UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO: 0051613

DATE: March 7, 2003

MEMORANDUM

SUBJECT: **BAS 510 F** - Report of the Hazard Identification Assessment Review Committee.

FROM: Alan C. Levy Alan C. Levy MAR. 12, 2003
Registration Action Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Yan Donovan, Risk Assessor
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 128008

On September 5, 2002 and January 23, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data submitted by the Registrant (BASF). After a review of the developmental neurotoxicity study (DNT) was discussed, the September 5, 2002 HIARC meeting was stopped for the following reasons: further explanation of the "startle response" was needed; additional statistical analyses were considered to be necessary; historical control data were needed; individual animal data were to be requested; individual morphometric measurements were to be requested; and positive control data were deemed necessary. The HIARC reconvened on January 23, 2003 after most of the above information had been received from the Registrant and had been evaluated by EPA. The conclusions drawn at this meeting are presented in this report.

(1)

Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, Paula Deschamp (RARC Representative), Elizabeth Doyle (Co-Chair), Pamela Hurley, John Liccione, Susan Makris, Elizabeth Mendez (present September 5, 2002 meeting), David Nixon, Jess Rowland (Co-Chair), Brenda Tarplee (Executive Secretary), Bill Dykstra (alternate) and PV Shah (alternate for Elizabeth Mendez, January 23, 2003 meeting).

Member(s) in absentia: Elizabeth Mendez (January 23, 2003 meeting)

Also in attendance were: Ed Budd, William Drew, Maria Rodriguez and William Sette.

Data Evaluation / Report Presentation

Alan C. Levy
Toxicologist
Registration Action Branch 2

2

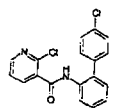
I. INTRODUCTION

BAS 510 F (3-pyridinecarboxamide,2-chloro-N-(4'chloro(chloro(1,1"-biphenyl)-2-yl). It is to be used as a fungicide. BAS 510 02 F Turf Fungicide is a 70% WG formulation of the BAS 510 F active ingredient and is intended for use in golf course turf only. BAS 510 02 F Crop Fungicide is a 70% WG and includes the terrestrial food crop uses of berries crop group, bulb vegetable crop group, beans, canola, carrots, fruiting vegetable crop group, grapes, lettuce, peanuts, potatoes, strawberries, stonefruit, tree nut crop group and pistachio. The BAS 516 02 F Crop Fungicide is a 38% WG mixture of BAS 510 F and pyraclostrobin. The target uses of BAS 516 02 F are berries crop group, bulb vegetables crop group, carrots, grapes, strawberries, stonefruit, tree nut crop group, bulb vegetables crop group, carrots, grapes, strawberries, stonefruit, tree nut crop group and pistachio.

Tolerances are requested for the target crops and crop groups of berries crop group, bulb vegetable crop group, beans, canola, carrots, fruiting vegetable crop group, grapes, lettuce, peanuts, tuberous and corm vegetables, strawberries, stonefruit, tree nut crop group and pistachio. The associated livestock tolerances for milk, muscle, fat and meat-by-products are also requested. A waiver is requested for tolerances in poultry.

Tolerances are also requested for crops to be used in rotation with the target crops: root vegetables crop group; leaves of root vegetable crop group; leafy vegetables crop group; brassica leafy vegetables crop group; legume vegetables crop group; foliage of legume vegetable crop groups; cucurbit crop group; cereal grains crop group; forage, fodder and straw of cereal grains crop group; grass forage and fodder and hay crop group, non-grass animal feed crop group, soybean seed, forage, hay and aspirated grain fractions, flax seed, sunflower seed, cotton seed and gin by-products and mint.

Chemical structure:



BAS 510F has a low toxicity profile (acute oral LD_{50} > 5000 mg/kg bw, acute dermal LD_{50} > 2000 mg/kg bw, inhalation LC_{50} > 6.7 mg/L). It is not an eye or skin irritant. The skin sensitization study (guinea pigs) was not acceptable because the highest dose tested was not considered to have been high enough to cause an effect. There was some evidence of carcinogenicity regarding the thyroid in rats only.

II. FQPA - HAZARD CONSIDERATIONS

1. Adequacy of the Data Base for FQPA

The HIARC concluded that the toxicology data base for BAS 510 F is adequate for an FQPA assessment based on the availability of the following studies:

- Developmental toxicity studies in rats and rabbits

- A two-generation reproduction toxicity study in rats

- Acute and subchronic neurotoxicity studies in rats

- A developmental neurotoxicity study in rats

2. Evidence of Neurotoxicity

HIARC concluded that there were no concerns for neurotoxicity based on the following considerations:

Acute Neurotoxicity

In an acute neurotoxicity study (MRID 45404820), groups of 10 male and 10 female 49-day old Wistar rats were given a single oral dose of BAS 510 F (96.3% a.i., batch N 46) in 0.5% carboxymethyl cellulose at doses of 0, 500, 1000 or 2000 mg/kg bw and observed for 14 days. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10 animals/sex/group on days -7, 0, 7 and 14. Cholinesterase activities were not measured. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5 animals/sex in the control and 2000 mg/kg bw groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no effects on mortality, body weight, motor activity, or clinical signs outside of the FOB. During the FOB, piloerection was observed in 2 female rats in the 2000 mg/kg dose group on day 0. No other FOB findings in either sex in any dose group were considered treatment-related. There were no gross organ lesions and no microscopically-observed lesions of the brain or peripheral nervous system tissues. Although the NOAEL for systemic effects in this study is 1000 mg/kg bw, in the absence of clinical signs related to neurotoxicity and in the absence of lesions of the brain or peripheral nervous system, the NOAEL for acute neurotoxicity is 2000 mg/kg bw.

Based on the effects seen in this study, the systemic LOAEL for BAS 510 F was 2000 mg/kg bw (based on piloerection in females), with a NOAEL of 1000 mg/kg bw.

The neurotoxicity LOAEL was >2000 mg/kg bw and the NOAEL was 2000 mg/kg bw.

This neurotoxicity study is classified as **Acceptable/Guideline** andl satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

Subchronic Neurotoxicity

In a subchronic neurotoxicity study (MRID 45404825), groups of 10 male and 10 female 49-day old Chbb. THOM (SPF) Wistar rats were administered BAS 510 F (96.3% a.i., batch # N 46) in the diet at dose levels of 0, 150, 1500 or 15000 ppm (equivalent ot 0, 10.5, 103.1 or 1050.0 mg/kg bw/day for males and 0, 12.7, 124.5 or 1272.5 mg/kg bw/day for females) for 3 months. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in 10 animals/sex/group on days -7, 22, 50 and 85. Cholinesterease activities were not measured. At study termination, 5 animals/sex in the control and high-dose groups were subjected to *in situ* perfusion and neuropathological examination of brain and nervous system tissues.

No deaths occurred and there were not treatment-related clinical signs or effects on body weight and food consumption. FOB and motor activity testing revealed no treatment-related effects. Brain weights were comparable to controls and there were no gross or histopahtologic findings that could be attributed to treatment with BAS 510 F.

