

liver in both sexes; slight hematologic effects and decreased absolute and relative kidney weights in males; and ovarian atrophy, decreased ovary and spleen weights and increased liver weights in females.

In a 90-day oral toxicity study in dogs (OPPTS Harmonized Guideline 870.3150), the NOAEL is 8.23 (males) and 9.27 (females) mg/kg/day. The LOAEL is 32.0 (male) and 33.9 (female) mg/kg/day based on slightly prolonged prothrombin times and decreased plasma albumin and A/G ration (both sexes); decreased calcium levels and ovary weights and delayed maturation in the ovaries (female); decreased cholesterol and phospholipid levels, testis weights, spermatogenesis, and spermatid giant cells in testes (male).

In a 28-day dermal study in rats (OPPTS Harmonized Guideline 870.3200), the NOAEL was 250 (male) and 60 (female) mg/kg/day. The LOAEL was 1,000 (male) and 250 (female) mg/kg/day based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity and inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females and hyaline change in renal tubules and a very slight reduction in body weight in males. At higher dose levels in females, chronic tubular lesions in the kidneys and inflammatory cell infiltration in the adrenal cortex were observed.

In a subchronic neurotoxicity screening study in rats (OPPTS Harmonized Guideline 870.6200) the NOAEL was 95.4 (male) and 216.4 (female) mg/kg/day, both at highest dose tested. The LOAEL was not determined. No treatment related observations at any dose level. LOAEL was not achieved. May not have been tested at sufficiently high dose levels; however, a new study is not required because the weight of the evidence from other toxicity studies indicates no evidence of concern.

5. Chronic toxicity. In a chronic toxicity study in dogs (OPPTS Harmonized Guideline 870.4100) the NOAEL was 4.05 (male) and 4.49 (female) mg/kg/day. The LOAEL was 21.0 (male) and 24.6 (female) mg/kg/day based on increase of creatinine in both sexes, transient decrease in food consumption in females, and occasional increase in urea levels, decrease in ALT, and atrophy of seminiferous tubules in males.

In a mouse carcinogenicity study (OPPTS Harmonized Guideline 870.4200), the NOAEL was 2.63 (male) and 3.68 (female) mg/kg/day. The LOAEL was 63.8 (male) and 87.6 (female) mg/kg/day based on hepatocyte hypertrophy, single cell necrosis, inflammatory cell infiltration, pigment

deposition, foci of cellular alteration, hyperplasia of kupffer cells and increased mitotic activity, also an increase in the incidence of hepatocellular adenoma (both sexes). At higher doses, there was an increase in the incidence of hepatocellular adenocarcinoma (both sexes) and the number of animals with multiple tumors, evidence of carcinogenicity.

In a combined chronic carcinogenicity study in rats (OPPTS Harmonized Guideline 870.4300) the NOAEL was 21.0 (male) and 50.3 (female) mg/kg/day. The LOAEL was 63.0 (male) and 255 (female) mg/kg/day based on increased incidence of lymphocytic infiltration of the renal pelvis and chronic nephropathy in males and decreased body weight gain, slight increase in the severity of hemosiderosis of the spleen, foci of cellular alteration in liver and chronic tubular lesions in kidney in females. No evidence of carcinogenicity.

In a hepatic cell proliferation study in mice, the NOAEL was 16 (male) and 20 (female) mg/kg/day. The LOAEL was 72 (male) and 87 (female) mg/kg/day based on proliferative activity of hepatocytes. At higher dose levels, increases in absolute and relative liver weights, speckled liver, hepatocellular glycogenesis/fatty change, hepatocellular necrosis, apoptosis and pigmentation were observed.

In a 28-day feeding study to assess replicative DNA synthesis in the male rat, the NOAEL was 711 mg/kg/day. The LOAEL was not established. Immunohistochemical staining of liver sections from control and high dose animals for proliferating cell nuclear antigen gave no indication for a treatment related increase in the fraction of DNA synthesizing hepatocytes in S-phase. CGA-293343 did not stimulate hepatocyte cell proliferation in male rats.

In a special study to assess liver biochemistry in the mouse, the NOAEL was 17 (male) and 92 (female) mg/kg/day. The LOAEL was 74 (male), 92 (female) mg/kg/day based on marginal to slight increases in absolute and relative liver weights, a slight increase in the microsomal protein content of the livers, moderate increases in the cytochrome P450 content, slight to moderate increases in the activity of several microsomal enzymes, slight to moderate induction of cytosolic glutathione S-transferase activity. Treatment did not affect peroxisomal fatty acid β -oxidation.

6. Animal metabolism. The metabolism of thiamethoxam in rats and livestock animals is adequately understood. The residues of concern

have been determined to be parent thiamethoxam and its metabolite N-(2-chloro-thiazol-5-ylmethyl)-N'-methyl-N-nitro-guanidine.

7. Metabolite toxicology. For risk assessment purposes, residues of the metabolite corrected for molecular weight are considered to be toxicologically equivalent to parent thiamethoxam.

C. Aggregate Exposure

1. Dietary exposure. Permanent tolerances have been established (40 CFR 180.565) for the combined residues of the insecticide thiamethoxam, 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine and its metabolite N-(2-chloro-thiazol-5-ylmethyl)-N'-methyl-N-nitro-guanidine, in or on a variety of raw agricultural commodities levels ranging from 0.02 parts per million (ppm) to 1.5 ppm (including barley, canola, corn, cotton, sorghum, wheat, cucurbit vegetables, fruiting vegetables, pome fruits, tuberous and corm vegetables and livestock commodities).

Pending tolerances include coffee (imported), grapes, raisins, grape juice, pecans, sunflower seed, stone fruits, succulent beans, peppermint and spearmint tops, head and stem brassica, leafy brassica greens and leafy vegetables.

Tier III chronic and Tier I acute dietary exposure evaluations were made using the Dietary Exposure Evaluation Model (DEEM™), version 7.76 from Exponent. All processing factors were taken from the EPA assessment of August 28, 2000 (DP Barcode D268606, PC Code 060109). These assessment results include all current tolerances and the proposed tolerances on stone fruit, mint, succulent beans, sunflower seed, pecans, leafy vegetables, leafy brassica vegetables, brassica head and stem vegetables and imported coffee.

For the Tier I acute assessment, the proposed tolerance residues for these commodities (stone fruit, 0.5 ppm; mint, 4.0 ppm; succulent beans, 0.02 ppm; sunflower seed, 0.02 ppm; pecans, 0.02 ppm; leafy vegetables, 2.0 ppm; leafy brassica vegetables, 2.0 ppm; brassica head and stem vegetables, 1.0 ppm; and imported coffee, 0.05 ppm) were used along with the published tolerances for all other commodities. One hundred percent of crop treated was assumed for all commodities in the acute assessment.

In the chronic assessments, residue values for secondary animal commodities, pome fruits, ginger, turmeric, peppers, potatoes, wheat and barley were taken from the EPA assessment of August 28, 2000 which