DATA EVALUATION RECORD

BAS 510 F

STUDY TYPE: 90-DAY ORAL TOXICITY - RAT
[OPPTS 870.3100 (§82-1); OECD 408]
MRID 45404822

7/23/2002

Prepared for

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

Prepared by

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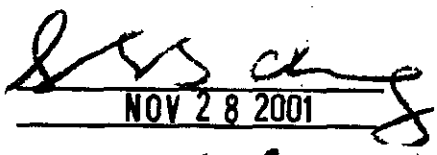
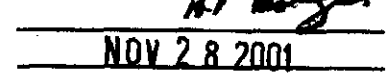
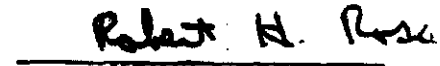
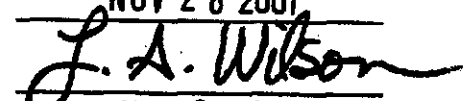
Task Order No. 02-06

Primary Reviewer: Susan Chang, M.S.	Signature: Date:	 NOV 2 8 2001
Secondary Reviewers: H. Tim Borges, Ph.D., D.A.B.T.	Signature: Date:	 NOV 2 8 2001
Robert H. Ross, M.S., Group Leader	Signature: Date:	 NOV 2 8 2001
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	 NOV 2 8 2001

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Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Department of Energy under contract number DE-AC05-00OR22725.

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DATA EVALUATION RECORD

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

PC CODE: 128008

DP BARCODE: D278384
SUBMISSION NO.: S604279

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

SYNONYMS: Reg. No. 300 355

CITATION: Mellert, W., K. Deckardt, W. Kaufmann, et. al. (2000) BAS 510 F - Subchronic oral toxicity study in Wistar rats, administration in the diet for 3 months. Experimental Toxicity and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, FRG. Laboratory project identification 50S0179/97058, April 27, 2000. MRID 45404822. 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 45404822) BAS 510 F (95.3% a.i., Tox Charge II/N 26) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 100, 500, 2000, 5000, or 15,000 ppm (equivalent to 0, 7, 34, 137, 347, or 1055 mg/kg bw/day for males and 0, 8, 40, 159, 395, or 1225 mg/kg bw/day for females). There were no treatment-related effects on the following parameters: clinical signs of systemic toxicity, mortality, body weight, food consumption, food efficiency, ophthalmology, hematology or urinalysis.

While there were several statistically significant effects of some clinical chemistry parameters, none were of biological or toxicological significance with the exception of γ-glutamyltransferase (GGT) activity. GGT activity was statistically increased >133% in male rats receiving ≥2000 ppm and female rats receiving ≥5000 ppm test material. The increase in GGT activity was consistent with hepatic centrilobular hypertrophy. In support, the absolute and/or relative liver weights of male and female rats receiving ≥5000 ppm test material were increased and the incidence of centrilobular hypertrophy was statistically increased in 5000 and 15,000 ppm male rats and in 15,000 ppm female rats.

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The absolute and relative thyroid weights were statistically increased >14% relative to controls in the 2000 ppm and 15,000 ppm male rats and in the 5000 and 15,000 ppm female rats. In conjunction, the incidence of diffuse hyperplasia and thyroid follicular epithelial hypertrophy were significantly increased in male rats (≥7/10) receiving ≥2000 ppm. However, no similar increase was noted in female rats. The increased absolute and relative thyroid weights of treated male and female rats and the increased hyperplasia and follicular cell hypertrophy suggests a disturbance of thyroid homeostasis.

The LOAEL for the study is 2000 ppm (137 mg/kg bw/day) BAS 510 F for male rats and 5000 ppm (395 mg/kg bw/day) for female rats based on the increases of absolute and relative thyroid weights in both sexes and the increased incidence of thyroid hyperplasia and follicular epithelial hypertrophy in male rats. The corresponding NOAELs would be 500 ppm (34 mg/kg bw/day) for male rats and 2000 ppm (159 mg/kg bw/day) for female rats.