A LOAEL was not attained in this study. The NOAEL for BAS 510 F is 15000 ppm in the diet (1050.0 mg/kg in male rats and 1272.5 mg/kg in female rats) based on the absence of treatment-related systemic effects; absence of effects in the FOB and motor activity tests; and the absence of histopathological lesions in the brain and nervous system tissues.

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b; OECD 424).

Developmental Neurotoxicity

In a developmental neurotoxicity study (MRID 45404907) BAS 510 F (96.3% a.i., N46) was administered to 35 female Crl: WI (GLX/BRL/HAN) IGS BR (Wistar) rats per dose in the diet at dose levels of 0, 100, 1000 or 10000 ppm [0, 14, 147 and 1442 mg/kg/day, average] from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND) 4, litters were standarized to 8 pups or more/litter. Offspring from culled litters (1 male or female pup/litter) were assigned to subgroups for further examination [brain weights, neuropathology (I,III), learning and memory (IV, V), motor activity (II), and auditory startle response (III)] no later than one day before examinations commenced. Pups were weaned on postnatal day 21, after which time maternal animals were killed.

No mortalities, significant treatment-related clinical signs or open field observations, changes in body weight or food consumption, or changes in the duration of gestation, numbers of litters, or intercurrent deaths were noted in maternal animals. The high dose (1442 mg/kg/day) exceeded the limit dose for this study.

A maternal LOAEL was not observed.

The maternal NOAEL is 10000 [1442 mg/kg/day].

In pups, no treatment effects on litter size or viability during lactation were seen. In high dose pups prior to weaning, there were significant decreases in body weight in males (↓6-14%; PND 4-12) and in females (↓6-16%; PND 1-21). In 1000 ppm pups, body weight gains were reduced 21% (PND 1-4), and body weights were significantly decreased in males (8%) and females (9%) on PND 4, but recovered by day 11. No effects on postweaning body weights, or the day of preputial separation or vaginal opening were found. In the FOB, increased head shaking among high dose male pups on PND 4, and slightly increased signs of increased activity or urination, or irregular respiration were seen amoung high dose pups. No consistent effects on motor activity were seen. Based on additional submitted data (MRID 45800101) that lead to removal of data from one low dose male rat, and analysis of historical control data, additional statistical analyses by EPA, and latency data, it is concluded that no consistent effects on startle reflex amplitude or latency were found.

No effects on learning and memory performance were seen, but reported data were somewhat limited. Both sexes of PND 11 pups in the 10000 ppm group showed statistically significant decreases in body weight (9%) and brain weight (6-7%). No changes in microscopic pathology were found. Significant decreases in brain length (3%) in high dose males on PND 11 were found. While significant decreases in the right hippocampus (8%) of high dose females on PND 11 were noted, and left hippocampus measures in this group showed a similar, but non-significant 6% decrease, additional data on the mid and low dose females lead to the conclusion that these changes were not consistent or dose dependent.

The offspring LOAEL is 1000 ppm [147 mg/kg/day], based on decreased body weights (8-9%) on PND 4 and decreased body weight gain (21%) on PNDs 1-4.

The offspring NOAEL is 100 ppm [14 mg/kg/day].

This study is classified **acceptable/non-guideline** but does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, 83-6); OECD 426 (draft). The bases for rating this study as non-guideline are the lack of positive control data, and limited data on the learning and memory test. This study can be re-classified if these deficiencies are adequately addressed.

3. Developmental Toxicity Conclusions

Developmental Toxicity Study, Rat

In a developmental toxicity study (MRID 45404904), BAS 510 F (94.4% a.i., batch/lot # N37) was administered to 25 female Wistar rats/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day from days 6 through 19 of gestation. Due to the unscheduled death (gavage error) of 3 animals each in the low- and high-dose groups, an additional section with 6 animals (3 each low and high doses) was added to guarantee at least 20 pregnant rats/group. On gestation day 20, dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally. The total numbers of fetuses examined (number of litters) was 319 (22), 246 (18), 333 (22), and 287 (21) for the 0, 100, 300, and 1000 mg/kg bw/day groups, respectively. Approximately one-half of the fetuses were examined viscerally, and the other one-half of the fetuses were examined for skeletal malformations/ variations.

There were no treatment-related effects in survival, clinical signs, body weight, food consumption, or gross necropsy. Deaths of several maternal animals were ascribed to gavage error. **The maternal toxicity NOAEL is ≥ 1000 mg/kg bw/day, and the maternal toxicity LOAEL could not be established.**

No treatment-related effects on pregnancy rates, number of corpora lutea, pre- or postimplantation losses, resorptions/dam, fetuses/litter, fetal body weights, or fetal sex ratios were observed in the treated groups compared with the controls.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any groups. Most treated and control litters contained fetuses with minor variations in skeletal ossification. **The developmental toxicity NOAEL is ≥ 1000 mg/kg bw/day, and the developmental toxicity LOAEL could not be established.**

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

Developmental Toxicity Study, Rabbit

In a developmental toxicity study (MRID 45404905), BAS 510 F (94.4% a.i., batch # N37) was administered to 25 Himalayan rabbits/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day from gestation days (GDs) 7-28. On GD 29, does were sacrificed and subjected to gross necropsy. All fetuses were examined for external, visceral, and skeletal malformations/variations. The total numbers of fetuses examined (number of litters) was 135 (23), 183 (24), 145 (22), and 136 (21) for the 0, 100, 300, and

7

1000 mg/kg bw/day groups, respectively.

No clinical signs related to dose were observed. However, treatment-related maternal toxicity was observed in the high-dose group as evidenced by an increased number of abortions and early delivery and decreased food consumption. One high-dose doe delivered early, and 3 high-dose does aborted: two on GD 27 and one on GD 29. Statistically significant decreases ($p<0.05$; 0.01) were observed in mean absolute body weights on GD 28 and 29 (95% of controls); mean corrected terminal body weight (94% of controls); mean maternal body weight gains on GDs 7-9 (-22.9 g compared to -3.1 g) and GDs 21-23 (-10.3 g compared to 10.2 g); and mean corrected body weight change (-233.3 g vs. -125.3 g). High-dose animals also consumed less food than the controls starting with the commencement of treatment and continuing throughout the treatment period (52-90% of controls; generally statistically significant at $p<0.05$; 0.01).

Over the entire treatment interval of GD 7-28, the high-dose group consumed 26% less food than the controls ($p<0.05$; 0.01). Upon inspection of individual animal data, 4 does in particular were affected: the doe that delivered early, two of the does that aborted (on GD 27 or GD 29), and a fourth doe. These does started to exhibit drastic decreases in food consumption accompanied by decreases in body weight gain generally starting between GDs 14-16. The other doe that aborted on GD 27 did not exhibit consistent decrements in food consumption and body weight gain.

Other findings noted in the high-dose group and in the low- and mid-dose groups were not definitively related to treatment.

The maternal LOAEL is 1000 mg/kg bw/day based primarily on abortions or early delivery. The maternal NOAEL is 300 mg/kg bw/day.

