DATA EVALUATION RECORD

BAS 510 F/128008

STUDY TYPE: 90-DAY ORAL TOXICITY [FEEDING-MICE] [OPPTS 870.3100 (§82-1A)] (RODENT); OECD 408.

MRID 45404821

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
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Task Order No. 02-06

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(1)

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DATA EVALUATION RECORD
TXR#: 0050193

STUDY TYPE: 90-Day Oral Toxicity [feeding-mice] OPPTS 870.3100 [§82-1a] (rodent); OECD 408.

PC CODE: 128008

DP BARCODE: D278384
SUBMISSION NO.: S604279

TEST MATERIAL (PURITY): BAS 510F (95.3%)

SYNONYMS: None given

CITATION: Mellert, W., K. Deckardt, W. Kaufmann, et. al. (2000) BAS 510 F - Subchronic oral toxicity study in C57BL mice. Administration in the diet for 3 months. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, FRG. Laboratory Project ID 60C0179/97060. March 1, 2000. MRID 45404821. Unpublished.

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

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 45404821) BAS 510 F (95.3% a.i., batch # N 26) was administered to 10 C57Bl/6JRj mice/sex/dose in the diet at dose levels of 0, 150, 1000, 4000, or 8000 ppm (equivalent to 0, 29, 197, 788, and 1518 mg/kg bw/day for males and 0, 42, 277, 1184, and 2209 mg/kg bw/day for females).

There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, hematology or gross pathology of either sex. Cholesterol levels were decreased 12-28% in 1000-, 4000-, and 8000-ppm group males, and total protein, albumin, and globulin values were slightly decreased (3-7%) in 4000- and 8000-ppm group males. Alanine aminotransferase activity was increased in 4000- and 8000-ppm group females. The liver was the target organ. Absolute liver weight was increased (8-27%) in 1000-, 4000-, and 8000-ppm group males and 150-, 4000-, and 8000-ppm group females. Relative liver weight was increased 8-29% in both sexes at 1000, 4000, and 8000 ppm. The livers of control and treated groups of both sexes showed a diffuse fatty infiltration with a centrilobular pronouncement, which was graded as severe in some 4000- and 8000-ppm group males. **Under the conditions of this study, the LOAEL for BAS 510F in mice is 4000 ppm (788 mg/kg/day) for males, based on increased liver weights and increased incidence of marked fatty change in the liver, and ≥8000 ppm (2209 mg/kg/day)**

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for females. The NOAEL is 1000 ppm (197 mg/kg/day) for males, and was not established for females.

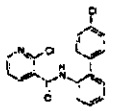
This 90-day oral toxicity study in the mouse is **acceptable (guideline)** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in mice.

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

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** BAS 510 F

Description:	pulverized white solid
Lot/Batch #:	N 26
Purity:	95.3 % a.i.
Compound Stability:	Proven by reanalysis after the in-life phase of the study (90 days)
CAS # of TGAI:	188425-85-6
Structure:	

2. **Vehicle and/or positive control:** The test material was incorporated into the diet. There was no positive control in this study.

3. **Test animals:**

Species:	Muse	
Strain:	C57BL/6JRj	
Age/weight at study initiation:	49 days/males 20.3-23.7 g: females 16.0-19.1 g	
Source:	Centre d'Elevage R. Janvier. France	
Housing:	Individually in Makrolon cages. Type M I with wire covers.	
Diet:	Ground Kliba maintenance diet rat/mouse/hamster meal, *ad libitum*	
Water:	Mnicipal drinking water, *ad libitum* (water bottles)	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Not given
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	6 days	

B. STUDY DESIGN:

1. **In life dates**: Start: October 27, 1997; End: January 28, 1998

2. **Animal assignment**: Animals were separated by sex and assigned randomly, according to weight, to the test groups in Table 1.

TABLE 1: Study design					
Test goup	Conc. in det (ppm)	Dose to animal (mg/kg/day)		# Male	# Female
		Male	Female		
Control	0	0	0	10	10
Low	150	29	42	10	10
Low-mid	1000	197	277	10	10
High-mid	4000	788	1184	10	10
High	8000	1518	2209	10	10

3. **Dose selection rationale:** The high dose level (8000 ppm) was selected to be equivalent to a test material intake of at least 1 g/kg bw/day (a limit test). The 1000 and 4000 ppm levels were projected as mid-range doses, and 150 ppm as a low dose.