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

COMPLIANCE: Signed and dated Flagging Criteria, GLP, Quality Assurance, and Data Confidentiality statements were provided. This study was conducted in compliance with the GLP provision of the "Chemical Act" (Chemikaliengesetz; Bundesgesetzblatt 1994, Teil 1, 29.07.94; FR Germany) and with the "OECD Principles of GLP (Paris, 1981)."

I. MATERIALS AND METHODS

A. MATERIALS:

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

Description:	white powder, stable for the duration of the study
Lot/Batch #:	Tox Charge II/N 26
Purity:	95.3% a.i.
Compound Stability:	"Proven by reanalysis after the in life phase of the study (purity 95.3%)"
CAS # of TGAI:	188425-85-6
	[Structure]

2. **Vehicle and/or positive control:** None; the test material was administered in the feed.

3. **Test animals:**

Species:	rat
Strain:	Wistar Chbb:THOM (SPF)
Age/weight at study initiation:	42±1 days: males: 167-201 g and females: 132-155 g
Source:	Boehringer Ingelheim Pharma KG
Housing:	singly in type DK III stainless steel wire mesh cages
Diet:	ground Kliba maintenance diet rat/mouse/hamster, meal, *ad libitum*
Water:	drinking water, *ad libitum* (water bottles)

Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	not reported
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	11 days	

B. STUDY DESIGN:

1. **In life dates** - Start: October 10, 1997; End: January 14, 1998

2. **Animal assignment**: Animals were assigned to the test groups noted in Table 1 according to body weight by computer randomization.

TABLE 1. Study design

Test Group	Conc. in Diet (ppm)	Dose to Animal (mg/kg/day)		# Male	# Female
		Males	Females		
Control	0	0	0	10	10
1	100	7	8	10	10
2	500	34	40	10	10
3	2000	137	159	10	10
4	5000	347	395	10	10
5	15,000	1055	1225	10	10

Data taken from pp. 20 and 42, MRID 45404822.

3. **Dose selection rationale:**

The dose levels were selected based on 100 ppm as the lowest concentration, 500-5000 ppm as the mid concentrations, and 15,000 ppm as high concentration. The high dose was equivalent to a test material intake of greater than 1000 mg/kg bw/day; the highest dose to be tested for non-toxic test material in a limit test. No evidence was presented to indicate a range-finding study was done.

4. **Diet preparation and analysis:**

Test diets were prepared by weighing the appropriate amount of the test material for each level and mixing it with a small amount of the ground Kliba maintenance diet rat/mouse/ hamster meal in a beaker. Subsequently a premix was prepared in a BOSCH household mixer by adding an appropriate amount of food. These premixes were then mixed in a GERB. LÖDIGE laboratory mixer for about 10 minutes with an appropriate amount of basal diet to obtain the proper concentration. Diets were prepared every 4 weeks.

Stability of the test material in feed was tested prior to the study using BAS 510 F, Batch No. N 21 at 100 ppm stored at ambient temperature for a test period of 32 days. Homogeneity was tested prior to the study using BAS 510 F, Batch No. N 26 in Kliba 3433 Mehl feed at 100 ppm and 15,000 ppm. Prior to the study, samples of treated food (BAS 510 F, Batch No.

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N 26 in Kliba 3433 Mehl feed) were analyzed at the start of dosing and after ~8 weeks (stored in freezer) at all dose concentrations.

Results -

Homogeneity analysis: The average analytical concentrations were 103.7-104.8 ppm and 15,097-15,284 ppm, respectively. The percent of nominal concentrations were 104.4% and 101.2%, respectively, for the 100 and 15,000 ppm diets.