Developmental toxicity was also evident in the high-dose group. As discussed, one high-dose doe delivered early, and 3 high-dose does aborted: two on GD 27 and one on GD 29. No treatment-related, statistically significant effects on pregnancy rates, number of corpora lutea, pre- or postimplantation losses, resorptions/dam, fetuses/litter, fetal body weights, or fetal sex ratios were observed in the treated groups as compared with the controls. One control and one mid-dose female had complete litter resorptions.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any groups. Most treated and control litters contained fetuses with minor variations in skeletal ossification.

The developmental LOAEL is 1000 mg/kg bw/day based on increased number of abortions and early delivery. The developmental NOAEL is 300 mg/kg bw/day.

The developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and

satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

4. Reproductive Toxicity Conclusions

A Two-Generation Reproduction Study, Rat

In a two-generation reproduction study (MRID 45404906), BAS 510F (94.4% a.i., batch #N 37) was administered to 25 Wistar (Chbb=THOM(SPF)) rats/sex/dose in the diet at concentrations of 0, 100, 1000, or 10,000 ppm. One litter was produced in each generation. Premating doses for the treated F_0 parental animals were 10.1, 101.2, and 1034.5 mg/kg/day, respectively, for males and 10.7, 106.8, and 1062.0 mg/kg/day, respectively, for females. Premating doses for the treated F_1 parental animals were 12.3, 123.9, and 1295.4 mg/kg/day, respectively, for males and 12.5, 124.7, and 1299.6 mg/kg/day, respectively, for females. F_0 and F_1 parental animals were administered test or control diet for at least 74 or 76 days, respectively, prior to mating, throughout mating, gestation, and lactation, and until sacrifice.

All parental animals of both generations survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed in any animal during the study. Food consumption was not affected by treatment with the test article in either sex of either generation. Absolute body weights and body weight gains of the F_0 animals were similar between the treated and control groups throughout the study. For the treated F_1 females, body weights and body weight gains were similar to those of the control group throughout premating. Absolute body weights of the high-dose F_1 males were significantly (91-94% of controls; $p \leq 0.05$ or 0.01) less than the controls beginning at week 1 of premating and continuing until termination. Weight gain by the high-dose F_1 males was significantly ($p \leq 0.01$) less than that of the control group during weeks 0-1 (89% of control), 3-4 (84% of control), and 13-14 (62% of control), with premating weight gain 93% of the controls and overall weight gain 91% of the control level.

At necropsy, no treatment-related gross lesions were found in any animal of either sex or generation. An increased incidence and severity of centrilobular hepatocyte hypertrophy in many mid- and all high-dose animals corresponded with increased liver weights only at the high dose. Additionally in the high-dose groups, hepatocyte degeneration was observed in three F_0 males, one F_0 female, and eight F_1 males. **The parental systemic LOAEL is 10,000 ppm for males (1034.5-1295.4 mg/kg/day) based on decreased body weights and body weight gains of the F_1 males and hepatocyte degeneration in F_0 and F_1 males; the systemic LOAEL was not identified for females. The parental systemic NOAELs are 1000 ppm for males (101.2-123.9 mg/kg/day) and 10,000 ppm for females (1062.0-1299.6 mg/kg/day).**

No treatment-related differences in estrous cycle length and periodicity were found in females of either generation. All control and almost all treated F_0 and F_1 animals showed regular estrous cycles and became sperm positive within a few days after pairing. No treatment-related differences were observed in any sperm measures. No treatment-related lesions occurred in the reproductive tracts from males or females from either generation. No differences in mating, fertility, or gestation indices were seen between the treated and control groups of either generation. The copulatory interval and gestation length of the treated groups were comparable to the control groups in both generations. **The reproductive toxicity NOAEL is ≥10,000 ppm (1034.5-1295.4 mg/kg/day for males and 1062.0-1299.6 mg/kg/day for females) and the reproductive toxicity LOAEL was not identified.**

For the F_1 litters, live birth, viability, and lactation indices, mean litter sizes, and sex ratios were similar between the treated and control groups. Pup survival in the high-dose F_2 litters was decreased during lactation days 0-4 as indicated by a significantly lower viability index (86% vs 93% for controls; $p \leq 0.01$). Post-implantation loss was significantly ($p \leq 0.05$) greater for the high-dose F_1 females, resulting in a mean live litter size of 12.5 pups for the high-dose group (n.s.) compared with 13.8 pups/litter for the control group. The live birth index, the lactation index, and pup sex ratio were similar between the treated and control groups. No treatment-related clinical signs of toxicity were observed in the F_1 or F_2 pups during lactation. For the F_1 pups, no differences in the rate of sexual maturation were noted between the treated and control groups.

Pups from the high-dose litters of both generations and mid-dose F_2 male pups had significantly reduced body weights and body weight gains during lactation as compared with their respective control group. High-dose male and female F_1 pups had significantly ($p \leq 0.05$) lower body weights on lactation day 21 compared with the controls due to consistently reduced body weight gains ($p \leq 0.05$ or 0.01; 89-93% of the control level) for all intervals after lactation day 4. Body weights of the high-dose F_2 male and female pups were 86-90% ($p \leq 0.01$) of the control levels on lactation days 14 and 21 due to consistently reduced body weight gains ($p \leq 0.05$ or 0.01; 83-88% of the control level) for all intervals after lactation day 4. In addition, body weights were significantly ($p \leq 0.05$) reduced for the mid- and high-dose F_2 males on lactation day 7 and the mid-dose F_2 males on day 21. Body weight gains by the mid-dose F_2 males were 88-93% ($p \leq 0.05$ or 0.01) of the control levels during lactation days 4-21. **The offspring toxicity LOAEL is 1000 ppm for males (101.2-123.9 mg/kg/day) based on decreased body weights and body weight gains by the F_2 male pups and 10,000 ppm for females (1062.0-1299.6 mg/kg/day) based on decreased body weights and weight gains. The offspring toxicity NOAEL is 100 ppm for males (10.1-12.3 mg/kg/day) and 1000 ppm for females (106.8-124.7 mg/kg/day).**

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproduction study (OPPTS 870.3800; OECD 416) in rats.

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5. Additional Information from Literature Sources (if available)

None available.

6. Pre- and/or Post-natal Toxicity

Based on the weight-of-the-evidence considerations, HIARC determined that there is a low concern for pre-and/or post-natal toxicity resulting from exposure to BAS 510 F.

A. Determination of Susceptibility

There was no evidence of increased susceptibility in the developmental rat study as no developmental toxicity was seen at the highest dose tested (Limit Dose).

There was evidence of qualitative (not quantitative) increased susceptibility in the developmental rabbit study as characterized by an increased incidence of abortions or early delivery at the highest dose tested (1000 mg/kg/day). It could not be ascertained if the abortions were the result of a treatment-related effect on either the dams, the fetuses or both.

There was quantitative evidence of increased susceptibility in the two-generation reproduction study in rats, where decreases in body weights and body weight gains in male offspring were seen in the F_2 generation at a dose that was lower than the dose that induced parental/systemic toxicity. The offspring NOAEL was 10.1/106.8 mg/kg/day in males and females, respectively and the parental/systemic NOAEL was 101.2/1062.0 mg/kg/day in males and females, respectively.

