

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
BAS 510 F

Chemical Code # 5790, Tolerance # 52882
Original date: 5/2/02. Revised date: 9/9/02

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effects
Chronic toxicity, dog:	No data gap, no adverse effects
Oncogenicity, rat:	No data gap, possible adverse effects
Oncogenicity, mouse:	No data gap, no adverse effects
Reproduction, rat:	No data gap, no adverse effects
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, no adverse effects
DNA damage:	No data gap, no adverse effects
Neurotoxicity:	Not required at this time †.

† There are acceptable rat acute and subchronic neurotoxicity studies. An unacceptable but upgradeable rat developmental neurotoxicity study has been submitted.

Toxicology one-liners are attached.

All record numbers for the above study types through 188025 (Document No. 52882-066) were examined. This includes all relevant studies indexed by DPR as of 9/5/02.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: t190605A
Leung, 9/9/02

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

(See chronic and oncogenicity rat categories).

CHRONIC TOXICITY, RAT

****52882-013 182899** Mellert, W., K. Deckardt, W. Kaufmann, K. Heider, and B. van Ravenzwaay, "BAS 510 F chronic toxicity study in Wistar rats: Administration in the diet for 24 months," BASF AG, Ludwigshafen, 2/28/01. Lab Project ID # 82C0179/97091. Twenty rats/sex/group were dosed with 0, 100, 500, 2500, or 15000 ppm BAS 510 F (94.4% purity) for up to 2 years in a chronic study design. Investigators terminated the 15000 ppm males and females at 17 months, without further processing. Estimated mean exposures were 4.4, 22, 110, and 739 mg/kg/day in males, and 5.9, 30, 150, and 1004 mg/kg/day in females. NOEL = 500 ppm (22 and 30 mg/kg/day in M and F, respectively). Major findings at 2500 ppm included elevated relative liver weight (F), elevated absolute thyroid gland weight (M), and elevated cholesterol (M and F). The associated histopathology at 2500 ppm included liver centrilobular hypertrophy and thyroid follicular cell hypertrophy and hyperplasia. There were various statistically significant clinical chemistry values at 500 ppm and occasionally at 100 ppm. These were not used to define the NOEL because they were either not in the direction of general diagnostic relevance, or they did not correlate with changes in target organs identified by histopathology. This study was originally unacceptable to DPR based on a poorly selected dosage range. The study has been upgraded to **acceptable**, based on the response provided in 52882-066 188022 and 188023. Findings other than oncogenicity (see Record No. 182900, below) do not constitute "possible adverse effects." There is no independent worksheet for Record No. 188023. The supplemental review which applies to Record Nos. 188022 and 188023 is under file name "w188022 832 suppl.wpd." Aldous, 4/19/02 and 9/4/02.

ONCOGENICITY, RAT

****52882-014 182900** (with rebuttal in 52882-066 188022). An additional record number (188023) has been assigned to this rebuttal, since the rebuttal relates to the chronic and oncogenicity studies, which share the same major deficiency). Mellert, W., K. Deckardt, W. Kaufmann, K. Heider, and B. van Ravenzwaay, "BAS 510 F carcinogenicity study in Wistar rats: Administration in the diet for 24 months", BASF AG, Ludwigshafen, 2/28/01. Lab Project ID # 82C0179/97090. Fifty rats/sex per group were dosed with 0, 100, 500, 2500, or 15000 ppm BAS 510 F (94.4% purity) for up to 2 years in an oncogenicity study. Investigators terminated the 15000 ppm males (769 mg/kg/day) and females (1024 mg/kg/day) at 17 months, without further processing. A need for termination was unclear, since neither sex showed clinical signs of toxicity nor food consumption effects at any dose. Body weight was unaffected at 15000 ppm in males, whereas 15000 ppm females had body weights which were 13 % below concurrent controls and 9-10% below the body weights of the apparently unaffected lower two dose groups

at 17 months. The 2500 ppm females had significant body weight decrements at study term, suggesting an adequate dose challenge for females. Chronic effects NOEL = 500 ppm (23 and 30 mg/kg/day in males and females, respectively). Both sexes at 2500 ppm had statistically significant increases in liver centrilobular hypertrophy and thyroid follicular lesions (hypertrophy and hyperplasia). Modest increases in follicular adenomas in both sexes (incidences of 0/70 for male and female controls after combining chronic and oncogenicity study rats, vs. 5/70 and 3/70 in 2500 ppm males and females, respectively) were above historical control values and are considered treatment-related. Males at 2500 ppm had significantly elevated thyroid weights. The thyroid findings are plausibly related to overstimulation of follicular cells. Study was originally classified **unacceptable** because males were not challenged at an MTD. Investigators responded by confirming that the thyroid lesions (including adenomas) were treatment-related effects in both sexes at 2500 ppm, and by citing additional studies previously reviewed by DPR, which indicate that thyroid findings were probably secondary to elevated liver metabolic activity. In addition, a new subacute/recovery study (52882-066 188025) has been submitted in support of this concept. That study confirmed elevated circulating TSH (without alterations in T3 and T4) after 4 weeks of treatment at 2500 or 15000 ppm, with no altered levels in any of these hormones at 4 weeks or 3 months after dosing cessation. This reviewer re-examined the oncogenicity study histopathology data for evidence of treatment effects at 2500 ppm, other than previously reported changes in liver and thyroids. No such changes were evident. Although no MTD was achieved in males, the 2500 ppm exposure was clearly in the toxic range in both sexes. It is recommended that the oncogenicity and chronic studies (Record Nos. 182899 and 182900) be upgraded to **acceptable** status. Aldous, 4/19/02 and 8/4/02.