Stability analysis: The mean value of the 100 ppm diet was 99.9, 97.4, and 97.8 ppm on days 0, 13, and 32, respectively. The percent of initial content was 97.5 and 97.9% on days 13 and 32, respectively.

Concentration analysis: At the beginning of the study, the analytical concentrations were 104.4, 100.2, 102.7, 101.7, and 101.2% of nominal for the 100, 500, 2000, 5000, and 15,000 ppm diets, respectively. Eight weeks later, the analytical concentrations were 104.8, 100.4, 103.1, 103.2, and 100.1% of nominal for the 100, 500, 2000, 5000, and 15,000 ppm diets, respectively.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable. However, the tests were conducted on BAS 510 F with a different Batch No. and prior to the current study.

5. **Statistics**: Means and standard deviations were computed. Parametric one-way analysis using two-sided ANOVA was done for each sex on body weight, body weight change, food consumption, and food efficiency. If the resulting p-value was ≤ 0.05, Dunnett's test was used to identify significant differences from control. Non-parametric one-way analysis was done using the Kruskal-Wallis test (two-sided) for each sex on clinical pathology data (except differential blood count); significant results ($p<0.05$) were analyzed by the Mann-Whitney U-test for differences from control. Urinalysis data, except volume, color, turbidity, and specific gravity, were computed by pairwise comparison of each treatment group with the control group using Fisher's exact test. Organ weight data were analyzed by two-sided Kruskal-Wallis and if the resulting p-value was ≤ 0.05, a pairwise comparison of each dose group with the control group was done using the Wilcoxon test. Levels of significance of 1%, 5%, and/or 0.2% were flagged.

   The reviewer considered the analyses appropriate.

C. METHODS:

1. Observations:

1a. Cageside observations: Animals were inspected twice daily on week days and once during weekends and holidays for signs of toxicity and mortality.

1b. **Clinical examinations**:

Clinical examinations were conducted twice daily during week days and once during weekends and holidays and a comprehensive clinical examination was conducted once weekly.

1c. **Neurological evaluations**: Neurological evaluations were not done.

2. **Body weight**: Animals were weighed prior to dosing on day 0, and weekly thereafter.

3. **Food consumption and compound intake**: Food consumption for each animal was determined and mean daily diet consumption was calculated as g food/animal/day. Food efficiency (body weight gain in g/food consumption in g per unit time X 100) and compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. **Ophthalmoscopic examination**: Eyes were examined on all animals one day before the start of dosing. The eyes of rats in the control and 15,000 ppm groups were examined on day 88.

5. **Hematology & Clinical Chemistry**: Blood was collected in the morning for hematology and clinical chemistry evaluations from all non-fasted unanesthetized animals on day 90. 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)		
x	(Prothrombin time)		

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

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 electrophores
-	Lactic acid dehydrogenase (LDH)		
x	Alanine aminotransferase (ALT/also SGPT)*		
x	Aspartate aminotransferase (AST/also SGOT)*		
-	Sorbitol dehydrogenase*		
x	Gamma glutamyltransferase (GGT)*		
-	Glutamate dehydrogenase		

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

6. Urinalysis[1]: Urine was originally collected overnight from fasted animals on day 89, but the samples were not examined due to technical failure. Additional urine was collected on days 94-96. 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)	x	Nitrate or nitrite
x	Protein*	x	Urobilinogen

[1] Optional for 90-day oral rodent studies
* Recommended for 90-day oral rodent studies

7. Sacrifice and pathology

All animals were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. 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/sciatic 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*	xx	Thyroid*
xx	Liver*+	xx	Testes*+		**Other**
NA	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/oviducts/vagina*+		
x	Lung*	x	Mammary gland*		
-	Nose*				
-	Pharynx*				
-	Larynx*				

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

II. RESULTS

A. OBSERVATIONS:

1. **Clinical signs of toxicity**: No abnormal clinical signs were noted during the study.

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

3. **Neurological evaluations**: Not done.