There was quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats, where decreases in pup body weights (PND 4) and body weight gains (PND 1-4) were seen in the absence of any maternal toxicity. The offspring toxicity NOAEL was 14 mg/kg/day and the maternal NOAEL was 1442 mg/kg/day.

B. Degree of Concern Analysis and Residual Uncertainties

The HIARC concluded that the degree of concern is low for the qualitative evidence of susceptibility seen in the rabbit developmental study as the increased abortions or early delivery was seen only at the Limit Dose and not at the lower levels (i.e. a high-dose effect) and the abortions may have been due to maternal stress.

11

The HIARC concluded that the degree of concern is low for the quantitative evidence of susceptibility seen in the two-generation reproduction study in rats because the decreases in body weight and body weight gains were seen only in the F_2 generations. These may have been due to exposure of the parental animals to high doses (above the Limit Dose). The dose selected for chronic dietary and non-dietary exposure risk assessments would address the concern for the body weight effects.

The HIARC concluded that the degree of concern is low for the quantitative evidence of susceptibility seen in the developmental neurotoxicity study because the decreases in pup body weights seen on post natal days 1 through 4 (and not at any other time periods) were most likely due to maternal toxicity (the maternal animals were exposed to a very high dose exceeding the limit dose, i.e., 1442 mg/kg/day); and no treatment-related effects on body weight, body weight gain or any other parameter were at post natal day 21.

The HIARC concluded that there are no residual uncertainties for pre- and post-natal toxicity as the degree of concern is low for the susceptibility seen in the above studies, and the dose and endpoints selected for the overall risk assessments will address the concerns for the body weight effects seen in the offspring. Although the dose selected for overall risk assessments (21.8 mg/kg/day) is higher than the NOAELs in the two-generation reproduction study (10.1 mg/kg/day) and the developmental neurotoxicity study (14 mg/kg/day), these differences are considered to be an artifact of the dose selection process in these studies. For example, there is a 10-fold difference between the LOAEL (106.8 mg/kg/day) and the NOAEL (10.1 mg/kg/day) in the two generation reproduction study. A similar pattern was seen with regard to the developmental neurotoxicity study, where there is also a 10-fold difference between the LOAEL (147 mg/kg/day) and the NOAEL (14 mg/kg/day). There is only a 2-3 fold difference between the LOAEL (57 mg/kg/day) and the NOAEL (21.8 mg/kg/day) in the critical study used for risk assessment. Because the gap between the NOAEL and LOAEL in the 2-generation reproduction and developmental neurotoxicity studies was large and the effects at the LOAELs were minimal, the true no-observed-adverse-effect -level was probably considerably higher. Therefore, the selection of the NOAEL of 21.8 mg/kg/day from the 1-year dog study is conservative and appropriate for the overall risk assessments. In addition, the endpoints for risk assessment are based on thyroid effects seen in multiple species (mice, rats and dogs) and after various exposure durations (subchronic and chronic exposures) which were not observed at the LOAELs in either the two-generation reproduction or the developmental neurotoxicity studies. Based on these data, the HIARC concluded that there are no residual uncertainties for pre- and post-natal toxicity.

C. Special FQPA Safety Factor(s):

The HIARC determined that the special FQPA Safety Factor can be removed (**1X**) because there is no evidence of susceptibility following *in utero* exposure to rats and there is low concern and no residual uncertainties in the developmental toxicity study in rabbits, in the 2-generation reproduction study or in the developmental neurotoxicity study after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment.

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. Recommendation for a Developmental Neurotoxicity Study

As discussed earlier in Section II. 2, a rat developmental neurotoxicity study was reviewed and was determined to be **acceptable/non-guideline** based on the lack of positive control data as well as limited data on the learning and memory test. This study can be re-classified if these deficiencies are adequately addressed.

III. HAZARD IDENTIFICATION

1. Acute Reference Dose (RfD)

Study Selected: None

Guideline #: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Establishing RfD: Not Applicable

Uncertainty Factor (UF): None

Comments about Study/Endpoint/Uncertainty Factor: No appropriate endpoint attributable to a single dose was available in the current database, including the developmental toxicity studies. The changes in brain morphometrics seen in the developmental neurotoxicity study were not selected as they were observed only at a dose exceeding the Limit Dose (1442 mg/kg/day). Therefore, an acute RfD was not established for any population for BAS 510 F.

2. Chronic Reference Dose (RfD)

Study Selected: Co-critical studies: Chronic Toxicity Dietary Study in Rats
Carcinogenicity Feeding Study in Rats
One-year Feeding Study in Dogs

Guideline #: 870.4100a (chronic rat)
870.4200 (carcinogenicity rat)
870.4100b (one-year dog)

MRID No.: 45404827 (chronic rat)
45404828 (carcinogenicity rat)
45404826 (one-year dog)

Executive Summary (chronic rat):

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 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.

Executive Summary (carcinogenicity rat):

In a carcinogenicity study (MRID 45404828) BAS 510 F (94.4% a.i., lot no. N37, Tox-batch III) was administered to 50 Wistar rats/sex/dose in the diet at concentrations of 0, 100, 500, 2500, or 15,000 ppm (equivalent to 0, 4.6, 23.0, 116.1, and 768.8 mg/kg bw/day for males and 0, 6.0, 29.7, 155.6, and 1024.4 mg/kg bw/day for females) for 24 months. The investigators determined that 15,000 ppm was causing excessive weight loss in females and mortality in males and these groups were sacrificed after approximately 17 months and not further analyzed.

No treatment-related effects were seen on clinical observations, survival rates, food consumption, food efficiency, differential blood count or morphology, or gross pathology. Body weights and body weight gains differed consistently from the controls in 2500 ppm females, starting on day 315 and persisting throughout the study (body weights, 84.1-95.3% of controls; overall weight gain, 75.8% of controls). The incidence of liver centrilobular hypertrophy was elevated at 2500 ppm in both sexes ($p \leq 0.01$). The incidence of liver eosinophilic foci was increased slightly but not statistically significantly in 500 and 2500 ppm males, but was not seen in females. The incidences of thyroid follicular cell diffuse hypertrophy and focal hyperplasia were increased in both sexes at 2500 ppm, although the changes were statistically significant in only males. The thyroid lesions (as well as thyroid adenoma) caused a 17-18% increase in the absolute and relative thyroid weight in 2500 ppm males. The liver and thyroid findings in this study, as well as in two separate mechanistic studies conducted by the registrant, are consistent with an adaptive response of the liver to a xenobiotic that resulted in a secondary toxic effect on the thyroid. **The LOAEL is 2500 ppm for both sexes of rats (116.1 and 155.6 mg/kg/day for males and females, respectively) under the conditions of this study, based on the significant decrease in body weight gain in females and the increased incidence of thyroid follicular cell hyperplasia and hypertrophy in both sexes. The NOAEL is 500 ppm (23.0 and 29.7 mg/kg/day for males and females, respectively).**

At the doses tested, there was a small but not statistically significant increase in thyroid follicular cell adenoma in 2500 ppm males and females when compared to controls. The incidence at 0, 100, 500, and 2500 ppm in males was 0/50, 0/50, 1/50, and

4/50, respectively and in females was 0/50, 1/50, 0/50, and 3/50, respectively. The thyroid adenomas were supported by correlating thyroid histological changes, and appeared to be a secondary effect of the chronically induced liver metabolism. No dose-related increase was seen for the number of animals with tumors (benign or malignant) or the total number of primary neoplasms/group. Dosing was considered adequate based on the body weight decreases in females and thyroid lesions in both sexes at 2500 ppm.

