

minimal carryover of residues ( $> 0.003$   $\mu\text{g/g}$ ) to succeeding crops.

2. *Analytical method.* A practical analytical method for detecting and measuring levels of quinoxifen in or on cherries, hops, grapes and its products allows monitoring of residues at or above the tolerances set for these crops. The analytical method uses capillary gas chromatography and mass selective detection (GC-MSD) with limits of quantitation (LOQ) of 0.01 parts per million (ppm) for cherries, grapes, grape juice, raisins and 0.05 ppm for hops. An independent laboratory has validated the method using hops, which is typically the more difficult matrix to analyze.

3. *Magnitude of residues.* The magnitude of residues for grape, hops, and cherry is adequately understood.

#### B. Toxicological Profile

1. *Acute toxicity.* Quinoxifen technical has low acute toxicity. The acute oral lethal dose ( $\text{LD}_{50}$ ) in rats was  $>5,000$  milligrams/kilogram (mg/kg) whereas, the dermal ( $\text{LD}_{50}$ ) in rabbits was  $>2,000$  mg/kg. The acute inhalation lethal concentration ( $\text{LC}_{50}$ ) in rats was greater than the highest attainable aerosol concentration (3.38 mg/L). Quinoxifen produced no dermal irritation and only mild eye irritation in rabbits. A guinea pig dermal sensitization study conducted by the modified Buehler method found no sensitization, whereas a study conducted by the Magnusson and Kligman maximization test showed a positive sensitization reaction. Formulations of quinoxifen are water based suspension concentrates that have similar low acute toxicity. These suspension concentrates are classified as non-sensitizer, based on the results from testing in guinea pigs.

2. *Genotoxicity.* Quinoxifen was negative for genotoxicity when tested in *in vitro* and *in vivo* systems.

3. *Reproductive and developmental toxicity.* Quinoxifen did not have any effect on reproductive parameters at dose levels that induced treatment-related effects in parental rats. Transient decreases in pup body weights were seen prior to weaning, but dietary concentrations were targeted for adults and consumption of treated diets by the pups resulted in dose levels to the pups approximately 3-fold higher than in adults. Post-weaning weights were comparable to controls. A teratogenic potential for quinoxifen was not demonstrated in either rats or rabbits at dose levels that induced maternal toxicity.

4. *Subchronic and chronic toxicity.* Quinoxifen caused increased liver

weights and microscopic hepatocellular hypertrophy when given at sufficiently high dose levels in rats and mice for 13 weeks; no effects were observed in the subchronic dog study at the highest dose tested. Very high dietary levels were associated with slight hepatocellular necrosis. Similar increases in liver weights were seen in chronic studies. In addition, increased kidney weights, and an increase in the incidence of chronic progressive glomerulonephropathy, were seen after 24 months in female rats given high dose levels of quinoxifen. Chronic toxicity seen in dogs included liver effects as noted above, along with regenerative anemia at high dose levels.

Using the Guidelines for Carcinogen Risk Assessment published September 24, 1986 (51 FR 33992), it is proposed that quinoxifen be classified as Group E for carcinogenicity (no evidence of carcinogenicity) based on the results of studies in two species. Dow AgroSciences believes there was no evidence of carcinogenicity in an 18-month mouse feeding study and a 24-month rat feeding study at any dosage tested.

5. *Animal metabolism.* Quinoxifen is rapidly absorbed, extensively metabolized and rapidly eliminated in the urine and feces. Studies conducted with  $^{14}\text{C}$ -quinoxifen, labeled in either the phenyl ring or the quinoline ring, indicated extensive cleavage of the diaryl ether linkage. There were no substantive differences in the metabolism and disposition of quinoxifen between males and females, or between single or repeated exposure. Parent quinoxifen was not found in the urine; although, it was identified in the feces. The major metabolites found in urine and/or feces included: (1) Acid-labile conjugates of the phenyl ring moiety (4-FP) and quinoline ring moiety (DCHQ); (2) lesser quantities of free 4-FP and DCHQ; and (3) isomers of fluorophenyl-ring hydroxy-quinoxifen, both free and glucuronide and/or sulfate conjugates. Trace quantity of the 3-OH metabolite was also identified in the urine and feces of rats.

6. *Metabolite toxicology.* The nature of residue studies of quinoxifen in plants indicated that the majority of applied radiolabeled material remained as the parent compound. Analyses from nature of residues studies in a number of crops revealed low residues of metabolites ( $<10\%$  TRR) identified as: (1) A quinoline-ring hydroxylated metabolite, most likely 3-OH; (2) a cyclized deschloro photoproduct (CFBPQ); (3) 4-FP; and (4) a metabolite in which the fluorine was replaced by a hydroxyl group. Of these metabolites, 4-FP

(formed by ether bridge cleavage), and DCHQ (corresponding to the other half of the molecule), as well as trace quantities of 3-OH, have been identified in rat urine and/or feces. These data suggest that most metabolites formed in plants are similarly formed in mammals and are of little toxicologic concern, based on the existing data for quinoxifen.

7. *Neurotoxicity.* Quinoxifen has been shown to have no neurotoxicologic potential based on acute and subchronic studies.

8. *Endocrine disruption.* There is no evidence from any studies to suggest that quinoxifen has an effect on any endocrine system.

#### C. Aggregate Exposure

1. *Dietary exposure.* Potential dietary exposure and risk assessment was estimated using DEEM (Dietary Exposure Evaluation Model, Version 7.76) with USDA food consumption data continuing survey of food intake by individuals (CSFII) Survey 1994–1998.

i. *Food*—a. Acute No acute dietary risk for quinoxifen was evaluated since no appropriate toxicity endpoint attributable to a single dose could be identified. Therefore, an acute reference dose was not established.

b. *Chronic.* The dietary exposure assessment was performed using a conservative approach (Tier I) and the estimated theoretical maximum residue contribution (TMRC) was based on the proposed tolerances for quinoxifen on or in grapes, hops, and cherries with the assumption that 100% of these crops were treated with quinoxifen.

ii. *Drinking water.* Based on the rapid degradation of quinoxifen in water and its high tendency to sorb to soils, no surface water or ground water contamination is expected. This agrees with EPA Tier 1 modeling using SciGrow and GENEEC which estimated concentration of quinoxifen at 0.006  $\mu\text{g/L}$  in ground water and 241  $\mu\text{g/L}$  in surface water, respectively.

2. *Non-dietary exposure.* Quinoxifen is not currently registered for non-crop uses. Therefore, aggregate exposure to quinoxifen will not include non-dietary, non-occupational exposures.

#### D. Cumulative Effects

The potential for cumulative effects of quinoxifen and other substances that have a common mechanism of toxicity is also considered. Quinoxifen is a member of the quinoline class of fungicides. No information is available to determine whether quinoxifen has a common mechanism of toxicity with other pesticides. Therefore, it is appropriate to consider only the