B. BODY WEIGHT AND WEIGHT GAIN: No test material-related changes were noted. See Table 2.

Table 2. Body weights (g) (± S.D.) and body weight gains (g) of rats fed BAS 510 F for 90 days.

Day	0 ppm	100 ppm	500 ppm	2000 ppm	5000 ppm	15000 ppm
Males						
body wt 0	184 ± 7.	186 ± 9	186 ± 8	185 ± 8	184 ± 8	187 ± 9
body wt 28	345 ± 20	343 ± 18	341 ± 14	327 ± 23	329 ± 15	344 ± 18
body wt 56	422 ± 28	423 ± 26	410 ± 19	408 ± 9	404 ± 27	424 ± 28
body wt 91	462 ± 33	470 ± 34	448 ± 28	456 ± 12	442 ± 33	464 ± 33
b.w. gain 0-91	278	284	262	271	258	277
Females						
body wt 0	146 ± 5	144 ± 6	143 ± 5	144 ± 5	143 ± 7	144 ± 7
body wt 28	211 ± 14	209 ± 17	209 ± 13	206 ± 10	209 ± 13	210 ± 15
body wt 56	245 ± 16	248 ± 23	247 ± 17	241 ± 11	241 ± 17	248 ± 20
body wt 91	259 ± 18	263 ± 28	259 ± 20	252 ± 14	254 ± 18	260 ± 24
b.w. gain 0-91	113	119	116	108	111	116

Data from Tables 1A007-1A010, pp. 65-68, MRID 45404822.
body wt = body weight
b.w. = body weight

C. FOOD CONSUMPTION AND COMPOUND INTAKE :

1. **Food consumption**: There was no effect of treatment on food consumption.

2. **Compound consumption**: Compound consumption was calculated by the study authors and is presented in Table 1.

3. **Food efficiency**: There were no patterns of test article related effects.

D. OPHTHALMOSCOPIC EXAMINATION: Ophthalmoscopic examinations revealed no treatment-related effects.

E. BLOOD ANALYSES:

1. Hematology

Statistically significant hematology changes are listed in Table 3. These included higher red blood cell counts (RBC) in males of the 2000, 5000, and 15,000 ppm groups (5%, 10%, and +8%, respectively, hemoglobin (HGB) of males in the 5000 ppm group (+8%) and 15,000 ppm group (+5%), and the hematocrit (HCT) of males in the 2000 ppm (+4%), 5000 ppm (+9%), and 15,000 ppm groups (+7%). The prothrombin time of females was slightly reduced at doses >500 ppm, but reached statistical significance at the 15,000 ppm dose (91%

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of the control value). While the slight increases of RBC, HGB, and HCT may indicate very mild dehydration, they are within historical limits for the laboratory and none of the hematological changes were of biological or toxicological significance.

TABLE 3. Hematology parameters of rats fed BAS 510 F for 90 days

Parameter	Dietary concentration (ppm)					
	0	100	500	2000	5000	15,000
Males (n = 10)						
Red blood cell count (tera/L)	8.10	8.39	8.47	8.52**	8.87***	8.77**
Hemoglobin (mmol/L)	9.2	9.3	9.4	9.5	9.9**	9.7*
Hematocrit (L/L)	0.412	0.421	0.422	0.430*	0.450***	0.441**
Females (n = 10)						
Prothrombin time (seconds)	30.2	30.5	29	28.8	29	27.4**

Data taken from Tables IB-001 to 008, pp. 83-90, MRID 45404822.
*Statistically significant, $p<0.05$.
**Statistically significant, $p<0.02$.
***Statistically significant, $p<0.002$.