A Fisher’s Exact Test comparison of high dose males vs. controls from chronic plus oncogenicity studies combined (Record Nos. 182899 and 182900) yields a significant response for a 1-tailed comparison at $p < 0.05$. The general increases in follicular adenomas, as well as associated hypertrophy and hyperplasia, had been noted in the investigators’ reports to represent treatment responses. Incidences of adenomas in other groups of males and of corresponding females were not significantly different in pairwise comparisons.

Microscopic Findings (from Record Nos. 182899 and 182900)

Tissue and lesion (page cited)	Dose (ppm)							
	Males				Females			
	0	100	500	2500	0	100	500	2500
Thyroid gland (N =)	(70)	(70)	(70)	(70)	(70)	(70)	(70)	(70)
Follicular cell hypertrophy, diffuse	5	6	9	28***	2	1	0	8*
Follicular cell hyperplasia, focal	2	2	3	13**	2	2	1	9*
Follicular cell adenoma	0	0	3	5*	0	1	1	3

*, **, *** Significant, $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively. Analysis by DPR reviewer, using 1-tailed comparisons.

CHRONIC TOXICITY, DOG

**52882-012 182898 Wiemann, C., K. Deckardt, W. Kaufmann, A. Kolling, and B. Hildebrand, "BAS 510 F - Chronic oral toxicity study in beagle dogs: Administration in the diet for 12 months," BASF AG, Ludwigshafen, 8/29/00. Lab Project ID # 33D0179/97118. Five beagles per sex per group were dosed with 0, 200, 800, 2000, or 20000 ppm BAS 510 F for 1 year in a chronic study design. Corresponding estimated achieved doses were 5.5, 22, 57, and 544 mg/kg/day in males, and 5.8, 22, 58, and 593 mg/kg/day in females. All dogs survived the study. NOEL = 800 ppm (22 mg/kg/day), based on general increases in liver and thyroid gland weights in both sexes, and on alterations in the following serum constituent activities or concentrations in males: decreased ALT, increased alkaline phosphatase (ALP), and marginally increased triglycerides. These serum findings were observed in both sexes at 20000 ppm. All major findings are consistent with altered liver function, with possible secondary effects on thyroid glands. Acceptable. No adverse effects are indicated. Aldous, May 1, 2002.

52882-065 186870 This appears to be the indexed version of a 4/30/02 response to concerns on the acceptability of the above record. The essential information was faxed to DPR during the writing of that review, and was considered in the May 1, 2002 review, above. Aldous 9/5/02.

ONCOGENICITY, MOUSE

52882-015 182901 Mellert, W., K. Deckardt, K. Küttler, and B. van Ravenzwaay, "BAS 510 F carcinogenicity study in C57BL mice: Administration in the diet for 18 months," BASF AG, Ludwigshafen, 2/28/01. Lab Project ID # 76C0179/97103. Fifty mice/sex/group were dosed with 0, 80, 400, 2000, or 8000 ppm BAS 510 F, 94.4% purity, for 18 months in a standard oncogenicity study. Estimated mean achieved dosages were 13, 65, 331, and 1345 mg/kg/day in dosed males, and 18, 90, 443, and 1804 mg/kg/day in females. NOEL for males = 80 ppm (13 mg/kg/day), based on slightly elevated relative liver weights at 400 ppm. NOEL for females = 400 ppm (90 mg/kg/day). Both sexes had elevated absolute and relative liver weights at 2000 and 8000 ppm. Females had dose-related liver periportal hypertrophy at those levels, whereas males were affected only at 8000 ppm. All doses were well tolerated, with no effects on survival nor clinical signs. Body weights were reduced meaningfully in 2000 and 8000 ppm males and in 8000 ppm females. There was no oncogenicity effect. **Acceptable, with no adverse effects. Aldous, 3/7/02.