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

Executive Summary (one-year dog)

In a chronic toxicity study (MRID 45404826), BAS 510 F (94.4% a.i., batch/lot N 37) was administered to 5 beagle dogs/sex/dose in the diet at dose levels of 0, 200, 800, 2000, or 20,000 ppm (equivalent to 0, 5.5, 21.8, 57.4, and 544.0 mg/kg bw/day for males, and 0, 5.8, 22.1, 58.3, and 592.9 mg/kg bw/day for females) for 12 months.

Biologically and statistically significant increases in alkaline phosphatase activities in the 2000-ppm males and in 20000 ppm males and females reflected hepatic enzyme induction, which would be consistent with the observed increases in triglyceride and cholesterol levels in high-dose animals. Increased absolute hepatic weights in high-dose males and females (130% and 142% of control, respectively) correlated with the clinical chemistry data, and were attributed to a toxicological effect of the compound. Although increased thyroid weights were observed at the high-dose in males and females (154% and 142% of control, respectively), the absence of additional clinical correlates precluded the identification of the thyroid as a target organ.

The LOAEL is 2000 ppm in beagle dogs (♂: 57.4 mg/kg/day; ♀: 58.3 mg/kg/day), based on elevated ALP activities in the 2000-ppm males, and elevated hepatic weights in the 2000-ppm males. The NOAEL is 800 ppm (♂: 21.8 mg/kg/day; ♀: 22.1 mg/kg/day).

This chronic study (MRID 45404826) is **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic toxicity oral study [OPPTS 870.4100, OECD 452] in the dog.

Dose and Endpoint for Establishing cRfD: NOAEL = 21.8 mg/kg/day based on thyroid and hepatic toxicity seen in rats and dogs.

Uncertainty Factor(s): 100X (10X for interspecies extrapolation and 10X for intraspecies variation).

Comments about Study/Endpoint/Uncertainty Factor: The HIARC selected the NOAEL of 21.8 mg/kg/day for establishing the chronic RfD based on the combined results of the three studies mentioned above. The HIARC noted that this NOAEL is higher than the NOAELs in the 90-day study in dogs (7.6 mg/kg/day), the two-generation reproduction study (10.1 mg/kg/day) and the developmental neurotoxicity study (14 mg/kg/day). However, these differences are due to an artifact of the dose selection process in these studies as shown below:

Study	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
90-day - dog	7.6	78.1
2-generation reproduction - rat	10.1	101.6
developmental neurotoxicity - rat	14.0	1442

Because the gap between the NOAEL and LOAEL in these studies was large and the effects at the LOAELs were minimal, the true no-observed-adverse-effect-level was probably considerably higher. Therefore, the selection of the NOAEL of 21.8 mg/kg/day from the 1-year dog study is conservative and appropriate for the overall risk assessments. In addition, the endpoints for risk assessment are based on thyroid effects seen in multiple species (mice, rats and dogs) and after various exposure durations (subchronic and chronic expoxures) which were not observed at the LOAELs in either the two-generation reproduction or the developmental neurotoxicity studies.

3. **Incidental Oral Exposure: Short-Term (1 - 30 days) and Intermediate-Term (30-180 days)**

Study selected: Co-critical studies: Chronic Toxicity Dietary Study in Rats
Carcinogenicity Feeding Study in Rats
One-year Feeding Study in Dogs

MRID No.: 45404827 (chronic rat)
45404828 (carcinogenicity rat)
45404826 (one-year dog)

These studies are described (Guideline Numbers, MRID Numbers, Executive Summaries and Dose and Endpoint for Establishing RfD) under **2. Chronic Reference Dose (RfD).**

Dose and Endpoint for Risk Assessment: NOAEL = 21.8 mg/kg/day based on thyroid and hepatic toxicity seen in rats and dogs.

Comments about Study/Endpoint/Margins of Exposure: In the 90-day dog study, increased alkaline phosphatase activity and liver weights were seen in both sexes, and these effects were also seen in the 1-year dog study.

The Committee determined that the NOAEL of 21.8 mg/kg/day from the 1-year dog study is appropriate for this risk assessment as discussed under chronic RfD. The lower NOAEL (7.6 mg/kg/day) in the 90-day study is an artifact of dose selection. This endpoint is appropriate for the population (infants and children) and duration (1-30 days and 30-180 days) of concern, because there are no concerns that the effects will worsen following longer treatment.

4. **Dermal Absorption:** 15%; this includes the 11% absorbed at 24 hours plus 4% found as bound residue on the skin.

Study Selected: Rodent *In vivo* Dermal Penetration Study - [Rat]

Guideline #: 870.7600

MRID No.: 45404920

Executive Summary: In a dermal penetration study (MRID 45404920), [^{14}C]-BAS 510 F (diphenyl label; Lot/Batch no. 641-2017; >95% radiochemical purity) in distilled water was applied to the shaved dorsal surface (~10 cm^2) of male rats (four/group) at nominal doses of 0.01, 0.10, or 1.0 mg/cm^2 for periods of 1, 4, 10, or 24 hours. At the low dose two groups were washed at 10 hours and sacrificed at 24 and 72 hours. At the intermediate and high-dose one group at each dose was washed at 10 hours and sacrificed at 72 hours.

Percent mean dose distribution, as absorbed and remaining in the washed application site skin, is presented in the table below;

Exposure Time (hours)	1	4	10	24	10	10
Sacrifice Time (hours)	1	4	10	24	24	72
0.01 mg/cm^2						
Absorbed % ug/cm^2	0.52 0.052	2.02 0.202	8.07 0.807	**10.93** **1.093**	6.26 0.626	5.72 0.527
Skin	2.80	2.36	2.69	3.76	0.77	0.50
0.1 mg/cm^2						
Absorbed % ug/cm^2	0.37 0.37	0.25 0.25	0.63 0.63	2.63 2.63	— ---	2.07 2.07
Skin	1.45	1.42	1.99	3.32	---	0.49
1.0 mg/cm^2						
Absorbed % ug/cm^2	0.17 1.7	0.33 3.3	0.42 4.2	0.41 4.1	— ---	1.48 14.8
Skin	2.65	2.13	2.05	2.22	---	0.15

18

The percent of the dose absorbed increased with duration of exposure to 24 hours but decreased with increasing dose. This latter pattern is indicative of approaching saturation of absorption. However, since the quantity absorbed increased with each dose, one cannot determine directly if saturation was reached at the high dose. By plotting the quantity absorbed by dose with time, it was determined that the absorption from the washed skin at the high dose continued at the same rate as before washing. This showed that absorption was saturated at the high dose. Test material remaining in the washed skin decreased significantly in the animals that were washed at 10 hours and then sacrificed at 24 or 72 hours.