2. **Clinical chemistry**: Clinical chemistry parameters attaining statistically significant differences are shown in Table 4. These included GGT activity in males in the 2000, 5000, and 15,000 ppm groups (250, 233, and 392% of the control value, respectively) and females in the 5000 and 15,000 ppm groups (264 and 300%, respectively); decreased AST activity of females in the 100, 500, and 2000 ppm groups (77, 86, and 82% of control, respectively); decreased ALK activity in females treated with ≥500 ppm (87, 76, 79, and 74%, respectively); elevated potassium in males of the 5000 ppm group (115%); lower triglyceride in 15,000 ppm males (72%); and higher cholesterol in 15,000 ppm females (130%). With the exception of GGT activity, the results shown in Table 4 are of little biological or toxicological significance. The slight increases of total protein, albumin, and globulin are consistent with very mild dehydration. The dose-related increase of GGT activity of male and female rats without associated increases in the activities of ALK, ALT, and AST is consistent with hepatic hypertrophy.

TABLE 4. Clinical chemistry parameters of rats fed BAS 510 F for 90 days						
Parameter	Dietary concentration (ppm)					
	0	100	500	2000	5000	15,000
Males (n = 10)						
GGT (nkat/L)	12	10	11	30***	28**	47***
Potassium (meq/L)	6.29	6.73	6.7	6.53	7.21***	6.75
Calcium (mmol/L)	2.70	2.79*	2.74	2.76	2.86***	2.86***
Total bilirubin (µmol/L)	2.48	2.73	2.15	1.74**	1.61**	1.66**
Total protein (g/L)	62.85	61.92	62.14	62.05	67.13**	67.51*
Albumin (g/L)	33.02	33.30	33.75	33.24	35.37***	35.39**
Triglyceride (mmol/L)	3.09	2.62	3.34	2.96	2.93	2.21*
Females (n = 10)						
AST (µkat/L)	1.99	1.53***	1.71**	1.63**	1.82	1.84
ALK (µkat/L)	4.05	4.70*	3.53**	3.06***	3.19**	2.99**
GGT (nkat/L)	14	14	18	21	37***	42***
Total protein (g/L)	65.45	64.52	64.07	66.73	65.69	70.29*
Globulin (g/L)	28.49	27.30	26.70*	28.79	29.37	31.27**
Triglyceride (mmol/L)	3.07	3.43	3.42	3.17	2.71	1.97
Cholesterol (mmol/L)	2.22	2.31	2.09	2.09	2.46	2.88**

Data taken from Tables IB-009 to 014, pp. 91-96, MRID 45404822.
*Statistically significant, $p<0.05$.
**Statistically significant, $p<0.02$.
***Statistically significant, $p<0.002$.

F. Urinalysis: There was no effect of treatment on any urinary parameter for either sex.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight:

At the end of treatment, statistically significant dose-related increases of relative liver weight were found in male rats of the 5000 and 15,000 ppm groups and the absolute liver weight of male rats in the 15,000 ppm group (Table 5). Both, the absolute and relative liver weight of female rats in the 5000 and 15,000 groups were statistically increased. The absolute and relative thyroid weights of male rats in the 2000 and 15,000 ppm groups and females in the 5000 ppm and 15,000 ppm groups were increased.

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TABLE 5. Terminal body weights (g), absolute organ weights and relative organ weights (% of body weight) of rats fed BAS 510 F for 90 days

