

cyazofamid. Assays conducted included *in vitro* reverse gene mutation tests in bacteria and an *in vitro* forward gene mutation test in a mammalian cell system, a chromosomal damage test in mammalian cells, a DNA repair test in bacteria, and an *in vivo* micronucleus test in mice. Cyazofamid did not elicit a genotoxic response in any of the studies conducted.

3. *Reproductive and developmental toxicity.* In a two-generation reproductive toxicity study, the only effects observed were body weight effects which were observed at 20,000 ppm in dams during gestation and lactation and in weanling pups. No reproductive effects were observed. The NOEL for reproductive effects was 20,000 ppm (1,338 mg/kg bwt/day). The NOEL for parental toxicity was 2,000 ppm (134 mg/kg bwt/day). In a rat developmental study, cyazofamid was dosed by gavage from Days 0 to 19 of gestation. There were no treatment-related effects observed in the study. The NOEL for maternal and developmental effects was 1,000 mg/kg bwt/day. In a rabbit developmental study, pregnant rabbits were dosed with cyazofamid by gavage on Days 4 to 28 of gestation. There were no treatment-related effects observed in the study. The NOEL for maternal and developmental effects was 1,000 mg/kg bwt/day. The developmental studies (prenatal developmental studies in rat and rabbit and the two generation reproduction study in rat) provided no indication of increased sensitivity of rats or rabbits from *in utero* or postnatal exposure to cyazofamid. Cyazofamid is not a developmental or reproductive toxicant.

4. *Subchronic toxicity.* The oral toxicity of cyazofamid was investigated in rats and dogs in 13-week studies. The exposure was by dietary administration for the rats and by capsule for the dogs. There were no treatment-related effects observed in dogs up to 1,000 mg/kg bwt/day which was the highest dose tested. In rats, treated at 5,000 ppm there was a treatment related increase in kidney and liver weights and increased observation of *basophilic tubules*. The latter was observed only in males. The NOEL was 500 ppm which was equivalent to a dosage of 29.9 mg/kg bwt/day to males and 33.3 mg/kg bwt/day to females.

5. *Chronic toxicity.* A combined chronic and oncogenicity study was conducted in rats. Cyazofamid was administered continuously for a period of 104 weeks to male and female Fischer rats. Cyazofamid was not carcinogenic in this study. The NOEL for chronic effects was 500 ppm (17 mg/kg bwt/day)

based on kidney and liver weight differences and increases in urine volume and chloride levels at 5,000 ppm. In a long-term feeding study, mice were dosed with cyazofamid in the diet for 78 weeks. No treatment related effects were observed and it was concluded, that cyazofamid was not carcinogenic. The NOEL was 7,000 ppm (985 and 1,203 mg/kg bwt/day for males and females, respectively). In a chronic dog study, four groups of six dogs/sex/group received the test material via capsule for 52 weeks. No treatment related effects were observed. The NOEL was 1,000 mg/kg bwt/day.

6. *Animal metabolism.* Studies on the metabolism of cyazofamid in animals using radioactive test material have been conducted with cyazofamid, labeled with ¹⁴C in two positions, the benzene [¹⁴C-Bz]- or imidazole [¹⁴C-Im] position. Absorption is rapid, but the percentage of cyazofamid absorbed after an oral dosage decreases as the dosage is increased. All absorbed radiocarbon is rapidly eliminated with urinary and biliary elimination of radiocarbon nearly complete within 24 hours. The metabolic pathway of cyazofamid includes the rapid hydrolysis of the dimethylsulfonamide group and the oxidation of the benzyl methyl group.

7. *Metabolite toxicology.* Comparison of the metabolism of cyazofamid by plants and in animals indicates that a number of the identified metabolites are common to both plants and animals but metabolism in plants is more extensive than in animals. The data indicate that the final products of the metabolism of cyazofamid in animals and plants represent differences in the extent of metabolism. Several of the metabolites resulting from cyazofamid are similar in plants and animals and, therefore, have already been evaluated toxicologically.

8. *Endocrine disruption.* An evaluation of the potential effects on the endocrine systems of mammals has not been determined; however, no evidence of such effects was reported in subchronic, chronic or reproductive toxicology. There was no observed pathological finding of the endocrine organs in these studies, and there were no reproductive effects at the maximum dose tested of 20,000 ppm. There is no evidence at this time that cyazofamid causes endocrine effects.

C. Aggregate Exposure

1. *Dietary exposure.* A reference dose (RfD) of 0.17 mg/kg bwt/day is proposed for humans, based on the NOEL from the 2 year rat study (17 mg/kg bwt/day) and dividing by an uncertainty factor of 100. The acute NOEL of 100 mg/kg bwt is from the acute neurotoxicity study

adjusted for oral absorption of 5%. No treatment related effects were observed at any dose level.

i. *Food.* Tier 1 chronic and acute dietary exposure analyses were conducted for cyazofamid in/on cucurbits, potatoes, tomatoes and wine grapes to determine the exposure contribution of these commodities to the diet and to ascertain the chronic and acute risk potential. The estimates were based on proposed tolerance level residues for all crops, potato and tomato processing studies, market share assumptions of 100% crop treated, and consumption data from the 1994 through 1996 United States Department of Agriculture (USDA) continuing survey of food intake.

Even using all of the worst case exposure scenarios listed above, the Tier 1 chronic dietary exposure estimates resulted in an estimated exposure for the U.S. population of 0.000594 mg/kg bwt/day. This exposure corresponds to 0.3% of the RfD of 0.17 mg/kg bwt/day. The highest exposure estimate was calculated for the children 1–6 years population subgroup. This exposure was determined to be 0.000939 mg/kg bwt/day (0.6% of the RfD).

The Tier 1 acute assessment for the U.S. population resulted in a margin of exposure (MOE) of 35,789 at the 95th percentile. This corresponded to an estimated exposure of 0.002793 mg/kg bwt/day. The highest acute exposure estimate (95th percentile) was observed in children 1–3 years subpopulation: 0.004580 mg/kg bwt/day. This correlates to an MOE of 21,833. It can be concluded that acute or long-term dietary exposure to cyazofamid through residues on treated cucurbits, potatoes, tomatoes and imported wine grapes should not be of cause for concern.

ii. *Drinking water.* Since cyazofamid is intended for application outdoors to field grown potato, tomato and cucurbits crops, the potential exists for parent and or metabolites to reach ground or surface water that may be used for drinking water. The calculated drinking water levels of comparison (DWLOCs) for chronic exposure for adult males, adult females and toddlers were estimated to be 5,929 parts per billion (ppb), 5,083 ppb, and 1,691 ppb, respectively. The calculated DWLOCs for acute exposure for all adults, adult females and toddlers were estimated to be 34,902 ppb, 29,923 ppb, and 9,954 ppb, respectively. The chronic and acute DWLOC values are well above the modeled chronic and acute drinking water estimated concentrations (DWECS) of 0.023 ppb (generic expected estimated concentration (GENEEC) 56-day) and 1.38 ppb (GENEEC