4. **Diet preparation and analysis:** Diet was prepared every four weeks by mixing appropriate amounts of test substance with Kliba maintenance diet rat/mouse/hamster meal (Klingentalmuhle AG, Kaiseraugst, Switzerland) and was stored at room temperature. Homogeneity of the 100 and 15,000 mg/kg treated diets (Kliba 3422 meal) was determined in a parallel three-month rat study (Project No. 50S0179/97058) that used the same mixing procedure. Stability of the test substance in the 100 ppm-diet was determined after 0, 13, and 32 days at room temperature prior to the current study. During the current study, samples of treated diet were analyzed for stability and concentration at the start of the study and after eight weeks.

Results:

Homogeneity analysis: At nominal concentrations of 100 and 15,000 mg/kg, results were 104.4±0.6% and 101.2±0.7% of the target values, respectively.

Stability analysis: The concentration of the test substance in the diet was 97.5% and 97.9% of nominal (100 ppm) after 13 and 32 days, respectively.

Concentration analysis: The mean concentration of the test substance in the diet was 96.3-102.1% of the target concentrations after eight weeks.

The analytical data indicate that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Body weight, body weight gain, and food consumption were analyzed by parametric one-way analysis using the F-test (ANOVA). If the p-value was ≤ 0.05, Dunnett's test was used to compare each group with the control group. For all clinical pathology parameters (except differential blood count), non-parametric one-way analysis was performed using the Kruskal-Wallis test. If the p-value was ≤ 0.05, a pairwise comparison with the control group was made using the Mann-Whitney U-test. Organ weights were analyzed by non-parametric analysis using the Kruskal-Wallis test. If the p-value was ≤ 0.05, a pairwise comparison with the control group was made using the Wilcoxon test for the hypothesis of equal medians. The reviewer considers the above analyses to be appropriate.

C. METHODS:

1. Observations:

1a. **Cageside observations:** Animals were inspected twice daily Monday-Friday (once daily weekends and holidays) for mortality and signs of toxicity.

1b. **Clinical examinations:** Clinical examinations were conducted weekly.

1c. **Neurological evaluations:** Neurologic evaluations were not conducted.

2. **Body weight:** Animals were weighed prior to the study start, on Day 0, and weekly thereafter.

3. **Food consumption and compound intake:** Food consumption (g/animal/day) was determined weekly and mean daily diet consumption was calculated as g food/kg body weight/day. Compound intake (mg/kg body weight) values were calculated from the food consumption and body weight gain data. Food efficiency was not calculated.

4. **Ophthalmoscopic examination:** Ophthalmoscopic examinations were not conducted.

5. **Hematology & clinical chemistry:**

Blood was collected from the retroorbital venus plexus for hematology and clinical chemistry from all surviving animals at study end after a 16-hour fast. 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
-	Blood clotting measurements*		
-	(Thromboplastin time)		
-	(Clotting time)		
-	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
- Not examined

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*	x	Globulins
x	Sodium*	x	Glucose*
	ENZYMES	x	Total bilirubin
x	Alkaline phosphatase (ALK)*	x	Total protein (TP)*
-	Cholinesterase (ChE)	x	Triglycerides
-	Creatine phosphokinase	-	Serum protein electrophoresis
-	Lactic acid dehydrogenase (LDH)		
x	Alanine aminotransferase (ALT/also SGPT)*		
x	Aspartate aminotransferase (AST/also SGOT)*		
-	Sorbitol dehydrogenase*		
x	Gamma glutamyl transferase (GGT)*		
-	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
- Not examined

6. **Urinalysis:** Urinalysis is not required and was not conducted.

