DATA EVALUATION RECORD

BAS 510 F

STUDY TYPE: CARCINOGENICITY FEEDING STUDY - MOUSE
[OPPTS 870.4200b (§83-2b); OECD 451]
MRID 45404901

Prepared for 7/23/2002

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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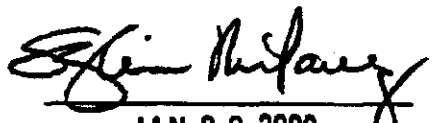
Primary Reviewer: S. Milanez, Ph.D., D.A.B.T.	Signature: Date:	 JAN 2 9 2002
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Registration Action Branch 3, Health Effects Division (7509C) **Date** _____

DATA EVALUATION RECORD
TXR#: 0050193

STUDY TYPE: Carcinogenicity feeding- mouse; OPPTS 870.4200b [§83-2b]; OECD 451.

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, K. Küttler , et al. (2001) BAS 510 F, Carcinogenicity study in C57BL mice; Administration in the diet for 18 months. Experimental Toxicology and Ecology BASF Aktiengesellschaft, D-67056 Ludwigshafen/Rhein, Germany. Laboratory Project No. 76C0179/97103, BASF Registration Document Number 2001/1000116, February 28, 2001. MRID 45404901. Unpublished.

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

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 45404901) BAS 510 F (94.4% a.i., batch no. N37, Tox-batch III) was administered to 50 C57BL/6 J Rj mice/dose in the diet at concentrations of 0, 80, 400, 2000, or 8000 ppm (equivalent to 0, 13, 65, 331, and 1345 mg/kg bw/day for males and 0, 18, 90, 443, and 1804 mg/kg bw/day for females) for 18 months.

No treatment-related effects were seen in clinical observations, survival rates, food consumption, food efficiency, differential blood count or morphology, or gross pathology. Body weights of males were statistically decreased occasionally at 400 ppm (≥92% of controls) and for most time points at 2000 ppm (≥92% of controls) and 8000 ppm (≥89% of controls). Overall body weight gains of males at 80, 400, 2000, and 8000 ppm were 94.0, 86.5, 82.0, and 75.9%, respectively, of controls, ($p \leq 0.05$ or 0.01 at ≥400 ppm). Body weights of all groups of females were within 8% of controls throughout the study, but the weight gains at 8000 ppm were consistently lower than for the controls or other dose groups starting on day 315, and their overall weight gain was 79.5% of controls (compared to gains of 92-99% of controls for the other dose groups; no dose-response). A dose-related increase in liver weights was seen in both males and females. The absolute liver weight was increased 16% in 8000 ppm males and 8-11% in 2000 and 8000 ppm females, and the relative (to body) liver weight was increased at ≥400 ppm in males (5-28%) and at ≥2000 ppm in females (8-18%). The liver weights were correlated with an increased

incidence ($p \leq 0.01$) of minimal or slight liver peripheral hypertrophy at 8000 ppm in both sexes and in 2000 ppm females. The liver effects are consistent with an adaptive response of the liver to a xenobiotic toxicant.

The LOAEL is 2000 ppm for males (331 mg/kg/day) and 8000 ppm for females (1804 mg/kg/day) under the conditions of this study, based on the significant decreases in body weight and body weight gains. The NOAEL is 400 ppm for males (65 mg/kg/day) and 2000 ppm for females (443 mg/kg/day). This disagrees with the investigators' conclusion that the LOAEL for males is 400 ppm based on lower body weights and weight gains (reviewer considers the change too small) and that the LOAEL for females is 2000 ppm based on liver effects (reviewer considers these to be a non-specific adaptive response and not appropriate as the basis for a LOAEL).

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. Dosing was considered adequate based on the body weight and weight gain decreases seen in males at ≥2000 ppm and in females at 8000 ppm.

This carcinogenicity study in the mouse is **Acceptable/Guideline**, and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

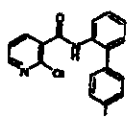
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. The GLP statement indicated that the study meets the requirements of 40 CFR Part 160, but was conducted in accordance with GLP provisions of FR Germany and the OECD. This study neither met or exceeded the criteria for flagging studies.

