

In the multi-generation rat reproduction study, the NOAEL was 300 ppm for both parental animals (13.5–32.8 and 16.3–67.0 mg/kg/day, respectively, for males and females) and their offspring. The effects at the highest dose of 1,800 ppm included the following: increased kidney weights and gross and histopathological alterations in the kidney. Findings noted in the top dose females included delayed vaginal opening and increased liver, kidney and spleen weights in the F1 generation and reduced ovary and adrenal weights in the parental generation and decreased uterine weights in the F1 female weanlings. There was an increase in the FSH and LH levels in F1 females tested for these endpoints. These findings did not affect the reproductive performance or survival of offspring in the study.

4. *Subchronic toxicity.* The NOAEL for flonicamid technical in the rat 28-day dermal toxicity study was 1,000 mg/kg/day, which was the highest dose tested.

In a 90-day rat feeding study the NOAEL was established at 200 ppm (12.11 mg/kg/day) for males and 1,000 ppm (72.3 mg/kg/day) for females. The NOAELs were based on effects on hematology, triglycerides, and pathology in the liver and kidney.

In a 13-week mouse study, the NOAEL was 100 ppm (15.25 mg/kg/day in males and 20.1 mg/kg/day in females). The LOAEL is 1,000 ppm (153.9 mg/kg/day in males and 191.5 mg/kg/day in females) based on hematology effects and changes in glucose, creatinine, bilirubin, sodium, chloride and potassium levels, increased liver and spleen weights and histopathology findings in the bone marrow, spleen and kidney.

In a subchronic toxicity study in dogs with capsule administration, the NOAEL was 20 mg/kg/day based on findings of severe toxicity at a dose exceeding the maximum tolerated dose; symptoms included collapse, prostration and convulsions leading to early sacrifice at the LOAEL of 50 mg/kg/day.

In a subchronic neurotoxicity study in rats, the NOAEL for dietary administration was 1,000 ppm (67 mg/kg/day in males and 81 mg/kg/day in females) for systemic toxicity based on body weight and food consumption effects. The NOAEL for neurotoxicity was 10,000 ppm (625 and 722 mg/kg/day in males and females, respectively (highest dose tested).

5. *Chronic toxicity.* In the chronic dog study with administration via using capsules, the NOAEL was 8 mg/kg/day. The LOAEL was 20 mg/kg/day based on

reduced body weights in females and effects on the circulating red blood cells.

In a rat 24-month combined chronic and oncogenicity study, flonicamid technical was not carcinogenic in rats. The NOAEL was 200 ppm (7.32 mg/kg/day) for males and 1,000 ppm (44.1 mg/kg/day) for females. The LOAEL was 1,000 ppm for males and 5,000 ppm for females based on histopathology in the kidney, hematology effects, hepatic effects including changes in biochemical parameters, increased organ weights, and histopathological changes. Atrophy of striated muscle fibers, cataract and retinal atrophy observed in the high dose females were considered to be due to acceleration of spontaneous age-related lesions.

In the 18-month mouse study, effects were observed in the lung, liver, spleen and bone marrow at 250 ppm or higher. Findings included, centrilobular hepatocellular hypertrophy, extramedullary hematopoiesis and pigment deposition in the spleen and decreased cellularity (hypocellularity) in the bone marrow. There were statistically significant increases in the incidence of alveolar/bronchiolar adenomas in both sexes of treated groups with hyperplasia/hypertrophy of epithelial cells in terminal bronchioles. There was a statistically significant increase in the incidence of alveolar/bronchiolar carcinomas in males at 750 ppm and 2,250 ppm and in females at 2,250 ppm only. These effects in the lungs of mice were not life threatening as most of effects were observed at the terminal sacrifice and there was no effect of treatment on mortality in the study. A NOAEL could not be determined from the dose levels administered. Mechanism-of-action studies have indicated that the lung effects are unique to the mouse and are not likely to translate to other species including the rat. Flonicamid technical was not carcinogenic in the rat.

6. *Animal metabolism.* Rat, goat and poultry metabolism studies were conducted using [^{14}C]-pyridyl-flonicamid. The majority of the dose was rapidly excreted. Flonicamid was a major component of rat urine 48 hours after dosing. TFNA-AM was the major metabolite found in rats (urine), goats (milk and tissues), and in laying hens (tissues and eggs). TFNG was found between 8–24% of the total radioactive residue (TRR) in the livers of rats sacrificed at intervals between 0.5–6 hours after dosing. The liver samples at these time intervals had ^{14}C -residues of 2.3%–4.6% of the dose. TFNA was not a major component in animal tissues. The metabolism of flonicamid in animals shows the main pathway of

metabolism involves hydrolysis of -CN and -CONH₂ functional groups in the molecule, identical to plant metabolism. The main metabolic reactions were hydrolysis of cyano to the amide function and ring hydroxylation. In rats, flonicamid was further metabolized by several routes, including nitrile hydrolysis, amide hydrolysis, N-oxidation, and hydroxylation of the pyridine ring, leading to multiple metabolites. The metabolism of flonicamid in animals is well understood.

7. *Metabolite toxicology.* The main metabolites of flonicamid were examined in acute oral toxicity studies in rats and bacterial reverse mutation tests. All the metabolites were less toxic than flonicamid and not mutagenic.

8. *Endocrine disruption.* No special studies investigating potential estrogenic or other endocrine effects of flonicamid have been conducted. Some suggestions of possible endocrine effects were reported at the highest dose tested (1,800 ppm) in the multi-generation reproduction study which showed increased FSH and LH levels, a delay in the time to vaginal opening in the F1 generation, and reduced ovary and adrenal weights in the parental generation. However, there were no effects on reproductive performance or survival of the offspring in the study. At levels that are expected to be found in the environment, flonicamid will not cause any endocrine-related effects.

C. Aggregate Exposure

1. *Dietary exposure.* Potential dietary exposures from food were estimated using the proposed tolerances for all crops using the Dietary Exposure Evaluation Model (DEEM) for acute and chronic exposure based on U.S. Department of Agriculture's (USDA) Continuing Surveys of Food Intake by Individuals (CSFII) conducted in 1994–1998, and percent crop treated of 100%. The following raw agricultural commodities were included: Leaf lettuce, head lettuce, celery, spinach, cotton, potatoes, fruiting vegetables, cucurbits, stone fruits, pome fruits and resulting secondary residues in meat, milk, poultry and eggs.

i. *Food.* Acute dietary exposure was compared to the acute population adjusted dose (aPAD) of 3.0 mg/kg/day based on the NOAEL of 300 mg/kg from the acute neurotoxicity study in rats and a 100-fold uncertainty factor. The U.S. population exposure is 0.26% of the aPAD and the most highly exposed subpopulation is children 1–2 with 0.56% of the aPAD (95th percentile).

Based on the available data, an appropriate cPAD is 0.073 mg/kg/day