7. **Sacrifice and pathology:** All animals were sacrificed by decapitation under carbon dioxide anesthesia on schedule and subjected to gross pathological examination, with the CHECKED (X) tissues collected for histological examination. The lungs, liver, kidneys, and gross lesions were examined for all groups; all other tissues were examined for the control and high-dose groups only. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
-	Tongue	x	Aorta*	xx	Brain*+
x	Salivary glands*	x	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*	x	Thymus*+		GLANDULAR
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		UROGENITAL	x	Lacrimal gland
x	Colon*	xx	Kidneys*+	x	Parathyroid*
x	Rectum*	x	Urinary bladder*	x	Thyroid*
xx	Liver*+	xx	Testes*+		OTHER
x	Gall bladder (not rat)*	x	Epididymides*+	x	Bone (sternum and/or femur)
-	Bile duct (rat)	x	Prostate*	x	Skeletal muscle
x	Pancreas*	x	Seminal vesicles*	x	Skin*
	RESPIRATORY	xx	Ovaries*+	x	All gross lesions and masses*
x	Trachea*	x	Uterus*+		
x	Lung*	x	Mammary gland*		
-	Nose*	x	Vagina		
-	Pharynx*	x	Oviduct		
-	Larynx*				

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
+ Organ weights required for rodent studies. - = Not taken

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity**: There were no treatment-related clinical signs of toxicity.

2. **Mortality**: No animals died during the study.

3. **Neurological Evaluations**: Neurological evaluations were not conducted.

B. BODY WEIGHT AND WEIGHT GAIN: There were no treatment-related effects on body weight. See Table 2.

Table 2. Body weights (g) and body weight gains (g) for mice fed BAS 510 F for 13 weeks.					
Day	Dietary concentration (ppm)				
	0	150	1000	4000	8000
Males					
body wt. 0	21.5 ± 0.6a	21.6 ± 1.0	21.6 ± 0.9	21.6 ± 0.8	21.4 ± 0.7
body wt. 28	25.3 ± 0.8	25.1 ± 1.6	24.8 ± 1.2	24.9 ± 0.8	25.0 ± 1.3
body wt. 63	27.9 ± 1.2	27.5 ± 2.0	27.2 ± 1.6	27.4 ± 0.9	27.5 ± 1.7
body wt. 91	28.9 ± 1.4	28.8 ± 2.2	28.5 ± 1.7	28.5 ± 1.0	28.9 ± 2.4
body wt gain 0-91	7.4 ± 1.5	7.2 ± 1.7	6.8 ± 1.1	6.9 ± 1.1	7.5 ± 1.9
Females					
body wt. 0	17.4 ± 0.5	17.5 ± 0.9	17.1 ± 0.6	17.5 ± 0.5	17.9 ± 1.0
body wt. 28	20.9 ± 0.8	21.4 ± 1.3	20.9 ± 1.0	20.8 ± 0.7	21.4 ± 1.2
body wt. 63	22.1 ± 1.0	23.0 ± 1.4	21.9 ± 1.3	21.9 ± 0.8	22.1 ± 0.9
body wt. 91	22.5 ± 1.1	23.1 ± 2.3	22.2 ± 1.4	22.6 ± 0.8	22.7 ± 0.9
body wt gain 0-91	5.1 ± 0.9	5.7 ± 2.3	5.1 ± 1.2	5.1 ± 0.5	4.9 ± 0.9

Data taken from Tables 1A007-014, pp. 56-63; MRID 45404821.
a Value is group mean ± S.D.
10 mice/sex/group

C. FOOD CONSUMPTION AND COMPOUND INTAKE :

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

2. **Compound consumption**: Compound consumption is given in Table 1.

3. **Food efficiency**: Food efficiency was not calculated.

D. OPHTHALMOSCOPIC EXAMINATION: Ophthalmoscopic examinations were not conducted.

E. BLOOD ANALYSES:

1. **Hematology**: There were no treatment-related changes in hematology parameters.

2. **Clinical chemistry**: Selected clinical chemistry results are presented in Table 3. In males, total protein, albumin, and globulin values were slightly but statistically decreased (3-7%, $p \leq 0.01$) in the 4000- and 8000-ppm groups. Cholesterol was statistically decreased (12-28%, $p \leq <0.001$) in the 1000-, 4000-, and 8000-ppm groups. In females, ALT activity was statistically increased (17-19%, $p \leq 0.05$) in the 4000- and 8000-ppm groups.