I. MATERIALS AND METHODS:

A. MATERIALS:

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

Description:	White solid powder
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:	Mouse
Strain:	C57BL/6 J Rj
Age/weight at study initiation:	~7 weeks old; males, 19.2-22.8 g; females, 16.4-19.9 g
Source:	Centre d'Elevage R. Janvier, France
Housing:	Singly in type MI Makrolon cages with wire mesh tops (Becker & Co., Castrop-Rauxel, Germany)
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 hours dark / 12 hours light
Acclimation period:	5-7 days for males, 10 days for females

B. STUDY DESIGN:

1. **In life dates:** Start: February 10, 1998 for males; February 27, 1998 for females; End: August 11-23, 1999 for males; August 30-September 8, 1999 for females

2. **Animal assignment/dose levels:** 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	50	50
1 (Low dose)	80	13	18	50	50
2 (Mid dose)	400	65	90	50	50
3 (Mid dose)	2000	331	443	50	50
4 (High dose)	8000	1345	1804	50	50

Data from pp. 18 and 34, MRID 45404901.

3. **Dose selection:** The high test concentration of 8000 ppm was expected to have a test substance intake of >1000 mg/kg body weight/day, which is a "limit" concentration for testing toxic substances. The other dietary concentrations were 2000 and 400 ppm as "mid concentrations" and 80 ppm as the "low concentration." No previous toxicity study results were mentioned for BAS 510 F.

4. **Diet preparation and analysis:** Diets were prepared approximately every 4 weeks by mixing appropriate amounts of test substance with ground Kliba maintenance diet rat/mouse/hamster meal and were stored at ambient temperature. The stability of the test material in the diet over 32 days at room temperature was determined prior to study initiation. Three or four 100 ppm samples were assayed at times 0, 13, 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 also tested after 6, 9, 12, 15, and 18 months of treatment. 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).

Results:

Homogeneity analysis: The mean and standard deviation of the measured concentration of 80 ppm samples (duplicate analyses of three samples) was 91.4 ± 0.3% of nominal at the beginning of the study and 109.6 ± 3.4% after 3 months. Analogous analyses for the 8000 ppm samples yielded 101.1 ± 1.8% of nominal at study initiation and 95.4 ± 0.6% 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 (mean of 97.5% and 97.9% of time 0 concentration).

Concentration analysis: The mean of duplicates (of 1 or 3 samples/dose) at 0, 3, 6, 9, 12, 15, and 18 months as a percent of nominal concentrations ranged from 91.4-110.0% at 80 ppm, 92.4-102.6% at 400 ppm, 92.2-100.5 at 2000 ppm, and 92.3-101.1% at 8000 ppm.

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. 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 Wilcoxon test (significance reported as p ≤0.05 or 0.01). The reviewer considers the analyses used to be appropriate, and additionally 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 - Friday and once a day on Saturday and Sunday and on holidays.

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

2. **Body weight:** Animals were each weighed prior to dosing (to randomize the animals), on study day 0, and weekly through week 13. Thereafter, mice 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:** Not conducted; not a guideline requirement.

5. **Hematology and clinical chemistry:** Blood was collected during the treatment period by tail puncture (non-fasted mice; no anesthesia) and at study termination by decapitation (fasted overnight; anesthetized) to prepare differential blood smears. Only the control and 8000 ppm groups were evaluated, which is the minimum required for carcinogenicity studies based on Guideline 870.4200 & OECD 451. Clinical chemistry studies were not conducted and are not required for carcinogenicity studies based on Guideline 870.4200 & OECD 451.

6. **Urinalysis:** Urinalysis was not conducted and is not required for carcinogenicity studies based on Guideline 870.4200 & OECD 451.

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 tissues in control and 8000 ppm animals, but only the lungs, liver, kidneys, and all gross lesions were examined in the 80, 400 and 2000 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*	x	Thyroids*
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 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 carcinogenicity studies based on Guideline 870.4200.
+Organ weight required in carcinogenicity studies.
- Not preserved

II RESULTS

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** The incidence of abnormal clinical observations was comparable in control and treated animals.

2. **Mortality:** Mortality rates were comparable among all treatment groups: mortality rates at study termination (day 546) were 6, 10, 8, 16, and 6% for males and 8, 8, 4, 4, and 2% for females administered 0, 80, 400, 2000, and 8000 ppm BAS 510 F, respectively.

