

ingredient in Toxicity Category II, III and IV. Pyrimethanil is non-irritating to the eyes and skin and is not a skin sensitizer.

2. *Genotoxicity.* Pyrimethanil is not mutagenic or genotoxic in any assay in either the presence or absence of metabolic activation.

3. *Reproductive and developmental toxicity.* Pyrimethanil is not a developmental or reproductive toxicant.

i. *Teratology—Rat.* Thirty Sprague Dawley rats/group received doses of 0, 7, 85, 1,000 milligrams/kilogram (mg/kg) of pyrimethanil by gavage from gestation days 6–15. At the highest dose tested (HDT), reduced maternal body weight gain was observed during gestation days 6–15, along with a slight but statistically significant decrease in food consumption, hair loss, hunched posture, slight emaciation, and slightly reduced mean fetal body weight. The maternal and developmental no observed adverse effect level (NOAEL) was 85 mg/kg.

ii. *Teratology—Rabbit.* Groups of at least 18 time-mated New Zealand white rabbits received oral gavage doses of 0, 7, 45 or 300 mg/kg/day pyrimethanil over gestation days 7–19. At the HDT, there was a decrease in body weight gain, production of feces and food consumption. Three females were euthanized due to severe emaciation. The HDT, 300 mg/kg/day exceeded the maternal maximum tolerated dose (MTD). The maternal NOAEL was 45 mg/kg/day due to reduced fecal production in 1/3 of the animals. The HDT resulted in reduced mean fetal body weight, increased incidence of runts, delayed skeletal ossification and incidence of fetuses with 13 thoracic vertebrae and ribs. The maternal NOAEL was 7 mg/kg/day. The developmental NOAEL was 45 mg/kg/day.

iii. *Two-generation reproduction—Rat.* Three groups of 30 Sprague-Dawley rats per sex received dietary exposure to pyrimethanil at levels of 0, 1.7, 20.9 or 266.7 mg/kg/day. In the parental generation at the highest dose tested there was a statistically significant decrease in mean body weight gain in both sexes. Mean pup weights, observed on postnatal day (PND1) through weaning, were reduced, though were within the range of historical controls. In the F1 generation at the HDT, mean body weights and mean food consumption were reduced. Though the mean score for the combined sexes was the same as the controls, a marginally different air-righting reflex at PND11 associated with reduced body weight was seen in high dose male pups. The NOAEL for maternal and developmental

toxicity was 20.9 mg/kg/day. The reproductive NOAEL was 266.7 mg/kg/day.

4. *Subchronic toxicity—28-day dietary—i. Rat.* Five Sprague-Dawley rats/sex/group received dietary exposure to pyrimethanil for 28 days at 0, 844, 1,161, 1,500, and 2,710 mg/kg/day. All doses exceeded the maximum tolerated dose. Severe emaciation was observed at all dose levels. Body weight gains and food consumption were reduced. Liver and thyroid histopathology were observed, along with reduced hemoglobin, Maximum Concentration Volume (MCV), and Mean Corpuscular Hematocrit (MCH). Kidney, adrenal and liver weights were altered. No NOEL or NOAEL was achieved.

ii. *90-Day dietary—Rat.* Ten Sprague-Dawley rats/sex/group received pyrimethanil in the diet at dose levels of 0, 5.4–6.8, 54.5–66.7, 545–667 mg/kg/day (males and females, respectively). High dose animals had reduced body weight gain and food consumption, increased urinary protein in males, colored urine (not blood or bilirubin) and minimal hepatocellular hypertrophy. The NOAEL in males was 54.5–66.7 (males and females, respectively) due to colored urine and a low incidence of minimal centrilobular hepatocellular hypertrophy. The NOAEL was 5.4 mg/kg/day (males) – 6.8 mg/kg/day (females).

iii. *28-Day dietary—Mouse.* Five CD-1 mice/sex/group received dietary doses of 0, 167–236, 567–667, 1,960–2,357 mg/kg/day males and females respectively, for 28 days (all the mice in one additional high dose group, 30,000 ppm, died within the first week of the study). At 1,960–2,357 mg/kg/day, animals experienced body weight loss (females), decreased body weight gain during the first 2 weeks (males), a statistically significant decrease in cholesterol, statistically significant decreases in relative liver weights (females), pigmentation of thyroid follicles, urolithiasis, moderate urothelial hyperplasia in urinary bladder, and slight kidney tubular degeneration (females). The NOAEL was 167–236 mg/kg/day.

iv. *90-Day dietary—Mouse.* Twenty CD-1 mice/sex/group received pyrimethanil diet exposure at dose levels of 0, 12–18, 139–203, 1,864–2,545 mg/kg/day males-females for 90 days. At the high dose, animals had decreased body weight and increased food consumption, cholesterol and total bilirubin. High dose females had increased relative liver weights. Histopathology in the high dose animals was found in the kidneys, liver, thyroid,

and urinary bladder. High dose males had slight urinary tract tubular dilation and slight to moderate hyperplasia of bladder epithelium. The NOAEL was determined to be 12 mg/kg/day (males) 18 mg/kg/day (females). Based on mild hepatic glycogen depletion, the NOAEL was 139–203 mg/kg/day (males and females, respectively).

v. *90-Day dietary—Dog.* Four beagle dogs/sex/group received pyrimethanil by gavage for 90 days at doses of 0, 6, 80, 1,000 mg/kg/day. The high dose was lowered to 800 mg/kg/day on day 7 due to frequent and consistent vomiting. Decreased body weight, food and water consumption were observed. Males had a significant reduction in phosphate, while females experienced a slight reduction in sodium, anion gap and total protein. At 80 mg/kg/day, infrequent vomiting after dosing and decreased water consumption were observed. After 4 weeks of dosing at 80 mg/kg/day, males had significantly reduced phosphate. The NOEL was 80 mg/kg/day. The NOAEL was 6 mg/kg/day.

vi. *Dermal toxicity evaluation.* No dermal studies have been conducted for pyrimethanil.

5. *Chronic toxicity—i. Chronic toxicity—Dog.* Four beagle dogs/sex/group received pyrimethanil by gavage at levels of 0, 2, 30, or 250 mg/kg/day for 12 months. The high dose was reduced from 400 to 250 mg/kg/day on day 8 of treatment due to excessive vomiting during the first week of treatment. At the high dose, there was a decrease in mean body weight gain and mean consumption of food and water. The NOAEL for the study was 30 mg/kg/day, with the high dose of 250 mg/kg/day being the NOAEL.

ii. *Combined chronic toxicity/oncogenicity—Rat.* Seventy Sprague-Dawley rats/sex/group received pyrimethanil by diet at levels of 0, 1.3–1.8, 17–22, 221–291 mg/kg/day (males and females, respectively) for 2 years. At the HDT, body weight gain and food consumption were decreased. Absolute liver weights were increased. Histopathology revealed centrilobular hepatocyte hypertrophy, increased incidence of eosinophilic foci (males), thyroid follicular hyperplasia, hypertrophy and colloid depletion, and the presence of a brown pigment, identified as lipofuscin in thyroid follicular cell epithelium. There was a statistically significant, dose-dependent increase in the incidence of benign thyroid follicular cell adenomas. There was no increased incidence in any malignant tumor or increase in tumor multiplicity as a result of daily dietary ingestion of pyrimethanil at any dose