REPRODUCTION, RAT

**52882-018 182906 Schilling, K., Chr. Gemhardt, and B. van Ravenzwaay, "BAS 510 F: Two generation reproduction toxicity study in Wistar rats. Continuous dietary administration." BASF AG, Ludwigshafen, 2/22/01. Laboratory Project ID 70R0179/97136. Wistar rats, 25/sex/group, were dosed continuously in diet with BAS 510 F, 94.4% purity, for 2 generations (1 litter per generation) in a reproduction study, at 0, 100, 1000, or 10000 ppm. Mean exposures of F0 males were 10.1, 101, and 1034 mg/kg/day. Mean exposures of F0 females during pre-mating periods were 10.7, 107, and 1062 mg/kg/day. Estimated mean exposures of F1 parents were slightly higher due to earlier onset of treatment. Adult toxicity NOEL = 100 ppm (10.1

mg/kg/day) [liver centrilobular (acinar zone 3) hypertrophy (M & F) and reduced spleen weights (M) at 1000 ppm]. Findings in adults at 10000 ppm included increased liver weights and decreased spleen weights (M & F), liver centrilobular degeneration (M) and diminished body weights in F1 females. Reproductive effects NOEL = 10000 ppm (no effects noted). Pup growth and viability NOEL = 1000 ppm [pup body weight decrements, especially postnatal day 14 onward; slightly increased early postnatal deaths (reduced F2 litter day 0-4 viability index)]. Acceptable, with no adverse effects. Aldous, 3/18/02.

TERATOLOGY, RAT

**52882-017 182905 Schilling, K. and J. Hellwig, "BAS 510 F - Prenatal developmental toxicity study in Wistar rats: Oral administration (gavage)," BASF AG, Ludwigshafen, Sept. 1, 2000. Laboratory Project ID: 30R0179/97140. Wistar rats, 25/group, were dosed by gavage with BAS 510 F (94.4% purity) in aq. 0.5% Tylose CB 30.000 suspension at 0, 100, 300, and 1000 mg/kg/day over gestation days 6-19 in a standard teratology study. There was no definitive maternal nor developmental toxicity (NOEL = 1000 mg/kg/day: the limit dose level). DPR review shows a statistically significant increase in incidence of incomplete ossification of the thoracic centra, without supportive evidence of treatment response in the vertebral column. The latter appears to be incidental. Acceptable, with no adverse effects. Aldous, 2/8/02.

TERATOLOGY, RABBIT

**52882-064 183074 Schilling, K. and J. Hellwig, "BAS 510 F - Prenatal developmental toxicity study in Himalayan rabbits: Oral administration (gavage)," BASF AG, Ludwigshafen, 6/26/00. Laboratory Project ID: 40R0179/97127. Himalayan rabbits, 25/group, were dosed by gavage with BAS 510 F (94.4% purity) in aq. 0.5% Tylose CB 30.000 suspension at 0, 100, 300, and 1000 mg/kg/day over gestation days 7-28 in a standard teratology study. Maternal NOEL = 100 mg/kg/day (based on abortions: 3 at 1000 mg/kg/day and 1 at 300 mg/kg/day). There was also one premature delivery at 1000 mg/kg/day, plausibly treatment-related. These 5 does generally had poor food consumption for sustained periods prior to abortion/premature delivery, suggesting that poor vitality was an important predisposing factor. Food consumption and maternal body weight gain decrements were generally seen at 1000 mg/kg/day. Developmental NOEL = 1000 mg/kg/day (no effects seen). Acceptable, with no adverse effects. Aldous, 2/7/02.

GENE MUTATION

** 52882 - 020 182908 Engelhardt, G. and H. D. Hoffmann "Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with BAS 510 F (Reg. No. 300 355)." (BASF, Department of Toxicology, Lab. Project Id. 40M0179/974089, Document Number 1998/11440, December 18, 1998) *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA were tested with BAS 510 F (95.3%) for induction of mutations in two trials with and without rat liver activation. Trial 1 used plate incorporation with concentrations of 0 (DMSO), 22, 110, 550, 2750 or 5500 : g/plate. Trial 2 used preincubation for 20 minutes with shaking before plating at

0, 20, 100, 500, 2500 or 5000 : g/plate. There were triplicate plates per concentration. BAS 510 F formed a precipitate at 500 : g/plate and above. There was evidence of cytotoxicity at the higher concentrations. Positive controls were functional. No evidence of mutagenicity with any strain - **no adverse effect**. **Acceptable**. Gee, 2/15/02.

** 52882 - 020 182909 Engelhardt, G. and H. D. Hoffmann "In vitro gene mutation test with BAS 510 F in CHO cells (HPRT locus assay)." (Experimental Toxicology and Ecology, BASF, lab no. 50M0179/974097, document no. 2000/1000180, January 25, 2000) CHO K1 cells were exposed for 4 hours to BAS 510 F (94.4% purity) in two trials with and without rat liver activation. Concentrations in trial 1 were 0 (untreated), 0 (DMSO), 15.625, 31.25, 62.5, 125, 250 or 500 : g/ml \pm S9. In the second trial, with S9, they were 0, 0, 10.24, 25.6, 64, 160, 400 or 1000 : g/ml. Without activation in the repeat trial, 0, 0, 3.125, 6.25, 12.5, 25, 50 or 100 : g/ml. There were duplicate cultures at each concentration and 6 replicate plates per culture for mutant frequency. The positive controls were ethyl methane sulfonate without activation and methylcholanthrene with activation. Both were functional. There was evidence of cytotoxicity around 31 to 50 : g/ml from reduced cloning efficiency 17 - 24 hours after exposure and from morphology. There was no evidence for an exposure-related increase in mutant frequency in either trial. **Acceptable with no adverse effect**. Gee, 2/15/02.