Terminal body and organ weights	Dietary concentration (ppm)					
	0	100	500	2000	5000	15000
Males						
Body weight	446.21±31.93	449.86±32.80	433.19±25.22	432.01±11.26	424.28±34.67	442.81±31.65
Liver						
Absolute weight (g)	13.95±1.88	14.66±1.73	14.03±1.52	14.33±1.02	15.03±1.59	16.64±1.39** (+19%)
Relative weight	3.12±0.26	3.25±0.22	3.23±0.23	3.32±0.17	3.53±0.20** (+14%)	3.76±0.20** (+21%)
Spleen						
Absolute weight (g)	0.96±0.27	0.98±0.12	0.80±0.10	0.79±0.11	0.75±0.12	0.73±0.12* (-24%)
Relative weight	0.21±0.05	0.22±0.02	0.18±0.02	0.18±0.03	0.18±0.02	0.17±0.02** (-19%)
Adrenal						
Absolute weight (mg)	104.4±35.19	86.4±12.10	95.8±11.65	92.8±11.57	70.1±12.12** (-33%)	83.6±9.17* (-20%)
Rrelative weight	0.023±0.008	0.019±0.003	0.022±0.003	0.022±0.003	0.017±0.003** (-26%)	0.019±0.002* (-17%)
Thyroid						
Absolute weight (mg)	23.4±4.53	23.2±1.81	23.7±4.11	28.3±4.24** (+21%)	24.2±2.7	31.4±4.67** (+34%)
Relative weight	0.005±0.001	0.005±0	0.005±0.001	0.007±0.001** (+40%)	0.006±0.001	0.007±0.001** (+40%)

TABLE 5. Terminal body weights (g), absolute organ weights and relative organ weights (% of body weight) of rats fed BAS 510 F for 90 days

Terminal body and organ weights	Dietary concentration (ppm)					
	0	100	500	2000	5000	15,000
Females						
Body weight	250.92±15.13	254.4±29.37	248.35±18.47	241.15±11.19	244.66±16.27	248.09±22.98
Liver						
Absolute weight (g)	7.51±0.51	7.59±0.87	7.84±0.93	7.66±0.38	8.19±0.72* (+9%)	9.24±0.99** (+23%)
Relative weight	2.99±0.18	2.99±0.19	3.15±0.16	3.18±0.20	3.35±0.20** (+12%)	3.73±0.26** (+25%)
Ovaries						
Absolute weight (mg)	101.2±18.45	97.6±15.10	94.7±10.02	104.6±8.21	112.8±13.25	96±19.98
Relative weight	0.040±0.007	0.038±0.005	0.038±0.004	0.043±0.004	0.046±0.005*	0.039±0.007
Thyroid						
Absolute weight (mg)	17.3±2.98	17.1±3.00	17.2±2.53	18.5±2.27	20.3±2.11* (+17%)	22.6±3.41** (+31%)
Relative weight	0.007±0.001	0.007±0.001	0.007±0.001	0.008±0.001	0.008±0.001** (+14%)	0.009±0.001** (+29%)

Data taken from Tables IC-1 to 4, pp. 101-104, MRID 45404822.
*Statistically significant, $p<0.05$.
**Statistically significant, $p<0.01$.

2. **Gross pathology**: In control males, one each had white foci on the glandular stomach, moderately enlarged adrenal cortices or yellow foci on the liver. The adipose tissue of one control female was necrotic and the thyroid of one control female was reduced in size.

   Yellow hepatic foci were noted in one 500 ppm female, two 2000 ppm females, one 5000 ppm female, and three males and one female in the 15,000 ppm group (also, one control male). All other findings were observed in no more than one rat in any one group.

3. **Microscopic pathology**: Treatment-related histopathologic effects are summarized in Table 6. In the liver, there was an increase of hepatic centrilobular hypertrophy in male rats of the 5000 ppm group and male and female rats of the 15,000 ppm group. The hypertrophy (minimal<slight<moderate) was graded as minimal in males of the 5000 ppm group, minimal to moderate in males in the 15,000 ppm group, and minimal to slight in females of the 15,000 ppm group. The centrilobular hypertrophy is consistent with the earlier findings of a dose-related increase of GGT activity and in the increase of absolute and relative liver weights.

   Slight thyroid follicular epithelial cell hypertrophy and diffuse hyperplasia were noted in male rats receiving ≥2000 ppm test material, however, these lesions were not noted microscopically in female rats. The latter result is inconsistent with the increased absolute and relative thyroid weights of female rats noted earlier.