B. **BODY WEIGHT:** Body weights of males were slightly(≤5.7%) lower than of controls in all dose groups until day 42, but the changes were not clearly dose-related. After this time, body weights of the 400, 2000, and 8000 ppm males were decreased relative to controls in a dose-related manner, the changes being statistically significant for some time points at 400 ppm (92.6-97.7% of controls) and for most time points at 2000 and 8000 ppm (91.2-97.3% and 89.4-96.2% of controls, respectively). The body weight gains of males followed a similar pattern, the decrease in overall gains being significant in the 400, 2000, and 8000 ppm groups (86.4, 81.9, and 76.2%, respectively, of controls, $p \leq 0.05$ or 0.01). The body weights and body weight gains of males are summarized in Table 2.

TABLE 2: Mean body weights and body weight gains (± standard deviation) for male mice fed BAS 510 F for 18 months.[1]

Study day	Dietary concentration (ppm)				
	0	80	400	2000	8000
Mean body weights (g) – males					
0	21.2 ± 0.8	21.3 ± 0.8	21.2 ± 0.8	21.2 ± 0.7	21.2 ± 0.6
91	29.0 ± 2.1	28.5 ± 1.8	28.2 ± 2.0	27.9* ± 1.8 (96.4)	27.5** ± 1.4 (94.8)
175	30.5 ± 2.6	29.5 ± 2.4	29.2* ± 2.4 (96.0)	28.8** ± 2.4 (94.6)	28.2** ± 2.0 (92.5)
287	32.9 ± 3.2	32.4 ± 3.1	32.1 ± 3.0	31.7 ± 3.2	30.8** ± 2.4 (93.7)
371	33.4 ± 3.3	32.8 ± 3.8	32.2 ± 3.3	31.8* ± 3.4 (95.1)	30.9** ± 2.2 (92.4)
455	34.5 ± 3.9	33.5 ± 3.2	32.6* ± 3.3 (94.5)	32.0** ± 3.3 (92.7)	31.5** ± 2.6 (91.2)
546	34.4 ± 4.1	33.8 ± 3.8	32.6* ± 3.9 (94.6)	32.1** ± 3.3 (93.2)	31.3** ± 2.5 (90.8)
Mean body weight gains (g) – males					
0-91	7.8 ± 2.0	7.3 ± 1.7	7.0* ± 1.7 (89.3)	6.7** ± 1.5 (85.9)	6.3** ± 1.2 (80.7)
0-175	9.3 ± 2.5	8.2 ± 2.3	8.1* ± 2.2 (86.7)	7.6** ± 2.1 (81.9)	7.0** ± 1.9 (75.5)
0-371	12.3 ± 3.1	11.6 ± 3.6	11.1 ± 3.0	10.6* ± 3.0 (86.1)	9.7** ± 2.1 (79.3)
0-546	13.3 ± 3.9	12.5 ± 3.5	11.5* ± 3.7 (86.4)	10.9** ± 2.9 (81.9)	10.1** ± 2.3 (76.2)
175-371[2]	2.9	3.3	3.0	3.0	2.7
371-546[2]	1.0	1.0	0.4	0.3	0.4

Data taken from pp. 69-72 and 77-80, MRID 45404901.
[1]Numbers in parentheses are the percent of control.
[2]Calculated by the reviewer and not statistically analyzed.
*p≤0.05, **p≤0.01, significantly different from the control group.

Body weights of the 80, 400, and 2000 ppm females were within 5% of the control group throughout the study with the exception of day 427 (93.6% of controls at 80 and 400 ppm) and the changes were sporadically statistically significant. Body weights of the 8000 ppm females were within 5% of controls until day 399, and were within 7.6% of controls

thereafter, with statistical significance achieved at most time points starting on day 231. Body weight gains of all dose groups were somewhat lower than of controls but the change was not dose-related until day 315, at which time the 8000 ppm group began to have consistently lower gain ($p \leq 0.05$ or 0.01) than the other dose groups. The overall weight gain for the 8000 ppm females was 79.5% of controls and of the other three dose groups was 92.0-99.0% of controls (no dose-response). The body weights and body weight gains of females are summarized in Table 3.

