

in urine and feces. At sacrifice (48 hours post dosing), the radioactivity remaining in the body was below 1 percent in the low dose groups and approximately 1 percent and 2 percent in the male and female rats, respectively, from the high dose group. Concentrations found in tissues and organs were relatively low: i.e., they do not exceed 0.04 µg/g. The highest concentrations were found in liver, thymus and adrenals. Slightly smaller concentrations were observed in the thyroid, spleen, fat, ovaries and uterus. The main metabolite in all dose groups is Spiroxamine oxidized to the carboxylic acid in the t-butyl-moiety. The identification rate was approximately 77 percent of the recovered radioactivity in all dose groups.

**7. Metabolite toxicology.** Toxicological studies have been conducted on KWG 4,168 N-oxide, a plant and animal metabolite of KWG 4168. In an acute oral toxicity study on KWG 4,168 N-oxide using female rats, the LD<sub>50</sub> was 707 mg/kg. In a subacute toxicity study, rats were administered KWG 4168 N-oxide at dietary concentrations of 0, 30, 150 and 1,000 ppm. The highest concentration resulted in treatment-related effects. The main targets were the epithelia of the digestive tract and the urinary bladder. A mild liver enzyme induction was observed without any correlating gross- or micropathological findings. In a subchronic study, rats were administered KWG 4168 N-oxide at dietary concentrations of 0, 25, 125 and 625 ppm, and KWG 4168 at 625 ppm. Toxic effects were observed at 625 ppm for both test substances. Similar effects included delayed body weight development, changes in clinical chemistries and micropathological findings of the esophagus and stomach. The effects were less pronounced for KWG 4168 N-oxide when compared to KWG 4168 (parent). Effects noted only in animals treated with KWG 4168 included changes in hematological parameters and micropathological findings of the urinary bladder (females). The mutagenic potential of KWG 4168 N-oxide was studied *in vitro* in bacteria and mammalian cells. It did not cause mutations *in vitro* in the Ames assay, the V-79-HPRT gene mutation assay, or produce clastogenicity in the chromosome aberration assay with or without metabolic activation.

**8. Endocrine disruption.** The toxicology database for Spiroxamine is current and complete. Studies in this database include evaluation of the potential effects on reproduction and development, and an evaluation of the pathology of the endocrine organs

following short- or long-term exposure. These studies revealed no primary endocrine effects due to Spiroxamine endocrine effects due to spiroxamine.

#### C. Aggregate Exposure

**1. Dietary exposure.** An aggregate risk assessment was conducted to assess the potential acute and chronic dietary exposure from applications of spiroxamine on grape, hop, and banana (imported). Novigen Sciences, Inc.'s Dietary Exposure Evaluation Model (DEEM) was used to estimate the chronic and acute dietary exposure.

For the acute dietary analysis, the proposed acute reference dose (aRfD) of 0.1 mg/kg/day was used. This aRfD is based on NOELs of 10 mg/kg from an acute oral toxicity and an acute neurotoxicity screening study and applying a 100-fold uncertainty factor.

For the chronic dietary analysis, the proposed chronic reference dose (cRfD) of 0.02 mg/kg/day was used. This cRfD is based on a parental toxicity NOEL of 2.13 mg/kg/day from the two-generation reproduction study and the application of a 100-fold uncertainty factor.

Results from the acute and chronic dietary exposure analyses described below demonstrate a reasonable certainty that no harm to the overall U.S. population or any population subgroup will result from the use of spiroxamine on grape, hop, and banana.

**i. Food.** An acute dietary (food) risk assessment was conducted using the highest residue values and 100% crop treated. The estimated percent of the aRfD for the overall U.S. population (all seasons) at the 95 percentile are 8.4%. The most highly exposed population subgroup, non-nursing infants, had an exposure equal to 33.3% of the aRfD at the 95 percentile. These exposure estimates are within EPA's criteria of acceptability.

A chronic dietary analysis was conducted using average residue values and 100% crop treated. The estimated percent of the cRfD for the overall U.S. population (all seasons) was 8.8%. For the most highly exposed population subgroup, children (1–6 years), the exposure equaled 30.6% of the cRfD. These exposure estimates are within EPA's criteria of acceptability.

**ii. Drinking water.** No monitoring data are available for residues of spiroxamine in ground water, and EPA has established no health advisory levels or maximum contaminant levels for residues of spiroxamine in drinking water.

Studies show low to no soil mobility for spiroxamine and its primary metabolites. In addition, field studies show that spiroxamine and its

degradates do not leach below the 6-inch depth level, and show very low potential to leach into ground water. Therefore, it can be concluded with reasonable certainty that no harm will result from acute or chronic aggregate exposure to spiroxamine residues in drinking water.

**2. Non-dietary exposure.** Spiroxamine is not registered nor are registrations pending for uses that would result in non-dietary exposure.

#### D. Cumulative Effects

Spiroxamine belongs to a new class of chemistry known as spiroketalamines. Therefore, for this tolerance petition, it is assumed that spiroxamine does not have a common mechanism of toxicity with other substances and only the potential risks of spiroxamine in its aggregate exposure are considered.

#### E. Safety Determination

**1. U.S. population.** Based on the above aggregate food exposure estimates for the overall U.S. population 8.4% of the aRfD and (8.8% of the cRfD), the low potential for spiroxamine and its degradates to leach into ground water, and the completeness of the toxicity data base, there is reasonable certainty that no harm to the U.S. population will result from aggregate exposure to spiroxamine.

**2. Infants and children.** In assessing the potential for additional sensitivity of infants and children to residues of spiroxamine, data from developmental toxicity studies in mice, rats, rabbits and a 2-generation reproduction study in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from maternal pesticide exposure during gestation. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity.

Based on the above aggregate food exposure estimates for the most highly exposed population subgroup, non-nursing infants (33.3% of the aRfD), and children 1–6 years (30.6% of the cRfD), the low potential for spiroxamine and its degradates to leach into ground water, and on the completeness of the toxicity data base, there is reasonable certainty that no harm to infants and children will result from aggregate exposure to spiroxamine.