CHROMOSOME EFFECTS

** 52882 - 020 182910 Engelhardt, G. and H. D. Hoffmann "In vitro chromosome aberration assay with BAS 510 F in V79 cells." (Department of Toxicology, BASF, Lab. Project ID 32M0179/974076, document no. 1999/10978, August 3, 1999) BAS 510 F (94.4% purity) was tested with Chinese hamster V79 cells for the induction of chromosomal aberrations. In the first trial, exposure was for 4 hours (without serum) and cells harvested at 18 hours (14 hours after the end of treatment) both with and without activation (rat liver S9). Concentrations were 0, 20, 100 or 500 : g/ml. In the second trial, exposure was for 18 hours without activation at concentrations of 0, 31.25, 62.5 or 125 : g/ml and exposure for 28 hours at 0, or 125 : g/ml. With activation, the exposure was for 4 hours and harvest at 28 hours with concentrations of 0, 125, 250 or 500 : g/ml. Ethyl methyl sulfonate, 350 : g/ml, and cyclophosphamide, 0.5 : g/ml, were the positive controls without and with activation, respectively, and were functional. There were duplicate cultures for each concentration in each trial. A total of 200 cells from each concentration (100 per culture) were scored and 1000 cells evaluated for mitotic index. Osmolality and pH were also checked as was cell morphology. The high concentration was selected on solubility in the culture medium rather than evidence of cytotoxicity. There was no effect of BAS 510F on cell count, mitotic index or chromosomal aberrations with or without activation. **Acceptable with no adverse effect**. Gee, 2/15/02.

DNA DAMAGE

** 52882 - 020 182912 Engelhardt, G. and H. D. Hoffmann "In vitro unscheduled DNA synthesis (UDS) assay with BAS 510 F in primary rat hepatocytes." (Experimental Toxicology and Ecology, BASF, Lab. Project Id. 81M0179/974096, Document Number 2000/1011413, April 14, 2000). Primary rat hepatocytes from male Wistar rats were used in two experiments to determine if BAS 510 F (94.4%, batch N37) induced unscheduled DNA synthesis with 18 - 20

hours of exposure. Concentrations in the first experiment were 0 (untreated), 0 (DMSO), 1, 5, 10, 50, 100, 250 and 500 : g/ml with slides from 1 through 50 : g/ml evaluated, 100 cells total per concentration from 2 - 3 slides using autoradiography with ³H-thymidine incorporation. In the second experiment, the concentrations were 0, 0, 1.563, 3.125, 6.25, 12.5, 25 and 50 : g/ml with 6.25 through 50 : g/ml evaluated. 2-Acetylaminofluorene was the positive control and was functional. Cytotoxicity was measured by LDH release, lactate concentration and morphology. There was no evidence for the induction of unscheduled DNA synthesis in either experiment. **Acceptable with no adverse effect.** (Gee, 2/20/02)

** 52882 - 020 182911 Engelhardt, G. and H. D. Hoffmann "Cytogenetic study in vivo with BAS 510 F in the mouse micronucleus test after two intraperitoneal administrations." (Department of Toxicology, BASF, Lab. Project No. 26M0179/974095, Document Number 1999/11048, August 16, 1999) BAS 510 F (batch N 37, 94.4% purity) was given by intraperitoneal injections to 5 male NMRI mice per group. Two injections were given 24 hours apart with sacrifice 24 hours after the second injection. Doses were 0 (0.5% carboxymethyl cellulose), 500, 1000 or 2000 mg/kg body weight, 20 ml/kg. The positive controls were cyclophosphamide for clastogenic effects and vincristine for spindle poison effects. For each animal, 2000 polychromatic erythrocytes were scored, the micronuclei in normal erythrocytes and the ratio of PCE/NCE reported. Also, the size of the micronuclei (< or > 1/4 diameter of the cell) were tabulated. Chromosome-breaking agents primarily induce small micronuclei and spindle poisons, larger micronuclei. The positive controls were functional. There was no evidence of effects from treatment at any dose except for clinical signs of squatting position and piloerection, which increased with dose and were seen at all doses. The use of males only was justified based on acute toxicity of males and females being similar (see worksheet). **Acceptable with no adverse effect.** (Gee, 2/27/02)