TABLE 3: Mean body weights and body weight gains (± standard deviation) for female mice fed BAS 510 F for 18 months. [1]

Study day	Dietary concentration (ppm)				
	0	80	400	2000	8000
Mean body weights (g) – females					
0	18.1 ± 0.8	18.0 ± 0.7	18.0 ± 0.7	18.2 ± 0.7	18.0 ± 0.8
91	22.4 ± 1.1	22.1 ± 1.1	21.9 ± 1.1	22.5 ± 1.2	22.3 ± 1.0
175	23.8 ± 1.7	23.6 ± 1.4	23.3 ± 1.5	24.2 ± 1.7	23.4 ± 1.4
287	25.0 ± 2.1	24.3 ± 1.7	23.9* ± 1.8 (95.6)	24.7 ± 2.3	23.9* ± 1.5 (95.6)
371	25.4 ± 2.2	25.2 ± 1.8	24.9 ± 1.7	25.9 ± 2.6	24.8 ± 1.7
455	27.5 ± 3.2	26.9 ± 2.3	26.5 ± 2.5	27.2 ± 3.1	25.7** ± 2.0 (93.5)
546	28.0 ± 3.1	27.6 ± 2.6	27.1 ± 3.0	28.0 ± 3.6	25.9** ± 2.8 (92.6)
Mean body weight gains (g) – females					
0-91	4.3 ± 0.9	4.1 ± 0.8	3.9 ± 0.9	4.3 ± 0.9	4.2 ± 0.9
0-175	5.7 ± 1.4	5.5 ± 1.2	5.3 ± 1.2	6.0 ± 1.5	5.4 ± 1.3
0-371	7.3 ± 1.8	7.2 ± 1.6	6.9 ± 1.5	7.8 ± 2.2	6.8 ± 1.7
0-546	9.9 ± 2.9	9.6 ± 2.5	9.1 ± 2.7	9.8 ± 3.3	7.9** ± 2.7 (79.5)
175-371[2]	1.6	1.6	1.6	1.7	1.4
371- 546[2]	2.6	2.4	2.2	2.1	1.1

Data taken from pp. 73-76 and 81-84, MRID 45404901.
[1]Numbers in parentheses are the percent of control.
[2]Calculated by the reviewer and not statistically analyzed.
*$p \leq 0.05$, **$p \leq 0.01$, significantly different from the control group.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption was slightly lower ($p \leq 0.05$ or 0.01) than of controls throughout much of the study for both sexes but did not differ among dose groups, indicating the differences were not treatment-related. The total food consumption (calculated by reviewer) was within 2.6% and 9.1% of controls, respectively, for males and females.

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

3. **Food efficiency:** No consistent differences were seen among the control and treated groups of either sex.

D. OPHTHALMOSCOPIC EXAMINATION: Not conducted.

E. BLOOD ANALYSES:

1. **Hematology:** No treatment-related changes were seen in the leukocyte differential count or in the morphology of leukocytes or erythrocytes.

2. **Clinical chemistry:** Not performed.

F. URINALYSIS: Not performed.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** A dose-related increase in liver weights was seen in both males and females. The absolute liver weight was increased statistically in 8000 ppm males (16%) and in 2000 and 8000 ppm females (8-11%), and the relative (to body) liver weight was increased statistically at ≥400 ppm in males (5-28%) and at ≥2000 ppm in females (8-18%). [The liver-to-brain weight ratios, calculated by the reviewer but not shown, were similarly increased.] Regarding other organs, there were absolute and/or relative weight differences between treated and control groups, but these were considered to be only of a questionable relationship to test article administration. The liver weights for both sexes are shown in Table 4.

TABLE 4. Liver weights (± standard deviation) in mice fed BAS 510 F for 18 months[1].

