DATA EVALUATION RECORD

BAS 510 F

STUDY TYPE: CHRONIC TOXICITY DIETARY STUDY - RAT
[OPPTS 870.4100a (§83-1a); OECD 452]
MRID 45404827

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

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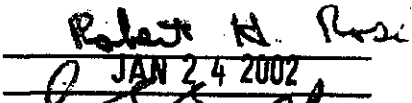
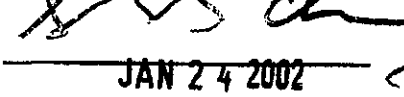
Robert H. Ross, Group Leader	Signature: Date:	 JAN 24 2002
Quality Assurance: S.S. Chang, M.S.	Signature: Date:	 JAN 24 2002

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DATA EVALUATION RECORD
TXR#: 0050193

STUDY TYPE: Chronic Toxicity, rat; feeding; OPPTS 870.4100a [§83-1a]; OECD 452.

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

TEST MATERIAL (PURITY): BAS 510 F

SYNONYMS: 2-chloro-N-(4'-chlorobiphenyl-2-yl)nicotinamide (IUPAC name)

CITATION: W. Mellert, K. Deckardt, W. Kaufmann, et al. (2001) Chronic toxicity study in Wistar rats; Administration in the diet for 24 months. Experimental Toxicology and Ecology BASF Aktiengesellschaft, D-67056 Ludwigshafen, Rhein, Germany. Laboratory Project No. 82C0179/97091, BASF Registration Document Number 2001/1000114, February 28, 2001. MRID 45404827. Unpublished.

SPONSOR: BASF Corporation Agricultural Products Division, Research Triangle Park, NC 27709.

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 45404827) BAS 510 F (94.4% a.i., lot no. N37, Tox-batch III) was administered to 20 Wistar rats/sex/dose in the diet at concentrations of 0, 100, 500, 2500, or 15,000 ppm (equivalent to 0, 4.4, 21.9, 110.0, 739.0 mg/kg bw/day for males and 0, 5.9, 30.0, 150.3, 1000.4 mg/kg bw/day for females, respectively) for 24 months. Due to excessive body weight losses, both 15,000 ppm groups were sacrificed after 17 months and not further analyzed.

At ≤2500 ppm, there were no statistically or biologically significant differences from controls in clinical observations, survival rates, body weights and weight gains, food consumption, food efficiency, ophthalmoscopy, hematology, or urinalysis parameters. The most notable clinical chemistry alteration was a dose-related increase in serum gamma-glutamyl transferase (1.2-18X), which was seen in 2500 ppm males throughout the study and in 2500 ppm females and 500 ppm males during the first year. The increase in gamma-glutamyl transferase was correlated with an increased incidence of centrilobular hypertrophy ppm in both sexes, liver eosinophilic foci in males, and an 11% increase in relative liver weight in females at 2500 ppm. Slight but non-significant increases occurred at 2500 ppm in gross thyroid gland foci in males, and in thyroid follicular cell diffuse hypertrophy and focal hyperplasia in both sexes, and were correlated with a significant increase in absolute thyroid weight in males (131% of controls, $p \leq 0.05$). The

2

LOAEL is 2500 ppm for both sexes of rats (110.0 and 150.3 mg/kg/day for males and females, respectively) under the conditions of this study, based on thyroid toxicity (organ weight and microscopic changes) that resulted indirectly from the liver adaptive response. The NOAEL is 500 ppm (21.9 and 30.0 mg/kg/day for males and females, respectively).

At the doses tested, there was not a treatment related increase in the incidence of any tumor type, or in the total number of tumors. Thyroid follicular cell adenoma was seen in only treated animals (0/20, 0/20, 2/20, 1/20 in males and 0/20, 0/20, 1/20, 0/20 in females given 0, 100, 500, and 2500 ppm, respectively), but was within the range of the testing laboratory's historical control values and near the mean of 0.8%. Dosing was considered adequate based on the liver and thyroid toxicity seen in both sexes at 2500 ppm.

This chronic toxicity study in the rat is **Acceptable/Guideline**, and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100a; OECD 452] in rats.

COMPLIANCE: Signed and dated GLP, Flagging Criteria, Quality Assurance, and Data Confidentiality statements were provided. The GLP statement indicated that the study meets the requirements of 40 CFR Part 160, but was conducted in accordance with GLP provisions of FR Germany and the OECD. This study met or exceeded the criteria for flagging studies.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: BAS 510 F

Description:	White solid
Lot/Batch #:	N37 (Tox-batch III)
Purity:	94.4% a.i.
Compound Stability:	Stable at room temperature during conduct of study
CAS # for TGAI:	188425-85-6
Structure:	

2. Vehicle and/or positive control: The test material was administered continuously in the diet; no positive control was used.

3. **Test animals:**

Species:	Rat
Strain:	Wistar Chbb:THOM (SPF)
Age/weight at study initiation:	42 days old: males, 163.5-206.2 g; females, 114.4-156.9 g
Source:	Boehringer Ingelheim Pharma KG, Biberach/Riss, Germany
Housing:	Singly in type DK III stainless steel wire mesh cages
Diet:	Ground Kliba maintenance diet rat/mouse/hamster, meal, supplied by 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 specified, but animal room was fully air-conditioned **Photoperiod:** 12/hrs dark/12 hrs light
Acclimation period:	8 days

B. STUDY DESIGN:

1. **In life dates:** Start: January 27, 1998; End: January 26-February 8, 2000 (necropsy), except 15,000 ppm rats were necropsied June 28-29, 2000.

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

TABLE 1: Study Design

Test Group	Conc. in Diet (ppm)	Dose to animal (mg/kg/day)		Number of animals	
		Male	Female	Male	Female
0 (Control)	0	0	0	20	20
1 (Low dose)	100	4.4	5.9	20	20
2 (Mid dose)	500	21.9	30.0	20	20
3 (Mid dose)	2500	110.0	150.3	20	20
4 (High dose)[1]	15,000	739.0	1000.4	20	20

Data from pp. 42 and 46, MRID 45404827.
[1]Surviving Group 4 animals were all sacrificed after 17 months due to excessive toxicity; other groups were sacrificed after 24 months.