This dermal penetration study (MRID 45404920) in rats is **Acceptable/Guideline** and satisfies the requirements for a Dermal Penetration Study [OPPTS 870.7600 (§85-13)].

5. Dermal Exposure (All Durations)

Studies Selected: Co-critical studies: Chronic Toxicity Dietary Study in Rats
Carcinogenicity Feeding Study in Rats
One-year Feeding Study in Dogs

MRID No.: 45404827 (chronic rat)
45404828 (carcinogenicity rat)
45404826 (1-year dog)

Dose and Endpoint for Establishing RfD: NOAEL = 21.8 mg/kg/day based on thyroid and hepatic toxicity seen in rats and dogs.

These studies are described (Guideline Numbers, MRID Numbers, Executive Summaries and Dose and Endpoint for Establishing RfD) under **2. Chronic Reference Dose (RfD).**

Comments about Study/Endpoint/Uncertainty Factor: The HIARC noted that neither dermal nor systemic toxicity was seen at the Limit Dose (1000 mg/kg/day) in the 28-day dermal toxicity study (MRID No. 45404824). The Committee, however, selected the oral NOAEL of 21.8 mg/kg/day because of the concerns for the decreases in the body weight and body weight gains seen in the offsprings in the two-generation reproduction and the developmental neurotoxicity studies. Additionally, this dose would address the concerns for thyroid and hepatotoxicity seen via the oral route in multiple species (mice, rats and dogs) after various exposure durations (90-day, 1-year and 2-years). There are no concerns that the effects will worsen following longer treatment.

6. Inhalation Exposure: ALL DURATIONS [Short (1-30 days), intermediate (1-6 months), and long-term (> 6 months)]

Selected Study: Co-critical studies: Chronic Toxicity Dietary Study in Rats
Carcinogenicity Feeding Study in Rats
One-year Feeding Study in Dogs

MRID No.: 45404827 (chronic rat)
45404828 (carcinogenicity rat)
45404826 (1-year dog)

These studies are described (Guideline Numbers, MRID Numbers, Executive Summaries and Dose and Endpoint for Establishing RfD) under **3. Chronic Reference Dose (RfD).**

Dose and Endpoint for Establishing RfD: NOAEL = 21.8 mg/kg/day based on thyroid and hepatic toxicity seen in rats and dogs.

Comments about Study/Endpoint/Uncertainty Factor: The HIARC selected the oral NOAEL for this risk assessment due to the lack of a repeated dose inhalation toxicity study. There are no concerns that the effects will worsen following longer treatment. Absorption via inhalation is assumed to be equivalent to absorption via the oral route.

7. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	100
Dermal	100	100	100
Inhalation	100	100	100

NA = Not applicable

20

8. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes may be aggregated as follows: short-, intermediate- and long-term exposures (incidental oral, dermal and inhalation exposure) can be aggregated because of the use of a common endpoint for oral, dermal (oral equivalent) and inhalation (oral equivalent) routes of exposure.

IV. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Chronic Rat Study

MRID No.: 45404827

Executive Summary: See chronic RfD

Discussion of Tumor Data: See comments for combined chronic rat and carcinogenicity rat studies.

Adequacy of Dose Levels Tested: See comments for combined chronic rat and carcinogenicity rat studies.

2. Carcinogenicity Rat Study

MRID No.: 45404828

Executive Summary: In a carcinogenicity study (MRID 45404828) BAS 510 F (94.4% a.i., lot no. N37, Tox-batch III) was administered to 50 Wistar rats/sex/dose in the diet at concentrations of 0, 100, 500, 2500, or 15,000 ppm (equivalent to 0, 4.6, 23.0, 116.1, and 768.8 mg/kg bw/day for males and 0, 6.0, 29.7, 155.6, and 1024.4 mg/kg bw/day for females) for 24 months. The investigators determined that 15,000 ppm was causing excessive weight loss in females and mortality in males and these groups were sacrificed after approximately 17 months and not further analyzed. No treatment-related effects were seen on clinical observations, survival rates, food consumption, food efficiency, differential blood count or morphology, or gross pathology. Body weights and body weight gains differed consistently from the controls in 2500 ppm females, starting on day 315 and persisting throughout the study (body weights, 84.1-95.3% of controls; overall weight gain, 75.8% of controls). The incidence of liver centrilobular hypertrophy was elevated at 2500 ppm in both

sexes ($p \leq 0.01$). The incidence of liver eosinophilic foci was increased slightly but not statistically significantly in 500 and 2500 ppm males, but was not seen in females. The incidences of thyroid follicular cell diffuse hypertrophy and focal hyperplasia were increased in both sexes at 2500 ppm, although the changes were statistically significant in only males. The thyroid lesions (as well as thyroid adenoma) caused a 17-18% increase in the absolute and relative thyroid weight in 2500 ppm males. The liver and thyroid findings in this study, as well as in two separate mechanistic studies conducted by the registrant, are consistent with an adaptive response of the liver to a xenobiotic that resulted in a secondary toxic effect on the thyroid. **The LOAEL is 2500 ppm for both sexes of rats (116.1 and 155.6 mg/kg/day for males and females, respectively) under the conditions of this study, based on the significant decrease in body weight gain in females and the increased incidence of thyroid follicular cell hyperplasia and hypertrophy in both sexes. The NOAEL is 500 ppm (23.0 and 29.7 mg/kg/day for males and females, respectively).**

Discussion of Tumor Data: When the data were combined from the rat chronic toxicity study and the carcinogenicity study, male rats had a significant increasing trend ($p<0.01$), and significant differences in the pair-wise comparison of the 2500 ppm dose group with the controls for thyroid follicular cell adenomas ($p<0.05$). There was no treatment-related increase in thyroid follicular cell carcinomas. However, when the one follicular cell carcinoma from the control was included, there was only a significant increasing trend for combined adenomas and carcinomas ($p<0.05$) in males. The increased incidence of the thyroid follicular cell adenomas exceeded the historical control mean and range. The increase in thyroid follicular cell adenomas to be treatment-related in males. This was supported by thyroid hypertrophy and hyperplasia of follicular cells at 2500 ppm, increased thyroid weights and mechanistic data.

When the data were combined from the rat chronic toxicity study and the carcinogenicity study, female rats had a significant increasing trend ($p<0.05$) for thyroid follicular cell adenomas. The increasing trend for adenomas to be treatment-related in females. This tumor response was consistent with the male response in terms of tumor types and hyperplasia. No carcinomas were observed.

Adequacy of Dose Levels Tested: The highest dose tested of 2500 ppm was considered to be adequate in both sexes to assess the carcinogenicity of BAS 510 F in Wistar rats. This was based on changes in clinical chemistry/enzymes and organ weights, as well as liver and thyroid lesions.

3. Carcinogenicity Mouse Study

MRID No.: 45404901

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.

Discussion of Tumor Data: No treatment-related increase in tumor incidence was found in this carcinogenicity study.

Adequacy of the Dose Levels Tested: Dosing was adequate based on the lack of an increase in tumors at the highest dose tested of 1345 and 1804 mg/kg/day in males and females, respectively.

