

one significant metabolite, M670H05, were found in low levels in the plant matrices with the majority of the radioactive residues incorporated into natural products. M670H05 resulted from oxidation of the carbonyl bridge to a carboxylic acid with concomitant loss and breakdown of the pyrazole ring. The significant metabolite M670H05 was found in the rat metabolism study.

2. *Analytical method.* Suitable independently validated analytical methods (for crop and animal matrices) are submitted for detecting and measuring BAS 670 H levels in or on food with a limit of detection that is satisfactory for enforcing the requested tolerances. Residues are first extracted from the matrices by aqueous solvent then cleaned up by acid partitioning into organic solvent, then base partitioned, and quantified with application to high performance liquid chromatography with dual mass selective detectors (LC/MS/MS).

3. *Magnitude of residues.* Field studies were conducted at 30 sites over 2 years with sites selected to fulfill both EPA and Canadian Pest Management Regulatory Agency (PMRA) requirements. The end product, BAS 670 00H, was applied broadcast over corn plants in two applications at 25 g active ingredient/ha (0.022 lb a.i./acre) + 75 g a.i./ha (0.067 lb a.i./acre) for a total of 100 g a.i./ha (0.089 lb a.i./acre) with the final application targeted for 45 days before milk stage. Samples of field corn were harvested at the milk stage to cover sweet corn harvest timing. All matrices were analyzed for parent and M670H05 with the limit of quantitation (LOQ) setting the proposed tolerances. No residues were detected above the LOQ in any of the corn RAC samples analyzed (fresh corn, forage, grain, and stover). To determine the fate of any BAS 670 residues in processed grain, the field study incorporated an exaggerated 5x application rate. No residues above LOQ were detected in the 5x treated grain samples; therefore, the analyses of the grain processed fractions was not required. The cow feeding study at three dosing levels show that food tolerances for parent in only kidney and liver matrices are necessary (and not for any other matrices such as meat, fat, and milk).

B. Toxicological Profile

1. *Acute toxicity—i.* Oral (rat): (LD)₅₀ = >2,000 milligrams/kilogram body weight (mg/kg bwt) (male/female) = Category III.

ii. Dermal (rat): (LD)₅₀ = >2,000 mg/kg bwt (male/female) = Category III.

iii. Inhalation (rat): (LC)₅₀ = >5.8 milligrams/per liter (mg/L) (male/female) = Category IV.

iv. Primary eye irritation (rabbit): Slightly irritating = Category III.

v. Primary dermal irritation (rabbit): Slightly irritating = Category III.

vi. Dermal sensitization (guinea pig): Not a sensitizer.

vii. Oral neurotoxicity (rat): NOAEL = 2,000 mg/kg bwt (male/female).

2. *Genotoxicity.* BAS 670 H was tested for its genotoxic potential in a battery of five *in vitro* or *in vivo* studies covering all required end-points (gene mutations, chromosomal and chromosome aberrations, and DNA damage and repair). Several batches of BAS 670 H have been tested over the time, from early laboratory produced material to current manufacturing process material. BAS 670 H did not demonstrate any genotoxic effects *in vivo*. *In vitro*, either batches tested for chromosomal aberrations caused a slight, significant clastogenic effect in the presence of S-9 mix, but the *in vivo* test for the equivalent end-point was negative. Three of the four batches tested in the bacterial reverse mutation assay were not mutagenic, but, the batch with the least purity displayed a weak mutagenic effect at the highest dose in *Salmonella typhimurium* TA98 in the absence of S-9 mix, most likely caused by impurities, which are not present in the current production batch. Overall, the weight of the evidence is that BAS 670 H is not genotoxic.

3. *Reproductive and developmental toxicity.* The reproductive and developmental toxicity of BAS 670 H was investigated in a 2-generation rat reproduction study as well as in rat, mouse and several rabbit teratology studies (with different batches of BAS 670 H) and a rat developmental neurotoxicity study.

There were no adverse effects on fertility of both genders and no effect on the reproductive performance of males in the two-generation study at any dose tested. There was, however, a high litter loss in F₀ and F₁ associated with insufficient maternal care at higher dose levels with clear maternal toxicity. General parental toxicity included eye and kidney effects, caused by elevated tyrosine levels due to hydroxyphenylpyruvate dioxygenase (HPPD) inhibition. The same organs were affected in subchronic and chronic feeding studies with rats. Pup effects were observed in the F₁ and F₂ generation including perinatal pup mortality and impaired body weight gain, the lower body weight effects were considered to lead to brain and spleen weight changes and delays in preputial

separation. As observed in the parental animals, effects on eyes and kidneys were observed in the pups. Renal pelvis dilation was observed at lower doses, although, there was no overt maternal toxicity, significantly elevated tyrosine levels were observed in the dams and pups. The no observed adverse effect level (NOAEL) for fertility (F₀ and F₁, both genders) was 4,000 ppm (about 450 mg/kg bwt/day); the NOAEL for reproductive performance was 40 ppm (about 4 mg/kg body weight/day) for the F₁ females. The NOAEL for general toxicity was 4 ppm (about 0.4 mg/kg bwt/day). The NOAEL for developmental toxicity (growth and development of the offspring) was 4 ppm (about 0.4 mg/kg body weight/day) for the F₁ pups, but was lower than 4 ppm for the F₂ pups due to renal pelvis dilations at all dose levels.

Developmental neurotoxicity was not observed at any dose in the developmental neurotoxicity study. At all dose levels, eye effects due to elevated tyrosine levels were found in dams and pups. Additionally, there were decreased body weights in the dams at the high and mid dose, but there were no indications of adverse effects on reproductive performance of the parental females. In pups of both genders, decreased preweaning and postweaning body weight gains and body weights were observed at the low dose level and above. This is an indicator of a retardation of the general physical development, which is considered to be responsible for a slight delay of maturation. The NOAEL for developmental neurotoxicity was 800 mg/kg bwt/day (highest dose tested). There is no NOAEL for the eye lesions and reduced body weight gain of the pups. NOAELs for these effects were determined in prenatal development studies in rats, rabbits and mice.

No developmental toxicity was noted in the mouse prenatal development study. In the prenatal development study in rats no teratogenic effect was observed, but there was maternal toxicity together with skeletal variations in the pups. The same skeletal variation (i.e. supernumerary ribs) was also found in rabbit prenatal development studies. This effect is associated with the family of HPPD inhibiting substances. In addition, several rabbits had pups with a soft tissue malformation: unilateral kidney agenesis. The NOAEL for the skeletal variations and the kidney agenesis was 0.5 mg/kg bwt/day, the NOAEL for overt maternal toxicity was 50 mg/kg bwt/day. The developmental effects in rabbits occurred at dose-levels below overt maternal toxicity; however, measured tyrosine blood levels in the