Organ	Dietary concentration (ppm)				
	0	80	400	2000	8000
Males [n=42-47]					
Body wt. (g)	31.7 ± 3.8	31.0 ± 3.7	29.8* ± 3.7 (94)	29.1** ± 3.2 (92)	28.6** ± 2.4 (90)
Liver (mg) % body weight	1260.0 ± 149.5 4.0 ± 0.4	1235.1 ± 120.9 4.0 ± 0.4	1245.7 ± 140.8 4.2** ± 0.4 (105)	1329.1 ± 169.5 4.6** ± 0.3 (115)	1465.5** ± 152.1 (116) 5.1** ± 0.4 (128)
Females [n=46-49]					
Body weight (g)	25.1 ± 2.9	24.5 ± 2.4	24.2 ± 2.9	25.1 ± 3.3	23.5** ± 2.5 (94)
Liver (mg) % body weight	1166.7 ± 172.1 4.7 ± 0.7	1251.4[2] ± 601.0 (107) 5.1[2] ± 2.4	1150.4 ± 151.2 (99) 4.8 ± 0.5	1261.0** ± 174.0 (108) 5.1** ± 0.6 (109)	1289.3** ± 132.0 (111) 5.5** ± 0.5 (117)

Data taken from pp. 115-118. MRID 45404901.
*p≤0.05; **p≤0.01, significantly different from the control group.
[1]Values were rounded by the reviewer to one decimal place (three were given) for ease of display. Numbers in parentheses are the percent of control, calculated by the reviewer using unrounded values.
[2]This mean includes an outlier (mouse #311 had weight of 4775 mg; also, # 306 had weight of 2792 mg); this group range without these two was 706-1451 mg; the heaviest liver weight in all other groups was 1901 mg; without the 4775 mg liver, the mean liver weight would be 1173.1 g absolute (101% of control) and 4.8% of body weight (102% of control).

2. **Gross pathology:** The incidences of all lesions were comparable to the control groups.

3. **Microscopic pathology:**

a. **Non-neoplastic:** The liver was affected by treatment in both sexes. The incidence of liver peripheral (periportal) hypertrophy was increased significantly ($p \leq 0.01$) at 8000 ppm in both sexes and in 2000 ppm females. The hypertrophy was minimal or slight (severity grade 1 or 2), and the cytoplasm of the enlarged cells stained eosinophilic and appeared "delicate granular." Females given ≥400 ppm had a shift from diffuse to centrilobular hepatocyte fatty infiltration (comparable severity grades), which was correlated at ≥2000 ppm with peripheral hypertrophy. An increased incidence of oval cell proliferation (minimal or slight in most animals) was also seen in 8000 ppm females ($p \leq 0.05$), although there was an inconsistent dose-response from 80-2000 ppm. These liver effects are correlated with the increases in liver weights in both sexes, and are consistent with an adaptive response of the liver to a xenobiotic toxicant. The liver lesions are summarized in Table 5.

Statistical differences from controls were seen for several other findings, although they were considered incidental to treatment because they lacked a clear dose-response and were not toxicologically significant. These findings included a decreased incidence of epididymide lymphoid infiltration and adrenal cortex focal atrophy in 8000 ppm males and of sternum fibro-osseous lesions in 8000 ppm females.

TABLE 5: Incidence [and severity grade] of non-neoplastic microscopic liver changes in mice fed BAS 510 F for 18 months.

Liver lesion	Dietary concentration (ppm)				
	0	80	400	2000	8000
	Males				
Peripheral hypertrophy	0/50	0/50	0/50	0/50	29/50** [1.66][1]
Fatty infiltration, centrilob.	38/50 [3.53]	39/50 [3.51]	39/50 [3.82]	41/50 [3.80]	37/50 [3.81]
Fatty infiltration, diffuse	10/50 [3.30]	7/50 [3.71]	7/50 [3.00]	3/50 [2.67]	10/50 [3.50]
Oval cell proliferation	4/50 [1.75]	2/50 [1.50]	2/50 [3.00]	0/50	6/50 [1.50]
	Females				
Peripheral hypertrophy	0/50	0/50	0/50	10/50** [1.50]	45/50** [1.84]
Fatty infiltration, centrilob.	10/50 [3.30]	11/50 [3.64]	25/50** [3.68]	25/50** [3.64]	37/50** [3.49]
Fatty infiltration, diffuse	35/50 [3.63]	35/50 [3.69]	22/50** [3.82]	23/50* [3.87]	10/50** [3.90]
Oval cell proliferation	7/50 [1.57]	3/50 [1.00]	2/50 [1.00]	6/50 [1.50]	15/50* [1.40]