TABLE 6. Microscopic changes in organs of rats fed BAS 510 F for 90 days						
Organ: lesion	Dietary concentration (ppm)					
	0	100	500	2000	5000	15,000
Males						
Liver Hypertrophy, central	0/10 [a]	0/10	0/10	0/10	8/10***	10/10***
Thyroid Hyperplasia, diffuse Hypertrophy, follicular epithelial cells	1/10 1/10	2/10 2/10	3/10 3/10	7/10** 7/10**	7/10** 7/10**	8/10** 8/10**
Females						
Liver Hypertrophy, central	0	0	0	0	2/10	7/10**

Data taken from Table IC-7 to 10, pp. 107-110, MRID 45404822.
[a] Number of animals affected/total number of animals.
**Statistically significant, $p<0.01$ - Fisher Exact test calculated by reviewer
***Statistically significant, $p<0.001$ - Fisher Exact test calculated by reviewer

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS:

The study author concluded that oral treatment with BAS 510 F to Wistar rats for three months caused changes in clinical pathology associated with microsomal enzyme induction and a reduction in alkaline phosphatase activity. The target organs were considered to be the liver and thyroid which had increased absolute and/or relative weights. On this basis, the study author established the NOAEL for both sexes as 500 ppm (34 mg/kg bw/day for males and 40 mg/kg bw/day for females).

B. REVIEWER COMMENTS:

In this study, six groups of 10 male and 10 female Wistar rats were fed BAS 510 F at concentrations of 0, 100, 500, 2000, 5000, or 15,000 ppm for 3 months. There were no treatment-related signs of systemic toxicity, effects on body weight, food consumption, or food efficiency, ocular effects, and there were no deaths. In addition, there were no biologically or toxicologically significant effects on hematology or urinalysis parameters.

Although there were several statistically significant effects on several clinical chemistry parameters, with the exception of γ-glutamyltransferase (GGT) activity, none were of biological or toxicological significance. GGT activity was statistically increased in male rats receiving ≥2000 ppm and female rats receiving ≥5000 ppm test material. The increase in GGT activity without associated increases in alkaline phosphatase, alanine or aspartate transaminase activities is consistent with hepatic centrilobular hypertrophy. In support of this, the absolute and/or relative liver weights of male and female rats receiving ≥5000 ppm test material were increased and the incidence of centrilobular hypertrophy was statistically increased in 5000 and 15,000 ppm male rats and in 15,000 ppm female rats.

The absolute and relative thyroid weights were statistically increased relative to controls in the 2000 ppm and 15,000 ppm male rats and in the 5000 and 15,000 ppm female rats. In conjunction, the incidence of diffuse hyperplasia and thyroid follicular epithelial hypertrophy were significantly increased in male rats (≥7/10) receiving ≥2000 ppm. However, no similar increase was noted for female rats. The increased absolute and relative thyroid weights of treated male and female rats and the increased hyperplasia and follicular cell hypertrophy suggests a disturbance of thyroid homeostasis.

The LOAEL for the study is 2000 ppm (137 mg/kg bw/day) BAS 510 F for male rats and 5000 ppm (395 mg/kg bw/day) for female rats based on the increases of absolute and relative thyroid weights in both sexes and the increased incidence of thyroid hyperplasia and follicular epithelial hypertrophy in male rats. The corresponding NOAELs would be 500 ppm (34 mg/kg bw/day) for male rats and 2000 ppm (159 mg/kg bw/day) for female rats.

Although the LOAEL and NOAEL for female rats is in disagreement with the study author, this 90-day oral toxicity study is acceptable and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408).

C. STUDY DEFICIENCIES:

There were no major study deficiencies.

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	45404822	subchronic	rat	3 months	oral	dietary	7-1055 for males; 8-1225 for females	0, 7, 34, 137, 347, and 1055 for males; 0, 8, 40, 159, 395, and 1225 for females	34 for males; 159 for females	137 for males; 395 for females	Liver, thyroid	Toxicity

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