

consumption. The NOAEL for cholinergic inhibition was greater than 400 ppm (20 mg/kg/day).

iii. *Thirteen-week dog feeding study.* Bifenazate was fed to male and female Beagle dogs for 13 weeks at dietary concentrations of 40, 400, and 1,000 ppm. At dosage levels of 400 and 1,000 ppm there was a reduction in RBC count, Hgb and hematocrit (HCT). Liver weights were increased at 400 and 1,000 ppm and centrilobular hepatocellular hypertrophy was seen in females at 400 ppm and males and females at 1,000 ppm. The NOAEL for subchronic toxicity in dogs was 40 ppm (1 mg/kg/day).

5. *Chronic toxicity—i. Dog chronic feeding study.* Bifenazate was fed to male and female Beagle dogs for 1-year at dietary concentrations of 40, 400, and 1,000 ppm. At dose levels of 400 and 1,000 ppm, there was a reduction in food consumption in males and reduced body weight gain in males and females. There was a reduction in RBC count, Hgb, and HCT and an increase in bilirubin at 400 and 1,000 ppm. Histopathological effects on bone marrow, kidney, and liver were also seen at these dose levels. The NOAEL for chronic toxicity in dogs was 40 ppm (1 mg/kg/day).

ii. *Rat chronic feeding/carcinogenicity study.* Bifenazate was not carcinogenic in rats when fed to male and female Sprague-Dawley CD rats for 2 years at dietary concentrations of 20, 80, and 160 in females or 20, 80, and 200 ppm in males. Body weight gain was reduced in males and females at the high dosage levels. A reduction in RBC count and an increase in splenic pigment were seen in females at 160 ppm, while high dose males exhibited a reduction in total cholesterol and an increase in splenic pigment. At a dose level of 80 ppm there was a reduction in body weight gain, a decrease in RBC count and an increase in splenic pigment in females. There was no increase in tumor incidence in males or females as a result of bifenazate administration. The NOAEL for chronic toxicity in rats was 20 ppm (1 mg/kg/day).

iii. *Mouse carcinogenicity study.* Bifenazate was not carcinogenic when fed to male and female CD-1 mice for 18 months at dietary concentrations of 10, 100, and 175 ppm in females and 10, 100, and 225 ppm in males. Body weight gain was reduced in males and females at the high dose level. A reduction in RBC, total leukocyte and lymphocyte counts was seen in males at 225 ppm. There was no increase in tumor incidence in males or females as a result of bifenazate administration.

6. *Animal metabolism.* In rat, ^{14}C -bifenazate, ^{14}C -phenyl hydrazine carboxylic acid, 2-(4-methoxy-1,1-biphenyl-3-yl)-1-methylethyl ester was extensively metabolized when it was given orally in 2 dose levels low (10 mg/kg), and high (1,000 mg/kg). Although $\frac{2}{3}$ of the dosed radioactivity was excreted in the feces, bifenazate depicted a good degree of absorption as indicated from the level of radioactivity in the bile. In the bile radioactivity study, about 70% of the C-14 was collected from the cannulated bile ducts of low dosed rats indicating an active level of absorption and enterohepatic circulation.

7. *Metabolite toxicology.* In a single dose oral toxicity limit test in rats, the oral LD_{50} of the diazene product of bifenazate was estimated to be approximately 5,000 mg/kg. At 2 hours and at 7 days post-dosing, no effects were seen on erythrocyte cholinesterase inhibition (ChEI) in male or female rats. In addition, no effect on plasma ChEI was seen in male rats at 7 days only. Since this effect was seen only in plasma of females at one time point, it is most likely a pseudo-cholinesterase effect without biological significance. In a dermal toxicity screen, the LD_{50} of the diazene was estimated to be >2,000 mg/kg.

8. *Endocrine disruption.* There are no known reported adverse reproductive or developmental effects in domestic animals or wildlife as a result of exposure to this chemical. A standard battery of required toxicity tests have been conducted on bifenazate. No effects were seen in the reproduction or developmental studies to indicate that bifenazate has an effect on the endocrine system.

C. Aggregate Exposure

1. *Dietary exposure.* Based on dietary, drinking water, and non-occupational exposure assessments, there is reasonable certainty of no harm to the U.S. population, any population subgroup, or infants and children from chronic exposure to bifenazate.

i. *Food.* Chronic dietary exposure was estimated using dietary exposure evaluation model DEEMTM tolerance levels, and 100% crop treated. Processing factors were used for apple and grape juice. The chronic dietary exposure to the U.S. population (total) was estimated as 0.003093 mg/kg bwt/day, and was 30.9% of the reference dose (RfD). Exposure to non-nursing infants, the highest exposed population subgroup, was 0.007238 mg/kg bwt/day (72.4% of the RfD), and exposure to children was 0.006627 mg/kg bwt/day (66.3% of the RfD).

ii. *Drinking water.* The residue of concern in drinking water was determined to be D1989. Chronic estimated environmental concentrations (EECs) of D1989 in surface water and ground water were generated using FIRST and the screening concentration in ground water (SCI-GROW) (1 application at 0.75 lbs active ingredient/acre). The FIRST model generated an EEC of 0.114 part per billion (ppb), whereas, the SCI-GROW model generated an EEC of 0.0119 ppb. These EEC values are much lower than the drinking water levels of concern (LOC) (227 ppb for adults, 27.6 ppb for infants and children). Therefore, exposure to potential residues in drinking water is expected to be negligible.

2. *Non-dietary exposure.* Food uses described in this petition are strictly agricultural, and will not add to any residential non-dietary exposure that may exist.

D. Cumulative Effects

The mechanism/mode of action of bifenazate on the mammalian RBC, which is the target organ in the species tested, remains to be elucidated. The lack of information on bifenazate mode of action precludes an assessment of cumulative effects.

E. Safety Determination

1. *U.S. population.* Based on the toxicology data base and available information on anticipated residues, chronic dietary exposure to the U.S. population (total) was 30.9% of the RfD. Exposure to potential residues in drinking water is expected to be negligible, as drinking water levels of concern (DWLOCs) are substantially higher than modeled acute and long-term EECs. The margin of exposure (MOEs) from the limited potential for short-term exposure from residential uses was >1,000. Based on these assessments, it can be concluded that there is reasonable certainty of no harm to the U.S. population or any population subgroup from exposure to bifenazate.

2. *Infants and children.* The chronic dietary exposure was 72.4% of the RfD for infants, and 66.3% for children. Exposure to potential residues in drinking water is expected to be negligible, as DWLOCs are substantially higher than modeled acute and long-term EECs. The MOEs from the limited potential for short-term exposure from residential uses was >1,000. Based on these assessments, it can be concluded that there is reasonable certainty of no harm to infants and children from exposure to bifenazate.