3. **Dose selection rationale:** The high test concentration of 15,000 ppm was expected to have a test substance intake of >1000 mg/kg body weight/day, which is a "limit test" concentration for testing toxic substances. The other dietary concentrations were 2500 and 500 ppm as "mid concentrations" and 100 ppm as the "low concentration." No previous toxicity study results were mentioned for BAS 510 F.

4. **Diet preparation and analysis:** Diets were prepared weekly (usually) by mixing appropriate amounts of test substance with ground Kliba maintenance diet rat/mouse/hamster meal and stored at ambient temperature. The stability of the test material in the diet was determined prior to study initiation using 100 ppm samples. Three or four samples were assayed at times 0, 12, and 32 days after preparation and storage at ambient temperature. Homogeneity and concentration were tested at the beginning of the study as well as after 3 months of treatment;

concentration only was tested after 6, 9, 12, 15, and 18 months of treatment (except 15,000 ppm diets were not assessed after 18 months). Three samples of the highest and lowest concentration were assayed for homogeneity and the dietary concentration was assayed for all doses (duplicate analyses were conducted for each sample). No dietary analyses were performed after 18 months due to protocol deviation, but the study investigators assumed that these concentrations were correct based on the results of the analyses up to 18 months.

Results:

Homogeneity analysis: The mean and standard deviation of the measured concentration of 100 ppm samples (duplicate analyses of three samples) was 100.1 ± 3.8% of nominal at the beginning of the study and 102.8 ± 1.8% after 3 months. Analogous analyses for the 15,000 ppm samples yielded 96.2 ± 1.7% of nominal at study initiation and 93.2 ± 1.5% at 3 months. The low standard deviations demonstrated the homogeneity of the feed.

Stability analysis: Concentrations of samples taken after 13 and 32 days ranged from 95.4-99.6% and 94.5-99.6% of nominal values (mean of 97.5 and 97.9% of time 0 concentration).

Concentration analysis: Through 18 months of the study, analytical concentrations (mean of duplicates) as a percent of nominal concentrations ranged from 89.9-102.9% at 100 ppm, 91.6-98.4% at 500 ppm, 90.5-104.5% at 2500 ppm, and 92.4-98.9% at 15,000 ppm (latter samples only taken through 15 months).

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

5. **Statistics:** Food consumption, body weight, body weight change, and food efficiency data were analyzed by parametric one-way analysis using the F-test and 2-sided ANOVA. If the resulting p-value was ≤0.05, Dunnett's 2-sided test was used to compare each test group with the control group; significance was reported as p ≤0.05 or 0.01. Hematology and clinical chemistry (except differential blood count and reticulocytes) and organ weights were evaluated with the two-sided Kruskal-Wallis test (non-parametric one-way analysis). If the resulting p-value was ≤0.05, each test group was compared with the control group using the Mann-Whitney two-sided U-test for clinical pathology (significance reported as p ≤0.05, 0.02, or 0.002) and the Wilcoxon test for organ weights (significance reported as p ≤0.05 or 0.01). Urinalysis (excluding volume, color, turbidity, and specific gravity) was evaluated by pairwise comparison of the treated and control groups with Fisher's exact test; significance was reported as p ≤0.05 or 0.01. The reviewer considers the analyses used to be appropriate, and also analyzed intergroup differences for histology and selected gross necropsy lesions using Fisher's exact probability test.

C. **METHODS:**

1. **Observations:**

1a. **Cageside observations:** Animals were inspected for signs of toxicity and for mortality twice a day Monday to Friday and once a day on Saturday and Sunday and on holidays.

1b. **Clinical examinations**: Thorough clinical examinations, including palpation, were conducted weekly.

1c. **Neurological evaluations**: Neurological evaluations were not performed in this chronic toxicity study. The registrant included an acute oral neurotoxicity rat study (MRID 45404820) and a subchronic oral neurotoxicity in rats (MRID 45404825) as a part of the present submission (S 604279).

2. **Body weight**: Animals were each weighed prior to dosing, then on study day 0 and weekly through week 13. Thereafter, rats were weighed every 4 weeks and prior to necropsy.

3. **Food consumption and compound intake**: Food consumption was determined once a week over a period of 7 days through the first 13 dosing weeks. Thereafter, food consumption was determined one week in 4 and prior to necropsy. The 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 food consumption and body weight gain data.

4. **Ophthalmoscopic examination**: Eyes were examined in all animals prior to the start of dosing and in the control and 2500 ppm groups shortly before study termination. A mydriatic agent and an ophthalmoscope were used.

5. **Hematology and Clinical chemistry**: Blood was collected without anesthesia from the retroorbital venous plexus from all surviving animals in each test group for hematology and clinical chemistry analysis. Collection was in the morning at approximately 3, 6, 12, 13, 18, and 24 months from non-fasted (3-12 months) or fasted (13-24 months) animals. Reticulocytes were counted in the control and high-dose animals during the first year only. 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*	x	Reticulocyte count
x	Blood clotting measurements*		
-	(Thromboplastin time)		
-	(Clotting time)		
x	(Prothrombin time)		

* Recommended for chronic studies based on Guideline 870.4100.

- 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(fasting)*
	ENZYMES (more than 2 hepatic 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/ SGPT)*		
x	Aspartate aminotransferase (AST/ SGOT)*		
x	Gamma glutamyl transferase (GGT)*		
-	Sorbitol		
-	Glutamate dehydrogenase*		

* Recommended for chronic studies based on Guideline 870.4100.
- Not examined

6. **Urinalysis**: Urine was collected overnight from animals in metabolism cages without food or water at approximately 3, 6, 12, 18, and 24 months. 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	Nitrite
x	Protein*	x	Urobilinogen

* Recommended for chronic studies based on Guideline 870.4100.

7. **Sacrifice and pathology**: All animals that died and those sacrificed on schedule (decapitation under CO_2 anesthesia) were subjected to gross pathological examination and the CHECKED (X) tissues were collected. Histological examination was conducted on all control and 2500 ppm animals, but the thyroid glands, lungs, liver, kidneys and gross lesions were also examined in the 100 and 500 ppm groups. The animals were fasted overnight prior to necropsy. The (XX) organs, in addition, were weighed.

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

* Required for chronic studies based on Guideline 870.4100.
+Organ weight required in chronic studies. - Not examined

II RESULTS

A. OBSERVATIONS:

1. **Clinical signs of toxicity**: There were no differences between control and treated animals in the incidence of abnormal clinical observations.

