high-dose in the 28-day study, and 250 and 100 mg/kg/day were selected as the mid- and low-doses, respectively.

4. **Preparation and treatment of animal skin**: One day before the first application and weekly thereafter, the fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface. The test substance was applied to the skin uniformly using 3 cc syringes, and administration volume was 5 mL/kg body weight, based upon the most recent individual body weight. The skin was then covered for six hours (5 days/week for 4 weeks) using a semiocclusive dressing consisting of 4 layers of porous gauze and an elastic dressing. Rats in the control group were exposed to the vehicle using the same procedure as described for the treated rats. After removal of the dressing, the treated skin was washed with lukewarm water. At the end of the 4 week period, all surviving rats were sacrificed after a 16-20 hour fasting period.

5. **Test Article stability, concentration and homogeneity:**

Stability: In 0.5% Tylose CB. At a nominal concentration of 50 mg/100 ml after 4 or 96 hours, the percents of initial values were 97 and 105, respectively. At a nominal concentration of 20 g/100 ml after 4 or 96 hours, the percents were 104 and 91, respectively.

Concentration and homogeneity: Analyses were performed for 2, 5 or 20 g/100 ml up to 3 samples/concentration (2 times/sample). The percent of nominal concentration was as follows: 2 = 104, 100, 102 and 92; 5 = 105, 102, 94 and 96; 20 = 82, 97, 89, 96 and 100.

6. **Statistics:** Food consumption, body weight, body weight change, and food efficiency data were analyzed using one-way analysis using the F-test. If the resulting p value was ≤ 0.05, a comparison of each group with the control was performed using Dunnett's test. Clinical chemistry and hematology parameters (except for differential blood count) were analyzed using one-way analysis with Kruskal-Wallace test. If the resulting p value was ≤ 0.05, a comparison of each group with the control was performed using the Mann-Whitney U-test for equal medians. Urinalysis parameters were evaluated by pairwise comparison of each dose group with the control using Fischer's exact test. The reviewer considers the analyses used to be appropriate.

C. METHODS:

1. Observations:

1a. **Cageside observations:** Animals were observed twice daily on weekdays and once daily on weekends and holidays for signs of mortality and toxicity.

1b. **Clinical examinations:** Clinical examinations, including detailed examination of the skin, were performed daily before treatment.

1c. **Neurological evaluations:** Open field observations were performed (in an arena 50 x 50 cm with sides 25 cm high) pretest on day -3 or -4 and weekly thereafter on days 2, 9, 16, and 23. Findings were ranked according to degree of severity, where applicable. The following parameters were evaluated: behavior during handling, fur, skin, posture, salivation, respiration, activity/arousal level, tremors, convulsions, abnormal movements, impairment of gait, lacrimation, palpebral closure, exophthalmus, feces (appearance/consistency), urine (volume/color), and pupil size.

2. **Body weight**: Animals were weighed prior to initiation of the study and at the beginning of each study week.

3. **Food consumption and food efficiency:** Food consumption was determined weekly over a period of 7 days and calculated as mean food consumption in grams per animal per day. Group mean food efficiency was calculated as:

   Change in body weight ÷ mean food consumption x 100

4. **Ophthalmoscopic examination:** Eyes were examined on day 0 (all males) or day -1 (all females) with an ophthalmoscope after administration of a mydriatic. Eyes of control and high dose males and females were also examined on day 28 or 27, respectively.

5. **Hematology & Clinical chemistry:** After an overnight fast, blood was collected from the retroorbital venus plexus (non-anesthetized) of all surviving animals on the morning of day 29. The CHECKED (X) parameters were examined.

a. **Hematology**

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count*	-	Reticulocyte count
x	Blood clotting measurements*		
-	(Thromboplastin time)		
-	(Clotting time)		
x	(Prothrombin time)		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200
- Not determined

b. Clinical chemistry

	ELECTROLYTES		OTHER
x	Calcium	x	Albumin*
x	Chloride	x	Creatinine*
x	Magnesium	x	Urea nitrogen*
x	Phosphorus	x	Total Cholesterol*
x	Potassium* (K)	x	Globulins
x	Sodium* (NA)	x	Glucose*
	ENZYMES (more than 2 hepatic enzymes, eg., *)	x	Total bilirubin
x	Alkaline phosphatase (AP)*	x	Total protein*
-	Cholinesterase (ChE)	x	Triglycerides
-	Creatine phosphokinase	-	Serum protein electrophoresis
-	Lactic acid dehydrogenase (LDH)		
x	Alanine amino-transferase (ALT/also SGPT)*		
x	Aspartate amino-transferase (AST/also SGOT)*		
x	Gamma glutamyl transferase (GGT)*		
-	Glutamate dehydrogenase		
-	Sorbitol dehydrogenase*		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200
- Not determined

6. **Urinalysis***: Individual animals were transferred to metabolism cages (food and water withdrawn) and urine was collected overnight on days 24 or 25. The CHECKED (X) parameters were examined.

x	Appearance*	x	Glucose*
x	Volume*	x	Ketones
x	Specific gravity / osmolality*	x	Bilirubin
x	pH*	x	Blood / blood cells*
x	Sediment (microscopic)	-	Nitrate
x	Protein*	x	Urobilinogen