3. Classification of Carcinogenic Potential

The Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met on September 25, 2002 to evaluate the carcinogenic potential of BAS 510 F. In accordance with the Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC classified BAS 510 F into the category **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"**, and, therefore, the quantification of human cancer risk is not recommended.

V. MUTAGENICITY

There are five acceptable mutagenicity studies on technical grade BAS 510 F. Together, they satisfy the revised mutagenicity guideline of 1991 (OPP Pesticide Assessment Guideline. Subdivision F, Series 84, Addendum 9) which are applicable to all new active ingredients. Results in all five studies were negative for mutagenic potential. The following summarize these studies:

A. *Salmonella/Escheichia*/Mammalian Activation Gene Mutation (Engelhardt, G., 1998, MRID 45404913

Executive Summary:

In repeat reverse gene mutation assays in bacteria (MRID 45404913), strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to BAS 510 F (95.3% a.i., Batch No.: N 26) in DMSO, initially at concentrations

of 22, 110, 550, 2750 or 5500 µg/plate, with and with mammalian metabolic activation (S9-mix), using a standard plate assay (EXPERIMENT 1). The same five strains were exposed to the test material in a repeat assay at concentrations of 20, 100, 500, 2500 or 5000 µg/plate in the presence and absence of S9-mix using a preincubation assay (EXPERIMENT 2). The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

BAS 510 F was tested up to and beyond a limit concentration of 5000 µg/plate. Precipitation was seen at concentrations of 500 µg/plate and higher and weak cytotoxicity was evident at concentrations of 2500 µg/plate and higher in the *S. typhimurium* strains. There was no increase in the number of revertants per plate over the solvent control value in any bacterial strain at any BAS 510 F concentration in either assay, with or without S9-mix. The solvent and positive control values were appropriate for the respective strains and within the testing laboratory's historical control ranges.. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline**. It satisfies the Test Guideline OPPTS 870.5100[1]; OECD 471 requirements for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

B. Mammalian Cells in Culture Gene Mutation Assay in Chinese Hamster CHO Cells (Engelhardt, G., 2000, MRID 45404914)

Executive Summary:

In repeat mammalian cell gene mutation assays at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus (MRID 45404914), Chinese hamster CHO-K1 cells cultured *in vitro* were exposed initially for four hours to BAS 510 F (94.4% a.i., Batch No.: N 37) in DMSO at concentrations of 15.625, 31.25, 62.5, 125, 250 or 500 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix). Subsequently, a second experiment was conducted using test material concentrations of 10.24, 25.6, 64, 160, 400 or 1000 µg/mL with and without S9-mix with a repeat of the nonactivated test at concentrations of 3.125, 6.25, 12.5, 25, 50 or 100 µg/mL. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

BAS 510 F was tested up to cytotoxic and precipitating concentrations. In the preliminary cytotoxicity assay without S9-mix, the relative cloning efficiency was reduced to approximately 10% at test material concentrations of 500 µg/mL and higher and a precipitate was seen in the culture medium at concentrations of 50 µg/mL and higher. In the presence of S9-mix the relative cloning efficiency was below 10% at concentrations of 500 µg/mL and higher. Results of the mutation assays were not affected by pH or osmolality changes. The mutant frequency of all BAS 510 F treated cultures was within the testing laboratory's

historical solvent control ranges in both assays, with and without S9-mix. Excessive cytotoxicity occurred in the absence of S9-mix in the second mutation assay necessitating a repeat at lower doses. The solvent and positive controls induced the appropriate responses within the testing laboratory's historical control ranges. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline.** It satisfies the guideline requirement for Test Guideline OPPTS 870.5300, OECD 476 for *in vitro* mutagenicity (mammalian forward gene mutation) data.

C. *In vitro* Chromosomal Aberration (Engelhardt, G., 1999, MRID 45404915)

Executive Summary:

In repeat mammalian cell cytogenetics assays (chromosomal aberrations) (MRID 45404915), Chinese hamster V79 cell cultures were exposed to BAS 510 F (94.4% a.i., batch # N 37) in DMSO in two independent assays. In the first assay, cells were exposed to the test material for four hours at concentrations of 0, 20.0, 100.0 or 500.0 µg/mL with and without metabolic activation and the cells harvested 14 hours after termination of treatment. In the second cytogenetic assay, cells were exposed to the test material for 18 hours at concentrations of 0, 31.25, 62.5 or 125.0 µg/mL in the absence of S9-mix and harvested immediately after exposure. Cells were also exposed to 0 or 125 µg/mL of test material for 28 hours in the absence of S9-mix and harvested immediately after exposure. Cells were exposed to test material concentrations of 0, 125.0, 250.0 or 500.0 µg/mL for four hours in the presence of S9-mix and harvested 24 hours after termination of exposure.

BAS 510 F was tested up to precipitating concentrations. A preliminary cytotoxicity test at concentrations up to 3500 µg/mL showed precipitation at BAS 510 F concentrations of 100 µg/mL and higher. Little or no cytotoxicity, as evaluated by mitotic index and cell morphology changes, was seen with or without S9-mix. The test material did not change the pH or osmolality of the treatment medium. Both structural and numerical aberrations were recorded. There were no statistically significant increases in the percentage of metaphases with structural aberrations or numerical aberrations, either including or excluding gaps, at any test material concentration or exposure/harvest time scenario. The types and frequencies of aberrations in test material treated cells were similar to those of the solvent controls. The solvent and positive controls induced the appropriate responses within the testing laboratory's historical control ranges. **There was no evidence of chromosomal aberration induction over background.**

This study is classified as **Acceptable/Guideline.** It satisfies the guideline requirement for an *in vitro* mammalian cytogenetics (chromosomal aberrations) assay in Chinese hamster V79 cells; OPPTS 870.5375; OECD 473.

In vivo Mammalian Cytogenetics - Micronucleus Assay in Mouse Bone Marrow Cells (Engelhardt, G., 1999, MRID 45404916)

Executive Summary:

In a mouse bone marrow micronucleus assay (MRID 45404916), 5 NMRI male mice/dose were treated via two intraperitoneal injections 24 hours apart with BAS 510 F (94.4% a.i., batch # N 37) at doses of 0, 500, 1000 or 2000 mg/kg bw. Bone marrow cells were harvested 24 hours after the second treatment. The vehicle was 0.5% carboxymethyl cellulose.

