

the concentration in the corresponding plasma, with only the liver and fat having significant levels of radioactivity. After multiple doses, peak concentrations of radioactivity in tissues occurred 2 hours after dosing and then declined. The distribution of radioactivity showed a similar profile to those found after single oral doses but were significantly higher, indicating some accumulation. Etoxazole was extensively metabolized by rats. The main metabolic reactions in rats were postulated to be hydroxylation of the 4,5-hydrooxazole ring followed by cleavage of the molecule and hydroxylation of the t-butyl side chain.

7. *Metabolite toxicology.* In an oral toxicity limit test in rats, the oral LD<sub>50</sub> of metabolite R-3 was estimated to be greater than 5 g/kg for both male and female rats. No treatment related body weight changes and no treatment related macroscopic abnormalities were observed in this study. In another test, the oral toxicity of metabolite R-7 (as the HCl salt) was assessed. The oral LD<sub>50</sub> of this metabolite was also estimated to be greater than 5 g/kg for both male and female rats. No treatment related macroscopic abnormalities were observed in this test although some clinical signs were observed within six minutes of dosing. Mutagenicity screens were performed with metabolite R-3 and metabolite R-7 (as the HCl salt). Neither metabolite was mutagenic when tested with multiple strains of two bacterial cultures (*Salmonella typhimurium* and *Escherichia coli*).

8. *Endocrine disruption.* No special studies to investigate the potential for estrogenic or other endocrine effects of etoxazole have been performed. However, as summarized above, a large and detailed toxicology data base exists for the compound including studies in all required categories. These studies include acute, sub-chronic, chronic, developmental, and reproductive toxicology studies including detailed histology and histopathology of numerous tissues, including endocrine organs, following repeated or long term exposures. These studies are considered capable of revealing endocrine effects. The results of all of these studies show no evidence of any endocrine-mediated effects and no pathology of the endocrine organs. Consequently, it is concluded that etoxazole does not possess estrogenic or endocrine disrupting properties.

#### C. Aggregate Exposure

1. *Dietary exposure.* A full battery of toxicology testing including studies of acute, chronic, oncogenicity, developmental, mutagenicity, and

reproductive effects is available for etoxazole. EPA has not had the opportunity to review all of the toxicity studies on etoxazole and has not established toxic endpoints. Thus, in these risk assessments Valent proposes as the chronic oral toxic endpoint the NOAEL for males from the rat chronic/oncogenicity feeding study, 4 mg/kg/day. To assess the chronic risk to the U.S. population from exposure to etoxazole, the daily chronic exposures were compared against an estimated chronic population adjusted dose (cPAD) of 0.04 mg/kg bwt/day. This endpoint is derived from the NOAEL from the 2-year chronic rat study by applying an uncertainty factor of 100 to account for intraspecies and interspecies variations. There is no evidence that any additional safety factors are needed to further protect vulnerable subpopulations. The proposed acute oral toxic endpoint is the NOAEL from the rabbit oral developmental toxicity study, 200 mg/kg/day. To assess the acute risk to the U.S. population from exposure to etoxazole, acute exposures were compared against an estimated acute population adjusted dose (aPAD) of 2 mg/kg bwt/day. This endpoint is derived from the NOAEL from the rabbit oral developmental toxicity study by applying an uncertainty factor of 100 to account for intraspecies and interspecies variations. 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 short-term or chronic exposure to etoxazole.

i. *Food.* Dietary exposure was estimated using DEEM™, proposed tolerances, and assuming 100% crop treated. Results of the acute analysis demonstrate that estimated exposure is 0.5% or less of the estimated aPAD (at the 95<sup>th</sup> percentile) for all population groups examined. Acute dietary exposure for the overall U.S. population was estimated to be 0.002572 mg/kg bwt/day at the 95<sup>th</sup> percentile of exposure (0.13% of the aPAD). Chronic dietary exposure was estimated for the overall U.S. population and 25 population sub groups. Daily exposure for the overall U.S. population was estimated to be 0.000574 mg/kg bwt/day, representing 1.4% of the estimated cPAD. Daily exposure for the most highly exposed population subgroup, children 1–6 years of age, was estimated to be 0.002293 mg/kg bwt/day, or 5.7% of the estimated cPAD.

ii. *Drinking water.* Since etoxazole is applied outdoors to growing agricultural

crops, the potential exists for the parent or its metabolites to reach ground or surface water that may be used for drinking water. But, because of the physical properties of etoxazole, it is unlikely that etoxazole or its metabolites can leach to potable groundwater.

Although, relatively stable to hydrolysis, etoxazole undergoes fairly rapid photolysis, degrades fairly readily in soil and is immobile in all soil types examined. To quantify potential exposure from drinking water, FIRST and SCI-GROW models were used to estimate surface and groundwater residues. Estimated surface water residues were much higher than estimated groundwater residues and therefore the surface residues were used as the drinking water environmental concentration (DWEc). The peak (acute) concentration predicted in the simulated pond water was estimated to be 2.47 ppb and the annual average (chronic) concentration predicted in the simulated pond water was estimated to be 1.93 ppb. To assess the contribution to the dietary risk from exposure to drinking water containing residues of etoxazole, these DWEc's are compared to drinking water levels of comparison (DWLOC's), the maximum drinking water concentration allowed before combined water, dietary, and other exposures will exceed the population adjusted doses. If the DWLOC is greater than the DWEc, then overall exposure will not exceed the population adjusted doses and combined exposure from water and food is considered to be acceptable. Acute DWLOC's for etoxazole range from 19,900 to 69,910 ppb and chronic DWLOC's range from 377 to 1380 ppb for all U.S. population subgroups examined. Since these DWLOC's exceed the modeled acute and chronic DWEc surface water residues by a wide margin, Valent concludes that exposure to potential residues in drinking water is negligible and that aggregate (food and water) exposure to etoxazole residues will be acceptable.

2. *Non-dietary exposure.* Etoxazole is proposed only for agricultural uses and no homeowner or turf uses. Thus, no non-dietary risk assessment is needed.

#### D. Cumulative Effects

Section 408(b)(2)(D)(v) requires that the Agency must consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Available information in this context include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of