2. **Mortality**: Survival was not affected by treatment in either sex. The mortality rates at study termination for rats administered 0, 100, 500, and 2500 ppm BAS 510 F were 25, 20, 30, and 30% for males and 35, 15, 35, and 5% for females, respectively. The mortality rate of the 15,000 ppm rats until their sacrifice at ~17 months was comparable to the other dose groups.

3. **Neurological evaluations**: None were performed.

B. **BODY WEIGHT AND WEIGHT GAIN**: Weekly body weights and body weight gains differed significantly ($p \leq 0.05$ or 0.01) from the controls for only the 15,000 ppm groups. Body weights were significantly decreased in the 15,000 ppm males for almost all time intervals from day 231-511 (90.6-93.2% of controls) and in females at days 14, 35, 147, and 231-511 (85.1-94.3% of controls). Body weight gains were significantly decreased over roughly the same time period in both sexes (males: 87.5-90.6% of controls; females: 78.1-89.1% of controls). On day 517-518, all the 15,000 ppm rats were sacrificed because the investigators determined that excessive toxicity was occurring (based on the lowered body weights and weight gains), which were expected to "progress with time." At ≤2500 ppm, there were no statistically or biologically significant differences in body weights and weight

gains from the respective control groups. Mean group body weights and weight gains are shown in Table 2. [Note that the same values are not obtained for the body weight gains from days 175-371 and 371-511 when using the weekly body weights vs. the cumulative weight gain data. The reason for this discrepancy is unknown but of no practical consequence since the values were within 3% of each other.]

TABLE 2: Mean body weights and body weight gains (± standard deviation) for male and female rats fed BAS 510 F for up to 2 years. [1]

Study day	Dietary concentration (ppm)				
	0	100	500	2500	15000
Mean body weights (g) – Males					
0	180.9 ± 11.1	181.9 ± 10.6	181.6 ± 9.7	182.3 ± 10.0	180.6 ± 8.3
91	484.1 ± 36.1	479.3 ± 43.9	489.3 ± 41.3	483.0 ± 44.2	466.2 ± 28.9
175	572.0 ± 39.9	559.0 ± 54.4	572.7 ± 52.4	567.7 ± 48.1	538.5 ± 36.4
371	660.7 ± 54.0	641.5 ± 67.6	668.4 ± 68.5	650.0 ± 50.2	605.2* ± 45.8 (91.6)
511	719.5 ± 68.3	699.5 ± 83.1	727.2 ± 86.5	725.9 ± 57.3	658.4* ± 49.4 (91.5)
728	726.6 ± 97.8	733.4 ± 103.5	735.3 ± 77.5	731.7 ± 61.2	N/A
Mean body weight gains (g) – Males					
0-91	303.2 ± 29.3	297.4 ± 36.2	307.7 ± 34.5	300.6 ± 38.3	285.6 ± 25.5
0-175	391.1 ± 36.0	377.1 ± 46.9	391.1 ± 45.7	385.4 ± 42.5	357.9 ± 34.0
0-371	479.8 ± 51.3	459.6 ± 61.2	486.8 ± 62.1	467.7 ± 45.9	424.9** ± 45.0 (88.6)
0-511	538.6 ± 65.4	517.5 ± 76.6	545.6 ± 80.9	542.8 ± 55.0	478.1* ± 49.4 (88.8)
0-728	545.3 ± 93.8	550.5 ± 98.5	552.5 ± 73.4	549.6 ± 59.9	N/A
175-371[2]	88.7	82.5	95.7	82.3	66.7 [67.0]
371-511[2]	58.8	58.0 [57.9]	58.8	75.9 [75.1]	53.2
Mean body weights (g) – Females					
0	142.2 ± 8.1	140.2 ± 7.9	138.2 ± 9.3	138.5 ± 8.7	137.0 ± 8.3
91	272.5 ± 23.0	272.3 ± 19.5	260.9 ± 19.2	260.6 ± 18.9	258.1 ± 21.1
175	304.7 ± 24.1	303.8 ± 23.0	293.9 ± 20.0	294.9 ± 20.4	285.8 ± 26.4
371	335.4 ± 31.5	322.7 ± 32.2	315.4 ± 29.4	312.8 ± 30.6	298.1** ± 33.1 (88.9)
511	365.1 ± 40.3	356.8 ± 47.7	351.3 ± 37.0	344.2 ± 43.2	312.6** ± 36.2 (85.6)
728	369.7 ± 37.7	372.8 ± 71.9	363.4 ± 36.8	353.9 ± 49.9	N/A
Mean body weight gains (g) – Females					
0-91	130.3 ± 19.1	132.0 ± 15.6	122.6 ± 15.2	122.1 ± 12.9	121.1 ± 14.6
0-175	162.5 ± 19.4	163.6 ± 19.7	155.7 ± 15.6	156.4 ± 15.7	148.8 ± 19.5
0-371	193.3 ± 25.7	182.5 ± 27.8	177.8 ± 23.5	174.3 ± 26.6	161.1** ± 26.3 (83.3)
0-511	223.6 ± 35.3	216.6 ± 42.6	213.8 ± 31.2	205.7 ± 40.5	176.0** ± 29.4 (78.7)
0-728	228.3 ± 34.9	233.5 ± 68.6	229.8 ± 33.8	215.2 ± 48.1	N/A
175-371[2]	30.7 [30.8]	18.9	21.5 [22.1]	17.9	12.3
371-511[2]	29.7 [30.3]	34.1	35.9 [36.0]	31.4	14.5 [14.9]

Data taken from pp. 89-108, MRID 45404827.
N/A = not available (animals were sacrificed prior to this time point).
[1]Numbers in parentheses are the percent of control.
[2]Calculated by the reviewer using the weekly body weights (not statistically analyzed). Slightly different gains were calculated in some cases using the cumulative body weight gains [shown in brackets]; the reason for these discrepancies is unclear.
*p≤0.05, **p≤0.01, significantly different from the control group.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption was similar for all groups of males and females throughout the study, with the exception of a few sporadic deviations in all dose groups.

2. **Compound consumption:** (time-weighted average): The time-weighted-average doses for each treatment group are presented in Table 1.

3. **Food efficiency:** Food efficiency was comparable among control and treated groups throughout the study.

D. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related findings.

