

No teratogenic effects were noted in either the rat or rabbit developmental studies. In the rat study, evidence of maternal or developmental toxicity was not observed at any dose (highest dose tested of 1,000 mg/kg/day). Neither a maternal nor developmental lowest observed adverse effect level (LOAEL) were found since the highest dose tested was the NOAEL in both studies. In the rabbit teratology study, maternal toxicity observed at the mid dose of 300 mg/kg bwt consisted of discolored/reduced feces in one dam and an abortion in one dam. This finding is not necessarily indicative of a definitive test substance related adverse effect. The dam which displayed the fecal alterations and abortion also displayed decreased body weight and body weight gain - compared to the group mean - during gestation. These decreases occurred even prior to compound administration. Food consumption was also dramatically decreased in this dam compared to the other animals in the group. Every day from gestation day (GD) 1 - 12, this dam had food consumption values, which were less than half the mean for the group (compound administration began on GD 7). From GD 13 to 26 (when the animal aborted and was sacrificed) this dam ate essentially nothing (food consumption during this time period was ≤ 1.5 grams/day). These decreases in body weight, body weight gain, and food consumption, prior to compound administration, all indicate an animal in poor health and this poor state of health, rather than compound exposure, was likely the reason for the fecal alterations and abortion.

At the high dose of 1,000 mg/kg bwt a maternal body weight gain decrease compared to controls of 81% was observed during the treatment period. Reduced food consumption, reduced body weight and abortions in three dams, were also seen at 1,000 mg/kg/day. Evidence of developmental toxicity was not seen at any dose tested.

Developmental neurotoxicity (DNT) was not observed at any dose in the developmental neurotoxicity study. No maternal toxic effects were noted at any dose in this study. No developmental toxicity was seen at the low dose of 12 mg/kg/day (100 ppm). Reduced body weights and body weight gains were seen at 118 mg/kg/day (1,000 ppm) during postnatal day (PND) 1-4. Reduced body weights and body weight gains were seen at 1,183 mg/kg/day (10,000 ppm) as well as decreased absolute pup brain weight at day 11 post partum (p.p.) (both sexes) and decreased brain length (males only) at day 11 p.p. The reduced pup brain weights and

decreased brain length go hand-in-hand and both are due to the decreased pup weights seen at this dose. In this respect, it should be noted that pup brain weights relative to body weight at p.p. 11 were not significantly different from controls at this dose.

Though no maternal toxicity was seen in this study, other studies using similar doses of BAS 510 resulted in maternal toxicity. A dose of 118 mg/kg/day in female rats of the same strain in the multi-generation study, resulted in an increased incidence of hepatic centrilobular hypertrophy a parameter which could not have been detected in the DNT study as liver histopathology on parental animals was not performed in the DNT study.

4. *Subchronic toxicity.* The subchronic toxicity of BAS 510 F was investigated in 90-day feeding studies with rats, mice and dogs, and in a 28-day dermal administration study in rats. A 90-day neurotoxicity study in rats was also performed. Generally, mild toxicity was observed. At high dose levels (doses above the LOAELs) in feeding studies, all three species displayed alterations in various clinical chemistry parameters. These clinical chemistry alterations were likely secondary to general toxicity. Statistically significant increased absolute and relative thyroid weights were observed in male rats only at doses at and above the LOAEL. Increased absolute and relative liver weights were observed in both sexes at doses above the LOAEL in rats and dogs. Increased absolute and relative liver weights were seen in both sexes of the mouse at lower doses. However, the increases in liver weights at these lower doses in the mouse were not deemed to be compound related due to the unusually low concurrent control liver weight values. At doses above the LOAELs, liver weight increases were supported by histopathology alterations in the rat and mouse, but not in the dog. Overall, only mild toxicity was observed in oral subchronic testing.

In the 28-day repeat dose dermal study, no systemic effects were noted up to the highest dose tested of 1,000 mg/kg/day.

In a 90-day rat neurotoxicity study, there was no mortality, signs of clinical toxicity, adverse effects on food consumption or body weight, at any dose level in either sex. No signs of neurotoxicity were observed during clinical observations, functional observation batteries, motor activity measurements of neuropathology. Therefore, there were no selective neurotoxic effects. Adverse effects were not seen even at the highest dose level

tested. A LOAEL was not found and the NOAEL is the highest tested of 15,000 ppm (1,050 mg/kg/day in males; 1,272 mg/kg/day in females).

5. *Chronic toxicity.* Based on review of the available data, the Reference Dose (RfD) for BAS 510 F will be based on a 24-month feeding study in rats with a threshold no observed effect level (NOEL) of 5 mg/kg/day. Using an uncertainty factor of 100, the RfD is calculated to be 0.05 mg/kg/day. The following are summaries of chronic toxicity studies submitted to EPA. The chronic toxicity/oncogenicity studies with BAS 510 F include a 12-month feeding study with Beagle dogs, an 18-month B63CF1 mouse feeding study, a 24-month Wistar rat chronic feeding study and a 24-month Wistar rat oncogenicity study.

At the highest dose tested in dogs, effects observed consisted primarily of increased liver and thyroid weights and some serum clinical chemistry changes. The NOAEL was 800 ppm (21.8 mg/kg bwt males; 22.1 mg/kg bwt females).

Decreased body weights were seen in males in the mouse chronic study at doses of 400 ppm and above. Decreased female body weight was seen at doses of 2,000 ppm and above. The target organ in this study was the liver. In both the rat chronic and oncogenicity studies, the highest dose tested of 15,000 ppm exceeded a maximum tolerated dose (MTD) and was discontinued after 17 months. Effects observed at the next highest dose of 2,500 ppm primarily centered around the thyroid and liver.

Overall, mild toxicity was observed with chronic exposure to BAS 510 F. No evidence of treatment-induced oncogenicity was observed in the mouse or dog studies. A slight increase in thyroid follicular cell adenomas was seen in both sexes at the high dose when the data from both rat bioassays are combined.

A mode of action (MOA) for the thyroid follicular cell adenomas has been proposed. This MOA is based on the EPA publication "Assessment of Thyroid Follicular Cell Tumors," March 1998, EPA/630/R-97/002. This document describes the criteria, which must be met in order for a compound to be considered under the MOA described in that publication. BASF Corporation believes that BAS 510 F has met the cited criteria.

Threshold effects. Based on a review of the available chronic toxicity data, BASF believes EPA will establish the Reference Dose (RfD) for BAS 510 F at 0.05 mg/kg/day. This RfD for BAS 510 F is based on the 2-year chronic and 2-year oncogenicity studies in rats with a threshold average NOAEL of 5 mg/kg/