TABLE 3. Selected clinical chemistry parameters for mice fed BAS 510 F for 13 weeks

Parameter	Dietary concentration (ppm)				
	0	150	1000	4000	8000
Males					
Alanine aminotransferase (mykat/L)	0.87±0.27	0.75±0.14	0.91±0.30	0.96±0.23	0.95±0.29
Creatinine (mymol/L)	38.6±1.4	37.5±4.5	35.0±3.3** (91)[a]	37.5±1.6	34.8±2.5** (90)
Total protein (g/L)	62.49±1.83	62.46±2.84	61.13±2.66	59.90±1.52** (96)	59.21±2.32** (95)
Albumin (g/L)	38.77±0.97	38.81±1.76	37.92±1.49	37.53±0.93** (97)	36.82±1.21** (95)
Globulins (g/L)	23.72±1.12	23.65±1.33	22.76±1.08	22.39±0.99** (94)	22.06±1.07** (93)
Cholesterol (mmol/L)	2.57±0.28	2.53±0.35	2.26±0.19** (88)	1.91±0.25*** (74)	1.84±0.16*** (72)
Females					
Alanine aminotransferase (mykat/L)	1.03±0.16	0.98±0.18	1.13±0.16	1.23±0.22* (119)	1.21±0.23* (117)
Creatinine (mymol/L)	38.3±2.8	37.9±4.5	38.5±3.1	37.9±2.4	36.5±3.8
Total protein (g/L)	60.33±3.02	58.17±2.43	58.75±3.64	58.54±1.92	57.30±3.40
Albumin (g/L)	39.15±1.87	36.94±2.38	38.56±2.45	38.53±1.08	37.63±2.17
Globulins (g/L)	21.18±1.43	21.05±2.22	20.51±1.43	19.92±1.32	19.67±1.32
Cholesterol (mmol/L)	1.76±0.29	1.96±0.49	1.66±0.45	1.59±0.30	1.57 ± 0.17

Data taken from Table IB, pp. 74-79, MRID 45404821

[a]Numbers in parentheses are percent of control value, calculated by the reviewer.

*Significantly different from controls, $p \leq 0.05$

**Significantly different from controls, $p \leq 0.01$

***Significantly different from controls, $p \leq 0.001$

F. Urinalysis: Urinalysis was not conducted.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight: Selected organ weight data are presented in Table 4. In males, absolute liver weight was significantly increased (11-27%, $p \leq 0.05$ or 0.01) in the 1000-, 4000-, and 8000-ppm groups. Relative (to body weight) liver weight was also significantly increased ($p \leq 0.01$, 13-29%) in those groups. In females, absolute liver weight was significantly increased (8-22%, $p \leq 0.05$ or 0.01) in the 150-, 4000-, and 8000-ppm groups. Relative liver weight was significantly increased (8-21%, $p \leq 0.05$ or 0.01) in the 1000-, 4000-, and 8000-ppm groups.

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TABLE 4. Selected mean organ weights (mg) and liver/body weight (%) of mice fed BAS 510 F for 13 weeks

Parameter	Dietary concentration (ppm)				
	0	150	1000	4000	8000
Males					
Final body weight (g)	24.97±1.271	24.89±2.275	24.58±1.836	24.57±1.112	24.87±2.526
Liver	1096.8±76.525	1113.5±100.272	1228.2±151.608* (112)[a]	1220.0±107.929** (111)	1396.5±74.256** (127)
Liver/body weight	4.392±0.193	4.509±0.56	5.005±0.574** (114)	4.969±0.425** (113)	5.658±0.563** (129)
Kidneys	362.3±25.369	379±16.337	360.8±20.65	354.2±29.996	351.5±20.184
Testes	226.8±14.773	223.6±12.376	235.6±17.815	228.6±13.201	224.2±13.661
Spleen	55.7±6.8	61.6±15.479	59.9±9.848	57.9±8.034	93.9±122.191b
Brain	458.3±14.507	471.7±12.858* (103)	474.7±22.191	461.1±13.835	457.4±8.168
Adrenals	4.1±0.568	4.1±0.568	4.1±0.568	4.6±0.966	4.3±0.675
Females					
Final body weight (g)	18.8±0.859	19.72±1.828	18.58±1.33	19.±1.017	19.08±0.795
Liver	886.9±66.427	955.6±86.01* (108)	946.6±91.757	995.2±138.421* (112)	1085±110.951** (122)
Liver/body weight	4.723±0.363	4.872±0.531	5.091±0.253* (108)	5.227±0.567* (111)	5.7±0.672** (121)
Ovaries	15±3.3	15.3±2.751	14±2.404	14.5±2.273	13.7±1.703
Kidneys	285.2±19.217	295.2±22.89	275.9±18.988	284.7±17.487	286.5±20.517
Adrenals	7.3±1.059	8.4±1.265	8.4±1.174	8.5±1.354	8.4±0.966