E. BLOOD ANALYSES:

1. **Hematology:** Hematological parameters for the 15,000 ppm animals were only evaluated for the first year and for the other groups were evaluated for 2 years. Several parameters differed slightly, but statistically significantly from the respective control groups ($p \leq 0.05$, 0.02, or 0.002) at one or more time points during the study. In males, these parameters included decreased leukocyte count (76-91% of controls) and increased erythrocyte count (105-107% of controls) at 15,000 ppm, and decreased MCV and MCH at 500, 2500, and/or 15,000 ppm (96-98% of controls). In females, all parameters were within 94% of controls.

2. **Clinical chemistry:** Parameters for the 15,000 ppm animals were evaluated for the first year and for the other groups for 2 years. Both males and females had statistically significant increases in gamma-glutamyl transferase activity and total protein, globulins, and cholesterol concentrations as well as decreased total serum bilirubin, triglycerides, and activities of alanine aminotransferase and alkaline phosphatase. Males also had increased serum albumin and females had decreased aspartate aminotransferase. All of these alterations were seen throughout the first year in the 15,000 ppm groups, and most of the changes were also seen in the 2500 ppm groups. As shown in Table 4 for males and Table 5 for females, the 500 ppm and/or 100 ppm groups also had changes in some of these parameters, but they occurred at only a few time points and/or were not clearly dose-related. The clinical chemistry changes were correlated with minor liver enlargement and an increased incidence of microscopic lesions (centrilobular hypertrophy and eosinophilic foci) in the 2500 ppm animals (15,000 ppm rats were not necropsied). Fasting (starting with day 395/400 blood collection) had no apparent effect on the clinical chemistry results because values obtained with and without prior overnight fasting were comparable.

TABLE 4. Selected clinical chemistry parameters (± standard deviation) in MALE rats fed BAS 510 F for 2 years[1].

Parameter (units)	Study day	Dietary concentration (ppm)				
		0	100	500	2500	15,000
Alanine aminotransferase (mykat/L)	86	1.12 ± 0.18	1.05 ± 0.16	1.08 ± 0.20	1.05 ± 0.17	0.95 ± 0.15
	176	1.19 ± 0.26	1.17 ± 0.22	1.09 ± 0.16	1.02** ± 0.14 (86)	0.96** ± 0.24 (81)
	365	1.13 ± 0.23	1.13 ± 0.18	1.12 ± 0.23	1.00 ± 0.12	0.95** ± 0.18 (84)
	395	0.91 ± 0.26	0.85 ± 0.15	0.89 ± 0.14	0.91 ± 0.28	0.75** ± 0.15 (82)
	547	0.88 ± 0.37	0.75 ± 0.15	0.87 ± 0.33	0.67** ± 0.13 (76)	N/A
	720	0.72 ± 0.20	0.87 ± 0.50	0.71 ± 0.21	0.65 ± 0.10	N/A
Alkaline phosphatase (mykat/L)	86	5.72 ± 0.50	5.41 ± 0.97	4.98** ± 0.54 (87)	4.38** ± 0.47 (77)	4.34** ± 0.49 (76)
	176	5.26 ± 0.58	5.25 ± 0.76	4.69** ± 0.56 (89)	3.91** ± 0.38 (74)	3.28** ± 0.57 (62)
	365	5.44 ± 0.49	5.41 ± 1.29	5.20 ± 0.74	3.87** ± 0.54 (71)	3.46** ± 0.50 (64)
	395	3.07 ± 0.42	3.20 ± 0.51	3.34 ± 0.73	2.65** ± 0.43 (86)	2.40** ± 0.43 (78)
	547	3.33 ± 0.68	3.22 ± 0.78	3.47 ± 0.93	2.63** ± 0.45 (79)	N/A
	720	3.43 ± 0.78	3.76 ± 0.75	3.35 ± 0.87	2.46** ± 0.36 (72)	N/A
