

0.135 lbs. active ingredient/acre/treatment is 0.32 ppm.

- The maximum expected etoxazole residues in cottonseed and cotton gin trash from two applications at 0.045 lbs. active ingredient/acre/treatment applied 28 days before harvest are 0.02 ppm and 0.60 ppm, respectively. Cotton gin trash was also analyzed for metabolite R-3 but was detected in samples from only one of seven test sites at a level only slightly above the 0.10 ppm limit of detection (LOD) (mean residue was 0.13 ppm). Therefore, no tolerance is being proposed for metabolite R-3 in cotton gin trash.

- The results of a cotton processing study indicate that etoxazole does not concentrate in hulls, meal, or oil.

- Following a single application to mandarin oranges of 0.05 lbs. active ingredient/acre, the maximum etoxazole residues in whole fruit harvested 14 days after application is 0.05 ppm.

- No processing of mandarins was required because only fresh or canned mandarins will be imported for direct consumption. Separate analysis of mandarin peel and pulp from residue field trials demonstrated that etoxazole residues are confined to the peel. Canned mandarins that contain only mandarin pulp would therefore not be expected to contain detectable residues of etoxazole.

These field trial data are adequate to support proposed tolerances of 0.2 ppm for pome fruit; 1.0 ppm for wet apple pomace; 0.5 ppm for strawberries; 0.05 ppm for cottonseed; 1.0 ppm in cotton gin trash; and 0.1 ppm in oranges.

Apple pomace and all cotton commodities are significant feed items for beef and dairy cattle and results of a goat metabolism study suggest the possibility that etoxazole residues in feed may transfer to edible tissues and milk. Therefore, a cow feeding study was conducted with etoxazole to determine the level of secondary residues and the need for corresponding tolerances. Etoxazole was detected in fat and cream only and Valent is therefore proposing tolerances of 0.03 ppm in the fat of animals and 0.04 ppm in milk fat. Cotton meal is the only commodity under consideration that is used as a poultry feed item and the results of the cotton processing study indicate that etoxazole residues in this commodity are very low. Additionally, the results of a hen metabolism study demonstrated very low potential for residues in feed to transfer to poultry tissues or eggs. Therefore, no hen residue feeding study was performed and tolerances are not proposed for secondary residues in poultry commodities.

B. Toxicological Profile

A full battery of toxicology testing, including studies of acute, chronic, oncogenicity, developmental, mutagenicity, and reproductive effects has been completed for etoxazole. The acute toxicity of etoxazole is low by all routes. Etoxazole is not a developmental or reproductive toxicant, and is not mutagenic or oncogenic. The toxicology reports for etoxazole have not yet been reviewed by EPA and thus, the Agency has not yet established toxic endpoints of concern, specifically chronic and acute oral toxicity endpoints for the compound. For the purpose of dietary risk analysis, Valent proposes 0.04 mg/kg bwt/day as the chronic Population Adjusted Dose (cPAD) and an acute Population Adjusted Dose (aPAD) of 2 mg/kg bwt/day. The cPAD is based on a chronic endpoint of 4 mg/kg bw/day NOEL for males from the rat chronic/oncogenicity feeding study and an uncertainty factor of 100. The aPAD is based on the 200 mg/kg bwt/day NOEL from the rabbit developmental toxicity study and an uncertainty factor of 100. Valent is unable to identify toxicity endpoints of concern for acute, short-term or chronic human exposures by any route other than oral.

1. *Acute toxicity.* The acute toxicity of technical grade etoxazole is low by all routes. The battery of acute toxicity studies place etoxazole in Toxicity Category III. The oral LD₅₀ in the rat was greater than 5 grams/kilogram (g/kg), the dermal LD₅₀ was greater than 2.0 g/kg, and the inhalation LC₅₀ in the rat was greater than 1.09 milligrams/liter (mg/L). Etoxazole technical was not an irritant to eyes or skin and was not a skin sensitizer.

2. *Genotoxicity.* Etoxazole was evaluated and found to be negative in an Ames reverse mutation assay, a chromosome aberration assay, a micronucleus assay, and an unscheduled DNA synthesis (UDS) assay. Etoxazole produced a positive result in the mouse lymphoma gene mutation assay but only in the presence of metabolic activation. Etoxazole does not present a genetic hazard.

3. *Reproductive and developmental toxicity.*—i. *Rat developmental study.* Etoxazole did not produce developmental toxicity in rats. Etoxazole technical was administered by oral gavage to pregnant rats at dosage levels of 40, 200, and 1,000 mg/kg/day on days 6 through 15 of gestation. There were no mortalities or treatment-related adverse effects in any dose group. Food consumption was slightly decreased in dams during the dosing period for the 1,000 mg/kg/day group. On cesarean

section evaluation there was no differences in number of corpora lutea, number of live and dead fetuses, percent resorption, placental weight, fetal weight or sex ratio in the dams and no treatment-related external, visceral or skeletal malformations noted in any of the fetuses. It was concluded that the maternal no observed adverse effect level (NOAEL) was 200 mg/kg/day, based on decreased food consumption at 1,000 mg/kg/day. The developmental NOAEL was 1,000 mg/kg/day, the highest dose tested.

ii. *Rabbit developmental study.* Etoxazole did not produce developmental toxicity in rabbits. Etoxazole technical was administered by oral gavage to pregnant rabbits at dosage levels of 40, 200, and 1,000 mg/kg/day on days 6 through 18 of gestation. No treatment-related adverse effects were found on maternal rabbits in the 40 and 200 mg/kg/day groups. One high dose rabbit died but it is unclear whether this death was attributed to treatment. Decreased body weight, body weight gain, food consumption and enlarged liver were noted at 1,000 mg/kg/day. Cesarean section findings showed that there was no differences in number of *corpora lutea*, number of live and dead fetuses, percent resorptions, placental weight, fetal weight and sex ratio in the dams and showed no treatment-related malformations (external, visceral, skeletal) in any of the fetuses. A statistically significant increased incidence of 27 presacral vertebrae with 13th ribs was observed in fetuses at 1,000 mg/kg/day compared with controls. This finding was within historical control range for fetal incidence but above the historical control range for litter incidence. No dose response was evident and the variation is considered to be equivocally treatment related. The NOAEL for maternal and developmental toxicity was 200 mg/kg/day based on decreased body weight and body weight gain, decreased food consumption, and liver enlargement at 1,000 mg/kg/day. The NOAEL for developmental toxicity was 200 mg/kg/day based on statistically significant increased incidence of 27 presacral vertebrae with 13th ribs in fetuses at 1,000 mg/kg/day.

iii. *Rat reproduction study.* Etoxazole showed no effects on reproduction in a two-generation rat study. Etoxazole technical was fed to two generations of male and female Sprague Dawley rats at dietary concentrations of 80, 400, and 2,000 ppm. No treatment-related adverse effects were observed in the 80 and 400 ppm groups for any parameter. In the 2,000 ppm group, relative liver