

applied as a dual application at rates of 2,000 and 4,000 ppm active ingredient (a.i.) in aqueous and wax line sprays, respectively. This rate is the maximum for the aqueous treatment and two times the proposed label rate for wax incorporation. Mean pyrimethanil residue levels found in/on the samples were: Whole citrus fruits 7.46 ppm, dried pulp 2.93, orange juice 0.05 ppm and citrus oil 131 ppm. No pyrimethanil-derived residue concentrated from the whole fruit into the orange juice or dried pulp. However, the pyrimethanil residues concentrated from the whole oranges into the citrus oil by a factor of 17.5. Citrus oil is not considered as a ready-to-eat food commodity and since none of the of the processed food products are likely to contain pyrimethanil residues above the proposed citrus tolerance of 6.0 ppm in the raw agricultural commodity of whole fruit utilizing dilution factors, tolerances are not necessary for citrus oil.

ii. *Pome fruit (apples, pears, Oriental pears, crabapples, loquats, mayhew, and quince)*. Ten trials were established for this study, four in Washington, four in California, and two in New York. Of the 10 trials, 4 were conducted on pears and 6 on apples. A pre-harvest formulation of pyrimethanil was applied to the apple or pear trees during a single application, at a nominal rate of 0.40 lb of a.i., 7 days prior to harvest. Mean pyrimethanil residue levels found in or on the apple fruit following both preharvest and postharvest applications ranged from 0.49 ppm for a single aqueous line spray at 1,000 ppm a.i. to 1.44 ppm for the dual treatment consisting of a drench (1,000 ppm) followed by an aqueous line spray (1,000 ppm). Individual sample residues ranged from a low of 0.11 ppm for the 1,000 ppm aqueous line spray to 2.84 ppm for the dual treatment of a 1,000 ppm drench followed by a 2,000 ppm wax application. The limit of quantitation of the analytical method was 0.05 ppm. A single trial was established in Washington as a processing study. Pyrimethanil was applied to apple trees four times prior to harvest. Applications were made at a nominal rate of 2.0 lb a.i./Acre, with 7 days between applications. This rate is approximately five times the proposed label application rate. Mean pyrimethanil residue levels found in or on the samples were: Whole apple fruit 0.17 ppm, wet pomace 0.69 ppm, and juice 0.06 ppm. No pyrimethanil-derived residue concentrated from the whole fruit into the apple juice. However, the pyrimethanil residues

concentrated from the whole apples into the wet pomace by a factor of 4.

#### B. Toxicological Profile

1. *Acute toxicity*. Pyrimethanil is of low acute toxicity placing the active ingredient in Toxicity Category II, III and IV. Pyrimethanil is non-irritating to the eyes and skin and is not a skin sensitizer.

*Acute neurotoxicity*. Groups of 10 rats/sex/group were dosed once by oral gavage at dose levels of 0, 30, 100, 1,000 milligrams/kilogram (mg/kg) of pyrimethanil bodyweight. On the day of dosing, high dose animals experienced transient behavioral effects attributable to receipt of a substantial bolus dose of test substance. No histopathological lesions accompanied these transient behavioral changes. The no observed adverse effect level (NOAEL) was 100 mg/kg due to reduced body temperature for males. The NOAEL was 30 mg/kg.

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 mg/kg of pyrimethanil by gavage from gestation days (GD) 6-15. At the highest dose tested, reduced maternal body weight gain was observed during GD6-15, 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 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 (GD) 7-19. At the highest dose tested, there was a decrease in body weight gain, production of feces and food consumption. Three females were euthanized due to severe emaciation. The highest dose, 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 high dose 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 PND1 through weaning, were reduced, though were within the range of historical controls. In the F1 generation at the highest dose tested, 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—i. 28-Day dietary 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, MCV and 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, and 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, 1960-2357 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 1960-2357 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