Serum gamma-glutamyl transferase (nkat/L)	86	4 ± 5	9** ± 5 (2.3X)	11** ± 7 (2.8X)	13 **± 10 (3.3X)	84** ± 25 (21X)
	176	24 ± 6	25 ± 10	29** ± 7 (1.2X)	41** ± 14 (1.7X)	97** ± 21 (4.0X)
	365	14 ± 7	15 ± 9	20** ± 7 (1.4X)	34 **± 20 (2.4X)	109** ± 24 (7.8X)
	395	1 ± 2	0 ± 2	1 ± 1	18* ± 45 (18X)	75** ± 31 (75X)
	547	19 ± 11	20 ± 8	19 ± 11	39** ± 18 (2.1X)	N/A
	720	38 ± 12	31± 13	44 ± 12	54** ± 19 (1.4X)	N/A
Total bilirubin (mmol/L)	86	1.70 ± 0.63	1.65 ± 0.56	1.54 ± 0.59	1.35 ± 0.49	1.22** ± 0.32 (72)
	176	2.10 ± 0.72	2.11 ± 0.71	1.87 ± 0.81	1.46** ± 0.57(70)	1.50** ± 0.40 (71)
	365	2.19 ± 0.69	2.11 ± 0.92	1.44** ± 0.80 (66)	1.21** ± 0.53 (55)	1.52** ± 0.34 (69)
	395	2.43 ± 0.53	2.37 ± 0.67	2.03 ± 0.63	1.94** ± 1.35 (80)	1.62** ± 0.28 (67)
	547	2.67 ± 0.69	2.37 ± 0.73	2.19* ± 0.83 (82)	2.04** ± 0.72 (76)	N/A
	720	3.06 ± 0.97	3.28 ± 0.73	2.67 ± 0.55	2.31** ± 0.54 (75)	N/A
Total protein (g/L)	86	65.31 ± 2.77	66.38 ± 4.15	65.49 ± 2.51	67.91** ± 2.44 (104)	70.19** ± 3.32 (107
	176	67.11 ± 3.42	68.64 ± 3.35	67.53 ± 2.74	69.45** ± 2.85 (103)	70.09** ± 3.22 (104
	365	64.90 ± 3.36	66.25 ± 3.23	65.39 ± 3.07	65.40 ± 3.24	68.66** ± 2.83 (106
	395	67.25 ± 2.80	66.62 ± 3.35	67.17 ± 3.18	69.29* ± 2.90 (103)	70.96** ± 3.28 (106
	547	63.24 ± 3.65	62.21 ± 2.29	62.27 ± 1.82	64.00 ± 3.78	N/A
	720	63.26 ± 3.48	64.37 ± 3.06	62.01 ± 4.87	64.44 ± 3.27	N/A
Albumin (g/L)	86	35.17 ± 1.17	35.58 ± 1.47	35.13 ± 1.07	35.64 ± 1.20	36.53** ± 1.31 (104
	176	30.83 ± 1.10	31.56 ± 1.06	31.16 ± 1.06	31.57 ± 1.05	31.45 ± 1.86
	365	28.45 ± 1.64	29.28 ± 1.58	28.97 ± 1.60	28.51 ± 1.50	30.05** ± 0.77 (106
	395	28.89 ± 1.10	28.99 ± 1.26	28.88 ± 2.03	29.41 ±1.24	30.21** ± 0.92 (105
	547	28.77 ± 1.24	28.72 ± 1.24	28.35 ± 1.05	29.45 ± 1.24	N/A
	720	26.06 ± 2.17	27.82** ±1.70(107)	26.60 ± 2.30	27.70* ± 1.38 (106)	N/A
Globulins (g/L)	86	30.13 ± 1.91	30.80 ± 3.02	30.36 ± 1.82	32.27** ± 1.62 (107)	33.66** ± 2.42 (112
	176	36.28 ± 2.60	37.08 ± 2.62	36.37 ± 2.06	37.88** ± 2.13 (104)	38.64** ± 2.92 (107
	365	36.45 ± 3.00	36.97 ± 2.40	36.41 ± 2.10	36.89 ± 2.51	38.61** ± 2.48 (106
	395	38.36 ± 2.12	37.63 ± 2.46	38.29 ± 2.33	39.89** ± 2.22 (104)	40.76** ± 2.74 (106
	547	34.48 ± 2.90	33.49 ± 1.78	33.93 ± 1.32	34.54 ± 2.94	N/A
	720	37.20 ± 2.90	36.56 ± 2.55	35.42 ± 4.07	36.75 ± 2.73	N/A
Triglycerides (mmol/L)	86	4.08 ± 1.33	4.83 ± 1.29	4.43 ± 1.88	3.47 ± 1.27	3.14* ± 1.24 (77)
	176	4.62 ± 1.70	5.48 ± 1.38	5.39 ± 2.43	4.43 ± 1.26	3.25** ± 1.21 (70)
	365	5.64 ± 1.96	6.14 ± 2.55	6.38 ± 3.10	4.99 ± 2.12	3.39** ± 1.34 (60)
	395	3.45 ± 1.43	4.33* ± 1.48 (126)	4.59 ± 2.37	3.68 ± 1.51	2.60 ± 1.00
	547	4.64 ± 2.37	5.07 ± 2.27	5.42 ± 3.01	4.52 ± 2.13	N/A
	720	3.17 ± 1.60	3.73 ± 1.60	4.43 ± 2.22	3.47 ± 1.80	N/A
Cholesterol (mmol/L)	86	2.01 ± 0.22	2.03 ± 0.29	2.02 ± 0.27	2.09 ± 0.27	2.30** ± 0.34 (114)
	176	2.02 ± 0.20	2.06 ± 0.26	2.15 ± 0.31	2.20 ± 0.29	2.16 ± 0.27
	365	2.29 ± 0.63	2.32 ± 0.26	2.45 ± 0.39	2.49 ± 0.51	2.41 ± 0.28
	395	2.50 ± 0.75	2.49 ± 0.26	2.72 ± 0.66	2.85** ± 0.73 (114)	2.81** ± 0.40 (112)
	547	2.87 ± 0.99	2.47 ± 0.38	2.73 ± 0.55	2.83 ± 0.44	N/A
	720	3.76 ± 1.73	3.43 ± 0.88	3.78 ± 0.95	3.70 ± 0.92	N/A