There were signs of toxicity during the study. A preliminary toxicity test with two i.p. injections of 2000 mg/kg test material in male and female mice showed squatting posture, piloerection and poor general state but no mortality. No sex differences were seen, therefore, males only were used in the micronucleus assay. In the micronucleus assay, the same clinical signs seen in the preliminary toxicity test were seen during the first four hours following both the first and second injections. All mice in the low dose group appeared normal 24 hours after each injection while all mice in the mid- and high-dose groups showed squatting posture at this time after the first injection and piloerection at this time after the second injection. The frequencies of micronucleated PCEs in the 500, 1000 and 2000 mg/kg groups were 1.4‰, 1.3‰ and 1.2‰, respectively, compared to the solvent control value of 1.2‰. There were no statistically significant differences between groups. Likewise, there were no statistically significant differences between groups in the frequency of micronucleated NCEs. Of the micronuclei that were observed in PCEs, virtually all were small micronuclei. The PCE/NCE ratios indicated no bone marrow cytotoxicity. BAS 510 F was tested to a toxic limit dose. The solvent and positive controls (cyclophosphamide and vincristine sulfate) induced the appropriate responses within the testing laboratory's historical control ranges.. **There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any dose.**

This study is classified as **Acceptable/Guideline**. It satisfies the guideline requirement for Test Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

D. Other Mutagenicity: Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell Cultures, (Engelhardt, G., 2000, MRID 45404917)

Executive Summary:

In repeat unscheduled DNA synthesis assays (MRID 45404917), primary rat hepatocyte cultures were exposed to BAS 510 F (94.4% a.i., Batch # N 37) in DMSO at concentrations of 0, 5, 10, 50, 100, 250, 500, 750, and 1000 µg/mL for 18 - 20 hours in the first UDS experiment. Due to excess cytotoxicity, the first experiment was repeated at BAS 510 F concentrations of 0, 0.5, 1.0, 5.0, 10.0, 50.0, 100.0, 250.0, and 500.0 µg/mL for 18 - 20 hours. A second experiment was conducted at BAS 51 F concentrations of 1.563, 3.125, 6.250, 12.500, 25.000, and 50.000 µg/mL for 18 - 20 hours.

BAS 510 F was tested up to cytotoxic concentrations. An upper dose of 500 µg/mL was chosen for the first UDS experiment based on results of a preliminary cytotoxicity test using lactate dehydrogenase activity and lactate concentration as the measure of cytotoxicity. A precipitate was seen in the culture medium at test material concentrations of 50 µg/mL and higher. The test material did not change the pH or osmolality of the culture medium. Cytotoxicity was greater than expected in the initial experiment and the cells were not evaluated for UDS. In the repeat first experiment, BAS 510 F concentrations of 1, 5, 10 and 50 µg/mL were evaluated for UDS. Concentrations of 100 - 500 µg/mL were excessively cytotoxic and were not evaluated. There was no evidence of induced UDS (all net nuclear grain counts were well below zero) or any increase in the number of cells in repair (net nuclear grain counts ≥ 5) compared to the solvent control in the first experiment. BAS 510 F concentrations of 6.25, 12.50, 25.00 and 50.00 µg/mL were evaluated in the second UDS experiment. The results confirmed those of the first experiment, with no induction of UDS (all net nuclear grain counts were well below zero) or increases in the percentage of cells in repair. The mean net nuclear grain counts were -5.74 ± 4.44 and 29.01 ± 15.00 for the solvent and positive controls, respectively, in the first experiment. Comparable values in the second experiment were -4.40 ± 3.62 and 10.24 ± 10.45 for the solvent and positive controls, respectively. The control values were within the testing laboratory's historical control ranges. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.**

This study is classified as **Acceptable/Guideline.** It satisfies the guideline requirement for Test Guideline OPPTS 870.5550; OECD 482/486 for other genotoxic mutagenicity data.

IV. HAZARD CHARACTERIZATION

Acute toxicity data indicated that all studies were in toxicity category III or IV. The dermal sensitization guinea pig study was considered to be unacceptable because the concentration used for the challenge was inadequate.

There were no maternal or developmental effects observed in the rat developmental toxicity study when BAS 510 F was administered at the LIMIT DOSE. In the rabbit developmental study, the LIMIT DOSE appeared to cause an increase in the incidence of abortions or early deliveries; this was considered to be an affect on either the mothers, fetuses or both. In the 2-generation rat reproduction study, parental effects of decreases in body weight/body weight gain and hepatocyte degeneration were noted at the LIMIT DOSE. No effects on reproduction were identified. For offspring, there was a decrease in body weight/body weight gains at the next to highest dose in males and at the LIMIT DOSE in females.

In both 2-year rat toxicity studies as well as in the 90-day rat study, the following effects were noted regarding the thyroid: increased weights as well as increased incidences of follicular cell hyperplasia and hypertrophy. The 1-year and 90-day dog studies showed elevated alkaline phosphatase activities and elevated hepatic weights. Only the 90-day (not the 18-month) mouse study showed an increase in liver weights and increased incidence of marked fatty change in the liver (males only).

Carcinogenicity, thyroid follicular cell adenomas, was noted in both 2-year rat studies, but not in the 18-month mouse study. When data were combined from both rat studies, males showed a significant increasing trend and significant differences in the pair-wise comparison. There was no treatment-related increase in thyroid follicular cell carcinomas. The increased incidence of the thyroid follicular cell adenomas exceeded the historical control mean and range. The CARC considered the increase in these adenomas to be treatment-related in males. The CARC classified BAS 510 F into the category "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential."

BAS 510 F was negative in a battery of five mutagenic assays.

In rat metabolism and pharmacokinetic studies, BAS 510 F was readily absorbed and excreted following a single oral dose of 50 mg/kg. At single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion was mainly by feces (80-98%). Biliary excretion was 40-50% of fecal activity at 50 mg/kg and 10% at 500 mg/kg. Urinary content was about 16% at 50 mg/kg and 3-5% at 500 mg/kg. Absorption was about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns were similar by gender or radiolabel position. Metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with glucuronic acid or sulfate, or by conjugation of the parent with glutathione with cleavage to sulfate metabolites.

VII. DATA GAPS/REQUIREMENTS

A 28-day rat inhalation study.

VIII. ACUTE TOXICITY

Acute Toxicity of BAS 510 F (active ingredient)

Guideline No.	Study Type	MRID #	Results	Toxicity Category
81-1, 870.1100	Acute Oral, rat **Acceptable**	45404814	LD_{50} > 5000 mg/kg bw	IV
81-2, 870.1200	Acute Dermal, rat **Acceptable**	45404815	LD_{50} > 2000 mg/kg bw	III
81-3, 870.1300	Acute Inhalation, rat **Acceptable**	45404816	LC_{50} > 6.7 mg/L	IV
81-4, 870.2400	Primary Eye Irritation, rabbit **Acceptable**	45404817	Not irritating	IV
81-5, 970.2500	Primary Skin Irritation, rabbit **Acceptable**	45404818	Not irritating	IV
81-6, 870.2600	Dermal Sensitization, guinea pig **Unacceptable** (1)	45404819	**Could not be determined**	NA

(1) Unacceptable because the 5% concentration used for the challenge was inadequate.

30

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for BAS 510 F

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	No appropriate endpoint identified	NA	NA
Chronic Dietary (All populations)	NOAEL = 21.8 mg/kg/day UF = 100 **Chronic RfD** = 0.218 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.218 mg/kg/day	Chronic rat, carcinogenicity rat and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Incidental Oral Short- and Intermediate-Term Residential Only	NOAEL = 21.8 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	Chronic rat, carcinogenicity rat and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Dermal All durations	Oral study NOAEL = 21.8 mg/kg/day (dermal absorption rate = 15%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	Chronic rat, carcinogenicity rat and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Inhalation All durations	Oral study NOAEL = 21.8 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	Chronic rat, carcinogenicity rat and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Cancer	Classification: "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential."		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

** **NOTE:*** The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.