NEUROTOXICITY (including developmental neurotoxicity)

006; 182892; "BAS 510 F- Acute Oral Neurotoxicity in Wistar Rats" (Mellert, W. et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Laboratory Project Identification 20C0179/97144, 11/9/00). 870.62. BAS 510 F (Batch No. N 46, purity = 96.3%), suspended in 0.5% carboxymethylcellulose in doubly distilled water, was administered as a single gavage dose to 10 Wistar rats per sex per dose at dose levels of 0 (vehicle only), 500, 1000, and 2000 mg/kg. No mortalities occurred. No treatment-related clinical signs were observed during the daily observation of the test animals. During the FOB conducted after dosing (day 0), piloerection was observed in 2 females at 2000 mg/kg during the open field observations. No treatment-related effects were observed during FOB assessments conducted on days 7 and 14. Motor activity assessments revealed no treatment-related effects in the mean total number of beam interrupts. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 2000 mg/kg (based on no effects at the highest dose tested), NOEL (F) = 1000 mg/kg (based on piloerection observed during FOB). **Acceptable.** (Corlett and Leung, 3/14/02)

011; 182897; "BAS 510 F- Subchronic Oral Neurotoxicity Toxicity Study in Wistar Rats Administration in the Diet for 3 Months" (Mellert, W. et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Laboratory Project Identification 50CS0179/97148, 2/6/01). 827. BAS 510 F (Lot No. N46, purity = 96.3%) was admixed to the

feed and fed to 10 Wistar rats per sex per dose at dose levels of 0 (untreated diet), 150, 1500, or 15000 ppm (0, 10.5, 103.1, 1050.0 mg/kg/day, respectively for males and 0, 12.7, 124.5, 1272.5 mg/kg/day, respectively for females) for 3 months. No mortalities occurred. No treatment-related clinical signs were observed. No treatment-related effects were observed during FOB assessments. Motor activity assessments revealed no treatment-related effects in the mean total number of beam interrupts. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 1050.0 mg/kg/day (15000 ppm) and NOEL (F) = 1272.5 mg/kg/day (15000 ppm) based on no effects at the highest dose tested. **Acceptable.** (Corlett, 4/8/02)

52882-019 182907 Kaufmann, W., K. Schilling, W. Mellert, van Ravenzwaay, B., "BAS 510 F: Developmental neurotoxicity study in Wistar rats: Administration in the diet," BASF AG, Ludwigshafen, Feb. 8, 2001. Laboratory Project ID 67R0179/97167. Mated Wistar rats, 35/group, were dosed in diet with 0, 100, 1000, or 10000 ppm BAS 510 F, 96.3% purity, from gestation day 6 until lactation day 21 in a developmental neurotoxicity study. Parameters studied included histopathology on perfusion-fixed neural tissues of rats killed on postnatal days 11 and 60, motor activity and open field examinations of pups on multiple days through day 60, auditory startle test and learning/memory tests at about 3 weeks of age and on day 60. Estimated achieved maternal dosages were 10, 109, and 1032 mg/kg/day during gestation, and 18, 186, and 1853 mg/kg/day during lactation. Developmental NOEL = 1000 ppm (body weight decrements in pups). Reproductive parameters were normal, and there were no evidences of structural or functional effects in pups (neurological or otherwise) except for minor (reversible) growth retardation at 10000 ppm. No toxicity was identified in dams. Not acceptable but upgradeable (with positive control data). No adverse effects. Aldous, 2/20/02.

52882-066 188024 Relating to the additional data requested to upgrade the above study, BASF noted that many of the parameters evaluated in developmental neurotoxicity studies are also evaluated in acute or subchronic neurotoxicity studies, for which validation test data were provided previously. Additional developmental neurotoxicity validation studies are underway, using ethanol and "MAM" as positive controls. DPR will review these studies when available, in considering the acceptability of the developmental neurotoxicity study. Aldous, 9/5/02.

METABOLISM

52882-021 182913 Leibold, E., H. D. Hoffmann, and B. Hildebrand, "¹⁴C BAS 510 F: Study of the biokinetics in rats," BASF AG, Ludwigshafen, Aug. 3, 2000. Laboratory Project ID # 02B0426/976030. Wistar rats, 3-4 animals/sex/dose in a given test/time interval group, were dosed with labeled BAS 510 F in a series of tests to evaluate fecal and urinary excretion patterns, plasma kinetics, tissue distribution, and biliary excretion. Dose levels were high (500 mg/kg) or low (50 mg/kg), in all cases administered by gavage as aqueous suspensions (10 ml/kg) in 0.5% Tylose CB 30,000 containing 1% Cremophor EL. Purity of unlabeled BAS 510 F was > 99%. In most tests, BAS 510 F was usually universally labeled in both rings of the diphenyl group. For comparison, one test employed the nicotinamide label (designated as the "phenyl" label in the report and in this review). The latter label was on the carbon #2 of the nicotinamide ring, adjacent to the Cl moiety. Position of the label had no apparent influence on excretion patterns. There was no radioactivity detected in exhaled air. The high dose appeared to diminish