Data taken from pp. 167-200. MRID 45404827.

*p<0.05, **p<0.02 or 0.002, significantly different from the control group.

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

TABLE 5. Selected clinical chemistry parameters (± standard deviation) in FEMALE rats fed BAS 510 F for 2 years[1].

Parameter (units)	Study day	Dietary concentration (ppm)				
		0	100	500	2500	15,000
Alanine aminotransferase (mykat/L)	87	0.92 ± 0.17	0.90 ± 0.12	0.89 ± 0.16	0.78 ± 0.11** (85)	0.80 ± 0.09** (87)
	177	0.95 ± 0.15	0.84 ± 0.12** (88)	0.84 ± 0.16** (88)	0.75 ± 0.09** (79)	0.73 ± 0.09** (77)
	366	1.12 ± 0.19	0.91 ± 0.14** (81)	0.88 ± 0.13** (79)	0.85 ± 0.15** (76)	0.78 ± 0.16** (70)
	400	0.78 ± 0.15	0.82 ± 0.42	0.80 ± 0.17	0.69 ± 0.08** (88)	0.67 ± 0.10** (86)
	548	0.63 ± 0.10	0.58 ± 0.11	0.67 ± 0.25	0.59 ± 0.07	N/A
	721	0.65 ± 0.15	0.68 ± 0.11	0.67 ± 0.20	0.59 ± 0.11	N/A
Aspartate aminotransferase (mykat/L)	87	2.03 ± 0.60	1.82 ± 0.42	2.05 ± 0.78	1.92 ± 0.87	1.67 ± 0.40
	177	1.97 ± 0.89	1.67 ± 0.32	1.84 ± 1.07	1.45 ± 0.26** (74)	1.35 ± 0.28** (69)
	366	1.83 ± 0.70	1.42 ± 0.29* (78)	1.57 ± 0.47	1.57 ± 0.81	1.32 ± 0.43** (72)
	400	1.91 ± 0.60	2.36 ± 1.05	2.32 ± 0.91	1.79 ± 0.55	1.69 ± 0.55
	548	1.45 ± 0.28	1.37 ± 0.23	1.60 ± 0.41	1.29 ± 0.28	N/A
	721	2.04 ± 1.30	1.76 ± 0.57	1.37 ± 0.25	1.71 ± 0.69	N/A
Alkaline phosphatase (mykat/L)	87	3.89 ± 0.60	3.84 ± 0.65	3.35 ± 0.55** (86)	2.96 ± 0.46** (76)	3.01 ± 0.71** (77)
	177	3.27 ± 0.57	3.23 ± 0.66	3.01 ± 0.49	2.58 ± 0.52** (79)	2.41 ± 0.75** (74)
	366	3.23 ± 0.42	3.19 ± 0.72	2.94 ± 0.53	2.40 ± 0.59** (74)	2.16 ± 0.89** (67)
	400	1.42 ± 0.29	1.44 ± 0.34	1.48 ± 0.29	1.23 ± 0.25* (87)	1.27 ± 0.88** (89)
	548	1.22 ± 0.27	1.28 ± 0.28	1.21 ± 0.25	1.01 ± 0.18** (83)	N/A
	721	1.27 ± 0.13	1.70 ± 0.74** (134)	1.57 ± 0.37** (124)	1.20 ± 0.25	N/A
Serum gamma-glutamyl transferase (nkat/L)	87	7 ± 7	9 ± 7	6 ± 7	18** ± 12 (2.6X)	68 ± 23** (9.7X)
	177	0 ± 0	0 ± 0	1 ± 4	0 ± 1	26 ± 25** (>26X)
	366	12 ± 6	12 ± 7	13 ± 7	20 ± 12** (1.7X)	45 ± 34** (3.8X)
	400	7 ± 6	8 ± 8	4 ± 5	10 ± 8	42 ± 53** (6.0X)
	548	10 ± 9	12 ± 9	7 ± 6	8 ± 5	N/A
	721	37 ± 7	47± 22	41 ± 8	43 ± 7	N/A
Total bilirubin (mmol/L)	87	2.55 ± 0.43	2.25 ± 0.39** (88)	1.97 ± 0.36** (77)	1.80 ± 0.47** (71)	1.79 ± 0.52** (70)
	177	2.47 ± 0.55	2.50 ± 0.52	2.25 ± 0.45	2.19 ± 0.51	2.19 ± 0.60
	366	2.01 ± 0.57	1.93 ± 0.41	1.81 ± 0.44	1.69 ± 0.78	1.70 ± 0.62
	400	3.33 ± 0.56	2.92 ± 0.70* (88)	2.65 ± 0.53** (80)	2.37 ± 0.53** (71)	2.45 ± 0.55** (74)
	548	2.54 ± 0.71	2.87 ± 0.57	2.57 ± 0.51	2.32 ± 0.68	N/A
	721	2.49 ± 0.72	2.74 ± 0.55	2.43 ± 0.79	1.96 ± 0.69* (79)	N/A
Total protein (g/L)	87	66.86 ± 3.34	65.63 ± 4.14	67.47 ± 3.02	69.24 ± 3.64* (104)	70.23 ± 3.33** (105)
	177	71.19 ± 3.90	71.12 ± 4.67	70.53 ± 3.17	72.17 ± 3.72	75.58 ± 3.51** (106)
	366	73.65 ± 5.10	73.88 ± 3.81	73.29 ± 3.98	77.48 ± 5.53* (105)	79.04 ± 3.62** (107)
	400	75.53 ± 4.26	76.15 ± 3.18	76.67 ± 3.98	79.97 ± 4.47** (106)	81.77 ± 4.06** (108)
	548	69.90 ± 4.87	68.69 ± 3.70	69.84 ± 4.00	74.69 ± 3.55** (107)	N/A
	721	71.19 ± 2.40	71.71 ± 4.23	71.07 ± 6.54	74.61 ± 3.22** (105)	N/A
Globulins (g/L)	87	28.42 ± 2.02	27.82 ± 2.60	29.07 ± 1.70	30.48 ± 2.14** (107)	32.22 ± 2.15** (113)
	177	35.66 ± 1.94	36.00 ± 2.42	35.82 ± 1.94	36.87 ± 2.37	39.74 ± 2.52** (111)
	366	39.42 ± 3.08	39.56 ± 2.38	39.69 ± 2.85	41.96 ± 3.33** (106)	43.69 ± 3.20** (111)
	400	40.44 ± 2.68	40.68± 2.21	41.12 ± 2.57	43.32 ± 3.22** (107)	45.18 ± 3.36** (112)
	548	35.91 ± 2.71	35.35 ± 3.39	36.11 ± 2.54	39.01 ± 2.37** (109)	N/A
	721	39.04 ± 2.06	40.40 ± 3.84	39.28 ± 4.76	41.45 ± 2.45	N/A
Triglycerides (mmol/L)	87	2.15 ± 1.13	2.38 ± 0.63	2.10 ± 1.35	1.84 ± 0.94	1.73 ± 0.91
	177	4.27 ± 1.85	4.04 ± 1.59	3.02 ± 1.24* (71)	3.89 ± 1.53	2.41 ± 0.87** (56)
	366	4.41 ± 1.75	4.62 ± 1.97	3.86 ± 1.53	4.34 ± 2.11	2.92 ± 1.36** (66)
	400	3.52 ± 2.14	3.75 ± 2.12	3.13 ± 1.54	3.33 ± 1.38	2.27 ± 0.91* (64)
	548	5.11 ± 4.41	4.40 ± 3.20	3.58 ± 1.99	4.43 ± 2.77	N/A
	721	3.83 ± 3.55	4.64 ± 3.50	3.40 ± 2.00	3.92 ± 2.33	N/A
Cholesterol (mmol/L)	87	2.04 ± 0.33	2.01 ± 0.29	2.13 ± 0.33	2.40 ± 0.33** (118)	2.84 ± 0.36** (139)
	177	2.13 ± 0.41	2.21 ± 0.35	2.15 ± 0.37	2.22 ± 0.28	2.81 ± 0.35** (132)
	366	2.41 ± 0.62	2.55 ± 0.52	2.53 ± 0.47	2.87 ± 0.58** (119)	3.47 ± 0.99** (144)
	400	2.48 ± 0.57	2.70 ± 0.66	2.77 ± 0.59* (112)	3.30 ± 0.82** (133)	3.99 ± 0.87** (161)
	548	2.90 ± 0.66	2.82 ± 0.68	2.93 ± 0.58	3.43 ± 0.73** (118)	N/A
	721	3.13 ± 0.60	3.48 ± 0.86	3.16 ± 0.52	3.56 ± 0.58	N/A

Data taken from pp. 167-200, MRID 45404827.
*p≤0.05, **p≤0.02 or 0.002, significantly different from the control group.
[1]Numbers in parentheses are the percent of control, calculated by the reviewer.

F. URINALYSIS: There were no treatment-related findings.

G. SACRIFICE AND PATHOLOGY: Rats treated with 15,000 ppm BAS 510 F were sacrificed after approximately 17 months of treatment, but necropsy and histopathology were not performed on these groups.