*Significantly different from control group, $p \leq 0.05$
**Significantly different from control group, $p \leq 0.01$
[a]Numbers in parentheses are percent of control value. calculated by the reviewer.
b "Outlier/error": 441 mg; next heaviest = 71 mg; without 441, mean = 55.3 mg.
Data taken from Table 1C, pp. 80-83, MRID 45404821

2. **Gross pathology:** There were no treatment-related gross pathology findings.

3. **Microscopic pathology:** The livers of the control and treated groups of both sexes showed a mostly diffuse, fatty infiltration with a centrilobular pronouncement. In males, the fatty change was more severe in the 4000- and 8000-ppm groups than in the lower-dose groups (Table 4). Greater severity at the higher doses did not occur in the females. All other microscopic findings in both sexes were incidental and not treatment-related.

TABLE 5. Incidence of diffuse fatty change in the liver of mice fed BAS 510 F for 13 weeks					
Dietary concentration (ppm)	0	150	1000	4000	8000
Males					
Minimal	0/10	0/10	0/10	0/10	0/10
Slight	5/10	3/10	6/10	1/10	1/10
Moderate	5/10	7/10	3/10	6/10	4/10
Marked, severe	0/10	0/10	0/10	3/10	5/10
Total	10/10	10/10	9/10	10/10	10/10
Females					
Minimal	2/10	1/10	0/10	4/10	2/10
Slight	2/10	3/10	2/10	3/10	4/10
Moderate	5/10	4/10	7/10	1/10	2/10
Marked, severe	0/10	0/10	1/10	0/10	1/10
Total	9/10	8/10	10/10	8/10	9/10

Information taken from Table IC, pp. 90-91, MRID 45404821

III. DISCUSSION AND CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that treatment-related effects were found at doses of 1000 to 8000 ppm, and that the target organ was the liver. The treatment-related effects for males were identified as decreased cholesterol at 1000, 4000, and 8000 ppm; increased liver weight at 8000 ppm; increased incidence of marked fatty change in the liver at 4000 and 8000 ppm; and decreased total protein, albumin, and globulin levels at 4000 and 8000 ppm. Treatment-related effects for females were increased liver weight and increased ALT activity at 4000 and 8000 ppm. Since the decrease in cholesterol in 1000-ppm males was considered to be of no toxicological relevance, the investigators designated the NOAEL as 1000 ppm (197 mg/kg/day in males, 277 mg/kg/day in females).

B. REVIEWER COMMENTS: The reviewer concurs that the decrease in cholesterol in the 1000-ppm males is of no toxicological consequence, and regards the decreases in the 4000- and 8000-ppm males to be inconsequential as well. While the decreases in total protein, albumin and globulins in the 4000- and 8000-ppm group males are statistically significant and likely treatment-related, they are of slight magnitude (≤7%), and are not considered to be biologically significant. The changes noted in the livers of the female mice are considered to be adaptive.

The LOAEL is 4000 ppm (788 mg/kg/day) for males, based on increased liver weights and increased incidence of marked fatty change in the liver, and ≥8000 ppm (2209 mg/kg/day) for females. The NOAEL is 1000 ppm (197 mg/kg/day) for males, and was not established for females.

C. STUDY DEFICIENCIES: Minor deficiencies were that the air change frequency of the animal room was not provided, and no blood-clotting measurement was performed. These deficiencies would not affect the outcome of the study. A major deficiency is that the OPPTS 870.3100-required ophthalmoscopic examinations were not conducted.

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DATA FOR ENTRY INTO ISIS

Subchronic (90 day) Oral Study - rodents (870.3100)

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	45404821	subchronic	mouse	90 days	oral	dietary	29-2209	males: 0, 29, 197, 788, 1518 females: 0, 42, 277, 1184, 2209	males: 197 females: none	males: 788 females: ≥2209	liver	

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