* Optional for 28-day dermal toxicity studies
- Not determined

7. **Sacrifice and pathology:** All animals were sacrificed on schedule by decapitation under CO_2 anesthesia and the exsanguinated animals subjected to gross pathological examination. Selected tissues were fixed in 4% formaldehyde solution and stained with Hematoxylin and Eosin. Microscopic examination was performed on control and high-dose tissues and on all gross lesions and the spleen from low- and mid-dose animals as well. The CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

6

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
-	Tongue	x	Aorta, thoracic*	xx	Brain*+
x	Salivary glands*	xx	Heart*+	x	Peripheral nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen*+	x	Eyes (optic nerve)*
x	Jejunum*	xx	Thymus*+		GLANDULAR
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		UROGENITAL	x	Lacrimal gland
x	Colon*	xx	Kidneys*+	x	Parathyroid*
x	Rectum*	x	Urinary bladder*	xx	Thyroid*
xx	Liver*+	xx	Testes*+		OTHER
-	Gall bladder* (not rat)	xx	Epididymides*+	x	Bone (sternum and/or femur)
-	Bile duct* (rat)	x	Prostate*	x	Skeletal muscle
x	Pancreas*	x	Seminal vesicles*	x	Skin* (treated & untreated areas)
	RESPIRATORY	xx	Ovaries*+	x	All gross lesions and masses*
x	Trachea*	xx	Uterus*+		
x	Lung*	x	Mammary gland*		
x	Nose*	x	Oviducts		
x	Pharynx*				
x	Larynx*				

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200
+ Organ weights required.
- Not taken

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** No treatment-related effects were noted. One male treated with 100 mg/kg showed piloerection on day 22. Due to the isolated occurrence and lack of a dose-response, this finding is considered incidental to treatment.

2. **Mortality** : No treatment-related deaths were noted. One female administered 1000 mg/kg exhibited red discolored urine from day 7 to 13 and died on day 13. This death was attributed to septicemia and is considered incidental to treatment (see Results Section G).

3. **Neurological evaluations:** No treatment-related effects were noted.

4. **Dermal irritation:** No dermal effects were noted.

B. BODY WEIGHT AND WEIGHT GAIN: There were no treatment-related effects on body weight or body weight gain.

C. FOOD CONSUMPTION AND EFFICIENCY:

1. **Food consumption:** There were no treatment-related effects on food consumption.

2. **Food efficiency:** There were no treatment-related effects on food efficiency.

D. OPHTHALMOSCOPIC EXAMINATION: No treatment-related effects were noted.

E. BLOOD ANALYSES:

1. Hematology: No treatment-related effects were noted.

2. Clinical chemistry: Decreased bilirubin was observed in high-dose females (N.S.; 2.04±0.60 treated vs. 2.61±0.41 control) and males ($p \leq 0.05$; 2.64 ± 0.39 treated vs. 3.02 ± 0.51 control). This decrease is considered treatment-related, but toxicologically insignificant due to the small magnitude of change and relatively large standard deviations.

F. URINALYSIS: There were no effects on any of the parameters examined.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight - Absolute spleen weight was decreased ($p \leq 0.01$) in males administered 250 mg/kg (16% decrease) and 1000 mg/kg (17% decrease) compared to controls. Relative spleen weight was also decreased ($p \leq 0.01$) in males administered 250 mg/kg (15% decrease) and 1000 mg/kg (15% decrease) compared to controls. In the absence of accompanying histopathology, the spleen weight effects are of questionable toxicological significance. No other organ weight effects were noted.

2. Gross pathology - No treatment-related effects were noted. In the high-dose female that died prior to study termination, a unilateral kidney "focus" and bilateral "pelvic dilation" were noted. This female also had a slight dilation of the ureter, dialation with a bloody fluid content in the urinary bladder, and slightly enlarged iliac lymph nodes. This rat also showed a grey-red discoloration of the adrenal cortex.

3. Microscopic pathology - No treatment-related effects were noted.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: There were no compound related dermal effects or effects on mortality, clinical signs, body weight, food consumption, hematology, or gross and histologic pathology. Decreases ($p \leq .01$) in absolute and relative spleen weight were noted in males at 250 and 1000 mg/kg/day; however, in the absence of any accompanying histopathology, these weight changes are considered toxicologically insignificant. The authors report that previous studies with BAS 510 F produced hepatic enzyme induction. It was assumed that the observed decreases in bilirubin concentration noted in high-dose males ($p \leq 0.05$) and females (N.S), was a result of this enzyme induction and thus may be considered a toxicologically insignificant adaptive response.

B. **REVIEWER COMMENTS:** This is an acceptable study. Animals were tested to the limit dose of 1000 mg/kg.

Based on the results of this study, the systemic and dermal LOAEL for BAS 510 F in male and female rats is not identified, and the systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day.

C. **STUDY DEFICIENCIES:** None identified.

DATA FOR ENTRY INTO ISIS

Subchronic Dermal (28 day) Study - rodents (870.3200)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
128008	45404824	subchronic	rat	4 weeks	dermal	dermal	100-1000	0, 100, 250, 1000	1000	not identified	NA	Systemic
128008	45404824	subchronic	rat	4 weeks	dermal	dermal	100-1000	0, 100, 250, 1000	1000	not identified	NA	Dermal

10