1. Organ weight: Statistically significant changes were seen in absolute thyroid weight of 2500 ppm males (131% of controls, $p \leq 0.05$), relative liver weight of 2500 ppm females (111% of controls, $p \leq 0.01$), and absolute brain weight of 100 ppm females (103% of controls, $p \leq 0.05$). The increase in brain weight was considered incidental to treatment because there was no dose-response. The increased thyroid weight in 2500 ppm males was correlated with slight but not statistically significant increases in the incidence of thyroid foci, enlarged thyroid, and follicular cell hypertrophy and hyperplasia. The increased relative liver weight in 2500 ppm females was correlated with an increased incidence ($p \leq 0.01$) of centrilobular hypertrophy (which was also increased in 2500 ppm males). The liver and thyroid weights are shown in Table 6.

TABLE 6. Selected organ weights (± standard deviation) in rats fed BAS 510 F for 2 years[1].

Organ	Dietary concentration (ppm)			
	0	100	500	2500
Males (14-16/dose)				
Body wt. (g)	692.207 ± 97.869	704.144 ± 102.859	698.35 ± 88.542	696.293 ± 60.763
Liver (g)	18.869 ± 2.255	19.982 ± 4.161	20.776 ± 3.546	20.641 ± 4.811 (109)
% body weight	2.764 ± 0.44	2.884 ± 0.783	2.975 ± 0.315	3.008 ± 0.95 (109)
Thyroid glands (mg)	40.2 ± 6.316	41.625 ± 7.06	44.0 ± 15.566	52.714 ± 18.163* (131)
% body weight	0.006 ± 0.001	0.006 ± 0.001	0.006 ± 0.002	0.008 ± 0.003 (133)
Females (13-19/dose)				
Body wt. (g)	351.1 ± 36.443	354.159 ± 68.202	344.046 ± 35.373	334.142 ± 49.19
Liver (g)	10.107 ± 1.56	10.441 ± 2.274	10.357 ± 0.957	10.673 ± 1.793 (106)
% body weight	2.871 ± 0.203	2.936 ± 0.382	3.03 ± 0.336	3.194 ± 0.217** (111)
Thyroid glands (mg)	29.462 ± 5.71	26.353 ± 4.729	35.385[2] ± 23.796	30.316 ± 4.522 (103)
% body weight	0.008 ± 0.002	0.008 ± 0.003	0.01 ± 0.006	0.009 ± 0.002 (113)

Data taken from pp. 221-224, MRID 45404827.
*$p \leq 0.05$. **$p \leq 0.01$, significantly different from the control group.
[1]Numbers in parentheses are the percent of control, calculated by the reviewer.
[2]This value is due to one outlier; excluding the outlier yields 28.9 ± 4.9.

2. Gross pathology: The only lesions with an incidence statistically significantly greater than in the control group ($p \leq 0.05$) were cystic degeneration of the testes in 2500 ppm males and ovarian cysts in 2500 ppm females (a similar incidence of ovarian cysts was also seen microscopically in this group). A significant increase was not seen in any microscopic testicular lesions in 2500 pm males. A slight but non-significant increase in thyroid gland foci occurred in the 2500 ppm males, and two males (500 ppm, 2500 ppm) and one female (500 ppm) had an enlarged thyroid that corresponded to follicular cell adenoma. The gross lesions are summarized in Table 7.

TABLE 7: Incidence of gross pathology findings in rats fed BAS 510 F for 2 years.								
Organ: lesion	Dietary concentration (ppm)							
	0	100	500	2500	0	100	500	2500
	Males				Females			
Testes: Cystic degeneration	2/20	3/20	2/20	9/20*	–	–	–	–
Ovaries: Cyst	–	–	–	–	5/20	10/20	8/20	13/20*
Thyroid glands: Focus Enlarged	0/20 0/20	0/20 0/20	1/20 1/20	3/20 1/20	0/20 0/20	1/20 0/20	0/20 1/20	1/20 0/20

Data taken from pp. 50 and 225-227, MRID 45404827.
*p<0.05. **p<0.01: Significantly different from controls, determined by reviewer using Fisher exact test.

3. Microscopic pathology:

a) **Non-neoplastic:** An increased incidence of centrilobular hypertrophy occurred at 2500 ppm ($p \leq 0.01$) in both sexes, and liver eosinophilic foci were increased ($p \leq 0.05$) in the 2500 ppm males. The hypertrophy was characterized by an increase in the hepatocyte size and organelle content, and the eosinophilic foci had cytoplasmic inclusions.

The incidences of thyroid follicular cell diffuse hypertrophy and focal hyperplasia were increased in both sexes of 2500 ppm rats, but not statistically significantly. The liver and thyroid lesions correlated with the minor increases in the weights of these two organs. Several lesions of unknown etiology and toxicological significance were found as well, including an increased incidence of ovarian cysts ($p \leq 0.05$) in 500 and 2500 ppm females, and of rectal lumen parasites in 2500 ppm males. The microscopic lesions are summarized in Table 8.

TABLE 8: Incidence of microscopic pathology findings in rats fed BAS 510 F for 2 years.								
Organ: lesion	Dietary concentration (ppm)							
	0	100	500	2500	0	100	500	2500
	Males				Females			
Liver: Eosinophilic foci Centrilobular hypertrophy	3/20 0/20	4/20 0/20	7/20 1/20	9/20* 6/20**	1/20 0/20	1/20 0/20	2/20 0/20	2/20 16/20**
Rectum: Parasites in lumen	1/20	0/4	0/6	6/20*	3/20	0/20	1/20	2/20
Ovaries: Cyst	–	–	–	–	5/20	10/20	12/20*	13/20*
Thyroid glands: Hypertr. Follic. Cell. diff. Hyperpl. Foll. Cell. focal	 3/20 1/20	 1/20 1/20	 3/20 2/20	 6/20 4/20	 0/20 0/20	 1/20 0/20	 0/20 0/20	 4/20 2/20

Data from pp. 52 and 236-263, MRID 45404827.
*p≤0.05. **p≤0.01: Significantly different from controls, determined by reviewer using Fisher exact test.