absorption or metabolism: urinary excretion as percent of administered dose averaged only about 4% at 500 mg/kg, compared to 16% at 50 mg/kg. Fecal excretion averaged over 90% and over 80% at respective dose levels. Pre-treatment at 500 mg/kg/day for 2 weeks did not influence excretion patterns. Plasma levels peaked at about 8 hr regardless of dose, and cleared with an initial $T_{1/2}$ of 7 to 9 hr, and terminal $T_{1/2}$ of 20 to 42 hr. Bile radioassays showed an increase in % biliary excretion at 50 mg/kg compared to 500 mg/kg (40% compared to 11%). Data are consistent with appreciable entero-hepatic recirculation. Study is acceptable for metabolism parameters covered in this report. Aldous, 3/15/02.

**52882-021 182914 Grosshans, F. and H.-E. Knoell, "The metabolism of ^{14}C BAS 510 (Reg. No. 300 355) in rats," BASF AG, Limburgerhof, 2/16/01. BASF Registration Document No. 2000/1017220. Most test samples were from Record No. 182913 of this volume. Three additional groups of Wistar rats were treated and sampled at the Limburgerhof facility, primarily for qualitative analyses of metabolites. The latter studies used olive oil vehicle (1 ml/rat) instead of an aqueous suspension, with no apparent effect on outcome. Collectively Record Nos. 182913 and 182914 meet the metabolism data requirements. There are no adverse effects. Metabolites were separated by HPLC. Primary identification was by mass spectrometry (MS). NMR was used in a few cases to validate MS analyses and to clarify structure. Unaltered BAS 510 F in feces comprised 30-41% of administered dose at 50 mg/kg, and 57-80% of administered dose at 500 mg/kg, indicating impeded absorption at the higher dose. The most important metabolites were hydroxyl or O-glucuronide metabolites on the diphenyl ring (usually *para* to the amide nitrogen), and S-glucuronide conjugation products displacing the chlorine on the pyridine ring of the parent compound. The sulfur originated from glutathione (GSH) addition to the ring. GSH was often cleaved to cysteine in bile or feces, or further degraded in feces to a thiol, which in turn was sometimes conjugated as a glucuronide). Tissue residues (liver, kidney, and plasma) were scant, but qualitatively similar to the above. Some parent BAS 510 F was found in kidneys and plasma. Thus BAS 510 F was effectively metabolized and efficiently excreted. Aldous, 3/15/02.

SPECIAL STUDIES RELATING TO ALTERED THYROID FUNCTION

52882-016 182902 Mellert, W., W. Kaufmann, E. Leibold, K. Deckardt, and B. Hildebrand, "BAS 510 F - Hepatic enzyme induction study in Wistar rats: Administration in the diet for 2 weeks," BASF Corporation, BASF AG, Ludwigshafen, 3/23/99. BASF Document # 1999/10522. Wistar rats (5/sex/group for enzyme induction studies: 3/sex/group for microscopy) were dosed with 0 or 15000 ppm BAS 510 F (95.3%) for 2 weeks. Enzyme induction groups were examined for liver cyanide-insensitive palmitoyl-CoA-oxidation, cytochrome P450 content, glutathione, lipoperoxidation [thiobarbituric acid-reactive material], and activities of ethoxyresorufin-O-deethylase and pentoxyresorufin-O-depentylase. Liver weights and cytochrome P450 content were each significantly elevated in both sexes. Thiobarbituric acid-reactive material was significantly elevated in treated males, however high inter-animal variability made this an uncertain treatment effect. The two enzymes assayed did not have increased activity. Light microscopy was performed on 3/sex/group, whereas electron microscopy (EM) was only performed on females. EM revealed increased smooth endoplasmic reticulum (SER) of grades "low" to "high" in the three treated females (p. 33). Decreased glycogen (moderate grade) was also observed in association with the more pronounced cases of

increased SER. Useful supplemental data indicative of enzyme induction. Aldous, 3/7/02.

52882-016 182903 Mellert, W., K. Deckardt, E. Leibold, and B. van Ravenzwaay, "BAS 510 F - Hormone and enzyme induction study in Wistar rats: Administration in the diet for 4 weeks," BASF Corporation, BASF AG, Ludwigshafen, 2/28/01, Lab Project ID # 99C0179/97174. Five rats/sex/group were dosed in diet for 4 weeks with 0 or 15000 ppm BAS 510 F (96.3%). Hormones associated with thyroid (TSH, T3 and T4) were assayed in all groups pre-test and on days 2, 4, 7, 14, 21, and 28. Liver glucuronyl transferase activities were assayed for 3 substrates: p-nitrophenol, 4-methylumbelliferone, and 4-hydroxybiphenyl. TSH levels were typically about doubled in treated rats, whereas T3 and T4 were frequently significantly reduced. Liver weights were significantly elevated with treatment in both sexes. Glucuronyl transferase activities were consistently elevated in treated rats (at least 2-fold for the latter two substrates). Data from this record and from Record No. 182902 were provided to address the basis for the thyroid lesions observed in the rat oncogenicity study. Data indicate that such lesions may have resulted from increased liver metabolism of T3 and T4, resulting in over-stimulation of the thyroid follicular cells by feed-back elevation of TSH levels. Valid supplemental data. Aldous, 3/7/02.

