

dogs based on decreases in red blood cells (RBC), hematocrit (HCT), and hemoglobin (HGB), increases in heinz bodies, methemoglobin, mean corpuscular volume (MCV), mean corpuscular hematocrit (MCH), reticulocytes, platelets, plasma total bilirubin, spleen weight, and spleen/body weight ratio. Hematopoiesis and sinusoidal engorgement occurred in the spleen, and hyperplasia occurred in the marrow of the femur and sternum. The liver showed an increased pigment in the Kupffer cells. The NOAEL for systemic toxicity in both sexes is 50 ppm (1.9 mg/kg/day).

5. *Chronic toxicity.* An 18-month mouse carcinogenicity study with no carcinogenicity observed at dosage levels up to and including 1,000 ppm.

A 2-year rat carcinogenicity with no carcinogenicity observed at dosage levels up to and including 2,000 ppm, 97 mg/kg/day and 125 mg/kg/day for males and females, respectively.

6. *Animal metabolism.* The pharmacokinetics and metabolism of tebufenozide were studied in female Sprague-Dawley rats (3–6/sex/group) receiving a single oral dose of 3 or 250 mg/kg of RH-5992 ¹⁴C labeled in one of three positions (A-ring, B-ring or butyl carbon). The extent of absorption was not established. The majority of the radio labeled material was eliminated or excreted in the feces within 48 hours; small amounts (1% to 7% of the administered dose) were excreted in the urine and only traces were excreted in expired air or remained in the tissues. There was no tendency for bioaccumulation. Absorption and excretion were rapid. A total of 11 metabolites, in addition to the parent compound, were identified in the feces; the parent compound accounted for 96% to 99% of the administered radioactivity in the high dose group and 35% to 43% in the low dose group. No parent compound was found in the urine; urinary metabolites were not characterized. The absorption and metabolism of tebufenozide were studied in a group of male and female bile-duct cannulated rats. Over a 72 hour period, biliary excretion accounted for 30% (males) to 34% (females) of the administered dose while urinary excretion accounted for about 5% of the administered dose and the carcass accounted for <0.5% of the administered dose for both males and females. Thus systemic absorption (percent of dose recovered in the bile, urine and carcass) was 35% male to 39% female. The majority of the radioactivity in the bile (20% male to 24% female of the administered dose)

was excreted within the first 6 hours post-dosing indicating rapid absorption. Furthermore, urinary excretion of the metabolites was essentially complete within 24 hours post-dosing. A large amount (67% female to 70% male) of the administered dose was unabsorbed and excreted in the feces by 72 hours. Total recovery of radioactivity was 105% of the administered dose.

7. *Metabolite toxicology.* A total of 13 metabolites were identified in the bile; the parent compound was not identified, i.e. unabsorbed compound, nor were the primary oxidation products seen in the feces in the pharmacokinetics study. The proposed metabolic pathway proceeded primarily by oxidation of the benzylic carbons to alcohols, aldehydes or acids. Bile contained most of the other highly oxidized products found in the feces. The most significant individual bile metabolites accounted for 5% to 18% of the total radioactivity (F and/or M). Bile also contained the previously undetected (in the pharmacokinetics study) “A” Ring ketone and the “B” Ring diol. The other major components were characterized as high molecular weight conjugates. No individual bile metabolite accounted for 5% of the total administered dose. Total bile radioactivity accounted for about 17% of the total administered dose. No major qualitative differences in biliary metabolites were observed between sexes. The metabolic profile in the bile was similar to the metabolic profile in the feces and urine.

8. *Endocrine disruption.* The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity.

C. Aggregate Exposure

1. *Dietary exposure—i. Food.* Tolerances have been established (40 CFR 180.482) for the residues of tebufenozide, in or on a variety of raw agricultural commodities. The current petition requests establishment of tolerances in or on grape at 3.0 ppm and vegetable, tuberous and corn, except potato, subgroup at 0.01 ppm. Risk assessments were conducted by Dow AgroSciences to assess dietary exposures and risks from tebufenozide, benzoic acid, 3,5-dimethyl-1-(1,1-dimethylethyl)-2-(4-ethylbenzoyl) hydrazide as follows:

a. *Acute exposure.* Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1-day

or single exposure. Neither neurotoxicity nor systemic toxicity was observed in rats given a single oral administration of tebufenozide at 0, 500, 1,000 or 2,000 mg/kg. No maternal or developmental toxicity was observed following oral administration of tebufenozide at 1,000 mg/kg/day (limit-dose) during gestation to pregnant rabbits. This risk is considered to be negligible.

b. *Chronic exposure.* The reference dose (RfD) used for the chronic dietary analysis is 0.018 mg/kg/day. In conducting the dietary exposure evaluation model (DEEM) analysis for chronic exposure to and risk from tebufenozide residues in food, Dow AgroSciences used tolerance level residues for all crops and other commodities with established or pending tebufenozide tolerances; and percent crop-treated (PCT) information for some of these crops.

ii. *Drinking water—*a. *Acute exposure.* Because no acute dietary endpoint was determined, Dow AgroSciences concludes that there is a reasonable certainty of no harm from acute exposure from drinking water.

b. *Chronic exposure.* The Agency calculated the Tier I Estimated Environmental Concentrations (EECs) for tebufenozide using generic expected environmental concentration (GENEEC) (surface water) and screening concentration in ground water (SCI-GROW) (ground water) models for use in the human health risk assessment. For chronic exposure, the worst case EECs for surface water and ground water were 16.5 parts per billion (ppb) and 1.04 ppb, respectively. These values represent upper-bound estimates of the concentrations that might be found in surface and ground water.

2. *Non-dietary exposure.* There is a potential for occupational exposure to tebufenozide during mixing, loading and application activities. However the Agency did not identify dermal or inhalation endpoints for tebufenozide and determined that risks from these routes of exposure are negligible.

D. Cumulative Effects

Cumulative exposure to substances with a common mechanism of toxicity, Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.” EPA does not have, at this time, available data to determine whether tebufenozide has a common mechanism