

2. *Genotoxicity*. Ames Test (1 Study; point mutation): Negative; *In Vitro* CHO/HGPRT Locus Mammalian Cell Mutation Assay (1 Study; point mutation): Negative; *In Vitro* V79 Cell Cytogenetic Assay (1 Study; Chromosome Damage): Negative; *In Vivo* Mouse Micronucleus (1 Study; Chromosome Damage): Negative; *In Vitro* Rat Hepatocyte (1 Study; DNA damage and repair): Negative. BAS 510 F has been tested in a total of 5 genetic toxicology assays consisting of *in vitro* and *in vivo* studies. It can be stated that BAS 510 F did not show any mutagenic, clastogenic or other genotoxic activity when tested under the conditions of the studies mentioned above. Therefore, BAS 510 F does not pose a genotoxic hazard to humans.

3. *Reproductive and developmental toxicity*. The reproductive and developmental toxicity of BAS 510 F was investigated in a two-generation rat reproduction study as well as in rat and rabbit teratology studies.

There were no adverse effects on reproduction in the two-generation study at any dose tested. Pup effects were observed, with parental toxicity, at the highest dose tested only. In both parental generations, reduced food consumption and reduced bodyweight gain were observed at 10,000 ppm. Both absolute and relative liver weights were increased 21% in F₁ generation parental females at the high dose of 10,000 ppm only. Hepatocellular centrilobular hypertrophy (usually slight) was observed in many animals of both sexes in both the F₀ and F₁ generations at 1,000 ppm, and in all animals of both sexes at 10,000 ppm. Additionally, some of the parental male rats at 10,000 ppm, in both generations, displayed centrilobular liver cell degeneration. Developmental toxicity was seen at 1,000 ppm in the form of decreased pup weights in the F₂ males, and at 10,000 ppm in the form of decreased pup weight for both males and females of both the F₁ and F₂ generations. The parental systemic and developmental toxicity NOAEL's are both 100 ppm (12 mg/kg/day).

No teratogenic effects were noted in either the rat or rabbit developmental studies. In the rat study, evidence of maternal or developmental toxicity were not observed at any dose (highest dose tested of 1,000 mg/kg/day). Neither a maternal nor developmental 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 milligrams/kilogram of body weight (mg/kg bw) 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 less than or equal to 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 bw 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 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 post natal 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 multigeneration study, resulted in an increased incidence of hepatic centrilobular

hypertrophy - a parameter which could not have been detected in the developmental neurotoxicity (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, or 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