52882-016 182904 Hawks, R., "BAS 510 F: Data pertaining to the mode of action for rat thyroid follicular cell adenomas." This is an analysis of evidence from several reports that have been evaluated by DPR with respect to the elevated incidences of thyroid follicular lesions (hypertrophy, hyperplasia, and adenomas), seen in rat chronic and oncogenicity studies (Document/Record Nos. 52882-013 182899 and 52882-014 182900, above). This analysis notes also the findings from subchronic rat data as well as the mechanistic studies summarized immediately above this paragraph. Page 17 of this record reveals a reversibility study in planning, which involves 4-week exposures at dose levels up to 15000 ppm, followed by 4 weeks off treatment for recovery groups. An additional satellite group will be kept in reserve in case the 4-week recovery groups do not demonstrate "sufficient" recovery to be judged conclusive by investigators. In addition to presentations by the author on the evidence of a non-genotoxic mechanism for thyroid lesions, this record includes a review entitled "The relevance of rat thyroid gland tumours to humans" by M. Costigan (June 1998), and a draft record by the European Commission Institute for Health and Consumer Protection Unit: Toxicology and Chemical Substances - European Chemicals Bureau. This draft includes criteria for evaluating "Non-genotoxic thyroid carcinogens in the rodent bioassay." This record does not present new reviewable data. Aldous, 3/5/02.

52882-066 188025 Mellert, W., K. Deckardt, W. Kaufmann, and B. van Ravenzwaay, "BAS 510 F reversibility study in Wistar rats: administration in the diet for 4 weeks followed by recovery periods of 4 weeks and 3 months." BASF AG, Ludwigshafen, 11/26/01. BAS 510 F, 94.1% purity, was administered in the diet to groups of 5 male rats at 0, 100, 2500, or 15000 ppm for 4 weeks. The same group sizes were maintained in the 4-week and 3-month recovery groups. Parameters assessed included gross and histopathology for all rats at respective terminations, plus blood sampling for T3, T4, and TSH at week 4 (just after treatment) for all rats, at recovery week 4 for all recovery rats, and at recovery week 13 for only the 13-week recovery rats. Achieved mean doses during the treatment period were 8, 190, and 1137 mg/kg/day. There were no apparent clinical signs, nor treatment-related changes in body weight. T3 and T4 levels were not influenced by treatment at any time. TSH was sharply elevated in the

two higher dosage groups after 4 weeks of treatment (9.7, 9.8, 16.4**, and 18.2*** : g/l, respectively: significance in the latter groups of $p < 0.02$ and $p < 0.002$, respectively). TSH was not influenced by treatment after recovery periods. Liver and thyroid weights were elevated significantly in the two higher dosage groups (respective liver weights of 7.7, 7.9, 9.6*, and 11.2** g, and thyroid weights of 16.6, 19.0, 24.8**, and 24.4** mg) [* , ** Significant, $p < 0.05$ and $p < 0.01$, respectively]. Liver weights lacked treatment differences at recovery sacrifices, whereas thyroid weights in recovering treated groups tended to be elevated, but without dose-response, hence of questionable meaning. Except for “enlarged” livers, no gross effects were observed in livers or thyroids. Livers of 2500 and 15000 ppm groups showed periportal fatty change and centrilobular hypertrophy. Thyroid hypertrophy and hyperplasia were elevated at these treatment levels after 4 weeks of treatment (all findings dose-related). These effects were not seen in recovery rats. Overall, study indicates that major treatment effects at 2500 and 15000 ppm were reversible. Aldous, 8/4/02.