Data from pp. 134-176, MRID 45404901.
*$p \leq 0.05$, **$p \leq 0.01$: Significantly different from controls, determined by reviewer using Fisher exact test.
[1]Numbers in brackets are severity ratings, calculated by the reviewer using only affected animals, with the rating scheme: Grade 1=minimal; 2=slight; 3=moderate; 4=marked, severe; 5=massive, extreme.

b. **Neoplastic**: Neither sex had statistically significant increases in the incidence or total number of any type of tumor (primary, benign or malignant), or in the number of tumor-bearing animals. The 8000 ppm males had a decreased incidence of lung adenomas (0/50 vs. 6/50 in controls, $p \leq 0.05$) and a slight decrease in the total number of neoplasms that were considered incidental to treatment.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The investigators considered as toxicologically significant the lower body weights and weight gains in males at ≥400 ppm and in females at 8000 ppm. The liver was identified as a target organ based on the increased incidence of peripheral hepatocellular hypertrophy and correlating increased liver weights (absolute and/or relative to body weight) in 8000 ppm males and in 2000 and 8000 ppm females. The shift from diffuse to centrilobular fatty infiltration in females given ≥400 ppm was not considered to be toxicologically relevant, and to perhaps reflect the cell hypertrophy that occurred in this area of the liver. Other changes in absolute and/or relative organ weights (increased liver weights in 400 and 2000 ppm males, increased testes weights in males, decreased kidney weights, increased brain and adrenal weights in both sexes) lacked histopathological correlates and/or were due to the animals' lower body weight gains and were considered incidental to treatment. The investigators concluded that the NOAELS were 80 ppm for males and 400 ppm for females. The LOAEL of 400 ppm for males was based on their lowered body weights and body weight gains, and the LOAEL of 2000 ppm for females was based on liver effects (weight increases and peripheral hypertrophy). The investigators also concluded that BAS 510 F was not carcinogenic to mice.

B. **REVIEWER COMMENTS:** The reviewer concurs with the investigators' conclusion that BAS 510 F was not carcinogenic to mice, under the conditions of this study. The reviewer disagrees with the investigators, however, that the LOAEL for males is 400 ppm (based on decreased body weight and weight gain) and for females is 2000 ppm (based on hepatocellular peripheral hypertrophy and the associated liver weight increase). A LOAEL should not be set based on liver effects for either sex because this is an adaptive response to exposure to a xenobiotic, and its severity was mild. Body weights of 400 ppm males were occasionally slightly (≤7%) but statistically lower than of controls and their overall weight gain was 86.4% of controls, which the reviewer does not consider toxicologically significant. Rather, the LOAEL for males is 2000 ppm, which resulted in lowered body weights (within 8% of controls) throughout most of the study, and an overall weight gain of 81.9% of controls. The LOAEL for females is 8000 ppm based on their decreased overall body weight gains (79.5% of controls, compared to gains of 97, 92, and 99% of controls, for the 80, 400, and 2000 ppm groups, respectively).

The LOAEL is 2000 ppm for males (331 mg/kg/day) and 8000 ppm for females (1804 mg/kg/day) under the conditions of this study, based on the significant decreases in body weight and body weight gains. The NOAEL is 400 ppm for males (65 mg/kg/day) and 2000 ppm for females (443 mg/kg/day).

BAS 510 F was not carcinogenic to mice under the conditions of this study. Neither sex had a statistically significant increase in the incidence or total number of any type of tumor (primary, benign or malignant), or in the number of tumor-bearing animals. Dosing was considered adequate based on the body weight and weight gain decreases seen in males at ≥2000 ppm and in females at 8000 ppm.

This carcinogenicity study in the mouse is **Acceptable/Guideline**, and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice. No major deficiencies were identified.

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.

DATA FOR ENTRY INTO ISIS

Carcinogenicity Study - mice (870.4200b)

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	45404901	carcinogenicity	mice	18 months	oral	diet	80-8000 (13-1804)	0, 80, 400, 2000, 8000 (♂: 0, 13, 65, 331, 1345; ♀: 0, 18, 90, 443, 1804)	♂: 400 (65) ♀: 2000 (443)	♂: 2000 (331) ♀: 8000 (1804)	Body weight decreases.	

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