a) Neoplastic: Significant increases were not seen for any type of neoplastic lesion. Thyroid follicular cell adenoma was seen in only treated animals (0/20, 0/20, 2/20, 1/20 in males and 0/20, 0/20, 1/20, 0/20 in females given 0, 100, 500, and 2500 ppm, respectively). The most commonly found tumor type in males was testicular Leydig cell adenoma (7/20, 9/14, 7/16, 10/20) and in females was pituitary gland adenoma (13/20, 7/17, 7/17, 9/20) at test concentrations of 0, 100, 500, and 2500 ppm, respectively. The number of animals with tumors and the total number of tumors (benign or malignant) were similar in the control and 2500 ppm group rats.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that the clinical chemistry changes (increased gamma-glutamyl transferase, prothrombin times, total protein, albumin, globulins, and cholesterol, and decreased total bilirubin) as well as the liver enlargement, liver weight increases and microscopic lesions (centrilobular hypertrophy and eosinophilic foci) were due to hepatic microsomal enzyme induction. A mechanistic study (Project No. 99C0179/97063, MRID 45404903) showed that various xenobiotic-metabolizing enzymes were induced by the test compound. These liver effects were considered to be an adaptive metabolic response to BAS 510 F, and not of toxicological relevance because there was no evidence of liver injury. The decreases in alanine and aspartate aminotransferase and alkaline phosphatase were considered treatment-related and due to the nutritional status of the animals, and not to be a toxicologically adverse effect in themselves. The increase in cystic degeneration of the testes in 2500 ppm males and the increase in brain weight of 100 ppm females were incidental to treatment, but the slightly decreased hemoglobin, hematocrit, MCV, and MCH in 2500 ppm females may have been due to a mild anemic process.

The small but statistically non-significant increase in the incidence of thyroid follicular cell hyperplasia and diffuse follicular cell hypertrophy in 2500 ppm animals was considered substance-related, and was in some cases correlated with thyroid foci at necropsy. These thyroid lesions, along with thyroid follicular cell adenomas, accounted for the increased thyroid weights of 2500 ppm males. A mechanistic study in which Wistar rats were given 15;000 ppm BAS 510F in the diet for 4 weeks showed a treatment-related decrease in T3/T4 thyroid hormone levels and increased thyroid stimulating hormone (MRID 45404903). Thus, the investigators postulated that the increased hepatocyte metabolic rate led to a higher turnover of T3/T4 thyroid hormones, causing a feedback stimulation of the thyroid gland that led to thyroid hypertrophy and hyperplasia and thyroid follicular cell adenoma in a few cases (2 males and 1 female at 500 ppm; 1 male at 2500 ppm). There was no evidence for any organ-specific carcinogenicity of BAS 510 F.

The investigators concluded that no treatment-related changes were observed at 100 ppm, which was therefore the no observed adverse effect level (NOAEL) under the conditions of this study. The 500 ppm animals had "slight changes indicative of enzyme induction and mild effects on the nutritional status of both sexes."

B. REVIEWER COMMENTS: The reviewer concurs with the investigators' conclusion that BAS 510 F caused centrilobular hypertrophy in both sexes and eosinophilic foci in males at 2500 ppm. The reviewer also agrees that there is sufficient evidence, especially when taking into consideration the two BASF mechanistic studies and the concurrent carcinogenicity 2-year study, to conclude that the thyroid lesions in both sexes were a secondary effect of the treatment-induced increase in liver metabolism and likely due to chronically decreased T3/T4 levels and elevated TSH levels at 2500 ppm. However, the reviewer disagrees with the investigators' assertion that 500 ppm is an effect level in both sexes based on slight changes in liver enzyme levels and in the animals' nutritional status. The body weight data shows that there were no statistically or biologically significant differences between the 500 ppm group and the control group, clinical chemistry alterations at 500 ppm were sporadic and/or not clearly dose-related, and the incidences of the thyroid and liver lesions were similar to that of the controls at 500 ppm.

The LOAEL is 2500 ppm for both sexes of rats (110.0 and 150.3 mg/kg/day for males and females, respectively) under the conditions of this study, based on thyroid toxicity (organ weight and microscopic changes) that resulted indirectly from the liver adaptive response. The NOAEL is 500 ppm (21.9 and 30.0 mg/kg/day for males and females, respectively).

At the doses tested, there was **not** a treatment related increase in the incidence of any tumor type, or in the total number of tumors. Thyroid follicular cell adenoma was seen in only treated animals (0/20, 0/20, 2/20, 1/20 in males and 0/20, 0/20, 1/20, 0/20 in females given 0, 100, 500, and 2500 ppm, respectively), but is within the range of the testing laboratory's historical control values and near the mean of 0.8%. Dosing was considered adequate based on the liver and thyroid toxicity seen in both sexes at 2500 ppm.

This chronic toxicity study in the rat is **Acceptable/Guideline**, and satisfies the guideline requirement for a chronic toxicity study [OPPTS 870.4100a; OECD 452] in rats.

C. STUDY DEFICIENCIES: No major deficiencies were identified. Minor deficiencies that are unlikely to affect the outcome or interpretation of this study include failure to weigh the spleen and uterus, and to evaluate microscopically the nose, pharynx, and larynx, and to perform neurological evaluations. Additionally, it is unclear why the same values are not obtained for the body weight from days 175-371 and 371-511 when using the weekly body weight vs. the cumulative weight gain data. Although not required, it would have been helpful for the interpretation of the study if an intermediate (12 month) sacrifice and analysis had been conducted and/or if the 15,000 ppm rats sacrificed after 17 months were necropsied and analyzed microscopically.

DATA FOR ENTRY INTO ISIS

Chronic Study: rodents (870.4100a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range: ppm, (mg/kg/day)[1]	Doses tested: ppm, (mg/kg/day)[1]	NOAEL: ppm, (mg/kg/day)	LOAEL: ppm (mg/kg/day)	Target organ(s)	Comments
128008	45404827	chronic	rats	24 months	oral	diet	100-2500 (4.4-150.3)	0, 100, 500, 2500 (♂: 0, 4.4, 21.9, 110.0; ♀: 0, 5.9, 30.0, 150.3)	500 (21.9 for ♂, 30.0 for ♀)	2500 (110.0 for ♂, 150.3 for ♀)	Thyroid	

[1]A fourth test concentration, 15,000 ppm (equivalent to 739.0 mg/kg bw/day for males and 1000.4 mg/kg bw/day for females), was given to males and females but was discontinued after 17 months due to excessive toxicity in both sexes.