SUBCHRONIC STUDIES

(90-day feeding study)

008; 182894; “BAS 510 F- Subchronic Oral Toxicity Study in Wistar Rats Administration in the Diet for 3 Months” (Mellert, W. et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification 50S0179/97058, 4/27/00). 821. BAS 510 F (Batch No. Tox Charge II/N 26, purity = 95.3%) was admixed to the feed and fed to 10 Wistar rats per sex per dose at dose levels of 0 (untreated diet), 100, 500, 2000, 5000, or 15000 ppm (0, 7, 34, 137, 347, 1055 mg/kg/day, respectively for males and 0, 8, 40, 159, 395, 1225 mg/kg/day, respectively for females) for 3 months. No mortalities occurred. No clinical signs were observed. A treatment-related increase in the mean serum -(-glutamyltransferase was observed in males at 2000 ppm and in both sexes at 5000 and 15000 ppm. A treatment-related increase in mean relative liver weight in both sexes at 5000, and 15000 ppm was observed along with a treatment-related increase in mean relative thyroid weight in both sexes at 15000 ppm, in males at 2000 ppm, and in females at 5000 ppm. Microscopic examination revealed treatment-related centrilobular hypertrophy of hepatocytes in both sexes at 5000 and 15000 ppm and treatment-related follicular hyperplasia of the thyroid and hypertrophy of the follicular epithelium of the thyroid in males at 2000, 5000, and 15000 ppm. **No adverse effects.** NOEL (M)= 34 mg/kg/day (500 ppm) based on microscopic findings in the thyroid and increased serum -(-glutamyltransferase; NOEL (F) = 159 mg/kg/day (2000 ppm) based on microscopic findings in the liver, increased relative liver and thyroid weights, and increased serum -(-glutamyltransferase level. **Acceptable.** (Corlett, 3/26/02)

009; 182895; “BAS 510 F- Subchronic Oral Toxicity Study in Beagle Dogs Administration in the Diet for 3 Months” (Schilling, K. et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification 31D0179/97101, 5/11/00). 821. BAS 510 F (Batch No. N 37, purity = 94.4%) was admixed to the feed and fed to 5 beagle dogs per sex per dose at dose levels of 0 (untreated diet), 250, 2500, or 25000 ppm (0, 7.6, 78.1, 728.9 mg/kg/day, respectively for males and 0, 8.1, 81.7, 824.8 mg/kg/day, respectively for females) for 2 hours per day for 3 months. No mortalities occurred. Treatment-related soft and/or discolored (light brown) feces were observed in both sexes at 2500 and 25000 ppm. A treatment-related increase in the mean serum alkaline phosphatase was observed in males at 25000 ppm and in females at 2500 and 25000 ppm and a treatment-related increase in

triglycerides was observed in both sexes at 25000 ppm. Treatment-related increases in mean absolute liver weight in both sexes at 2500 and 25000 ppm, in mean relative liver weight in males at 25000 ppm and in females at 2500 and 25000 ppm, and in mean relative thyroid weight in females at 25000 ppm. Necropsy and microscopic examination revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)= 7.6 mg/kg/day (250 ppm) and NOEL (F) = 8.1 mg/kg/day (250 ppm) based on clinical signs and increased liver weights. **Acceptable.** (Corlett, 3/29/02)

007; 182893; "BAS 510 F- Subchronic Oral Toxicity Study in C57BL Mice Administration in the Diet for 3 Months" (Mellert, W. et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification 60C0179/97060, 3/1/00). BAS 510 F (Batch No. N 26, purity = 95.3%) was admixed to the feed and fed to 10 C57BL mice per sex per dose at dose levels of 0 (untreated diet), 150, 1000, 4000, or 8000 ppm (0, 29, 197, 788, 1518 mg/kg/day, respectively for males and 0, 42, 277, 1184, 2209 mg/kg/day, respectively for females) for 3 months. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related increase in the mean alanine aminotransferase was observed in females at 4000 and 8000 ppm. In males, statistically significant decreases in mean cholesterol at 1000, 4000, and 8000 ppm and in mean total protein, albumin, and globulins at 4000 and 8000 ppm were observed. A treatment-related increase in mean relative liver weight in both sexes at 1000, 4000, and 8000 ppm was observed. Microscopic examination revealed a treatment-related higher incidence of marked fatty change in the liver in males at 4000 and 8000 ppm. **No adverse effects.** NOEL (M) = 29 mg/kg/day (150 ppm) and NOEL (F) = 42 mg/kg/day (150 ppm) (based on increased mean relative liver weight). **Supplemental** (because no ophthalmological examinations were conducted on the test animals). (Corlett, 3/20/02)

(Dermal)

010; 182896; "BAS 510 F- Repeated Dose Dermal Toxicity Study in Wistar Rats Administration for 4 Weeks" (Mellert, W. et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification 33C0179/97151, 6/16/00). 822. BAS 510 F (Batch No. N 46, purity = 96.3%) was suspended in an aqueous solution of 0.5% carboxymethyl cellulose and 0.5% Cremophor® EL and applied to the clipped dorsal skin of 10 Wistar rats per sex per dose at dose levels of 0 (vehicle only), 100, 250, or 1000 mg/kg/day for 6 hours per day, 5 days per week for 4 consecutive weeks using a semi-occlusive dressing. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. No skin irritation was observed. Body weight, food consumption, ophthalmology, serum chemistry, urinalysis, and hematology data revealed no treatment-related effects. Necropsy and microscopic examination revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and skin) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested. **Acceptable.** (Corlett, 4/3/02)