

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 NOAEL was 80 mg/kg/day. The NOEL was 6 mg/kg/day.

vi. *Subchronic neurotoxicity*. Groups of 12 Sprague-Dawley rats per sex were treated for 13 weeks with pyrimethanil via the diet at 0, 4, 38.7-44.3, 391.9-429.9 mg/kg/day (males and females, respectively). There were no treatment-related findings in behavioral assessments, neuropathology or brain morphometrics. The NOAEL for this study is 38.7-44.3 mg/kg/day (males and females, respectively) based upon decreased body weight and food consumption in the high dose group.

vii. *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, and 221-291 mg/kg/day (males and females, respectively) for 2 years. At the highest dose tested, 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 level. The results of special studies, discussed below, demonstrate that the benign thyroid tumors are likely a secondary result of a disruption of thyroid-pituitary homeostasis, a well-known, threshold-mediated mechanism. The NOAEL was 17 mg/kg/day (males) and 22 mg/kg/day (females).

iii. *Oncogenicity - mouse*. Fifty-one CD-1 mice/sex/group received pyrimethanil by diet at 0, 16, 160, and 1,600 ppm (corresponding to 0, 2-2.5, 20-24.9, and 210.9-253.8 mg/kg/day in males and females, respectively). There was an increase in the number of high dose male deaths caused by urogenital tract lesions. Urinary bladder histopathology on those dying during the course of the study indicates an increase in the incidence of male urinary bladder distension, cystitis, urothelial hyperplasia and inflammation of the penis. These findings are consistent with the findings of both the 28- and 90-day studies indicating that high dose administration of pyrimethanil resulted in urolith formation leading to irritation, distension and hyperplasia of the urinary bladder and urinary tract. Chronic dietary treatment with pyrimethanil produced no increased incidence of tumor-bearing mice nor of any specific tumor type suggestive of a carcinogenic effect. The NOAEL for both sexes was 20-24.9 mg/kg/day (males and females, respectively).

iv. *Special studies*. Since rodent thyroid tumors are fairly common, and since the EPA has established that five lines of evidence are required to prove the thyroid-pituitary disruption mode of

action for rodent thyroid tumors, special studies were undertaken

a. *Thyroid mechanistic study (14-Day)*. Sprague Dawley rats received 378.5 mg/kg/day of pyrimethanil for 14 days to study the effects of pyrimethanil on the thyroid and liver microsomal enzymes. An increase in the levels of UDPGT and a corresponding statistically significant increase in liver weight were observed. Thyroid hormones T4 and T3 were decreased, while TSH levels were significantly increased. All effects were shown to be reversible.

b. *Dietary thyroid function test using perchlorate discharge (7-Day)*. Sprague Dawley rats received 509 mg/kg/day pyrimethanil or 177 mg/kg/day propylthiouracil, or 109 mg/kg/day phenobarbital in order to study the function of the thyroid gland. The animals fed pyrimethanil had 43% decreased body weight gain, 21% decreased food consumption and a 150% increase in uptake of iodine-125. There was no significant discharge of radioactive iodine from the thyroid after administration of perchlorate.

The required five lines of evidence to support the threshold mode of action for thyroid pituitary disruption and rat thyroid tumors are satisfied in the pyrimethanil studies.

EPA's final rule establishing a tolerance for pyrimethanil in wine stated that "The Agency's Carcinogenicity Peer Review Committee (CPRC) chose a non-linear approach Margin of Exposure (MOE) based on a NOAEL of 17 mg/kg/day for increased incidences of thyroid tumors in rats. The MOE methodology was selected because of thyroid tumors associated with administration of pyrimethanil in the rat, which may be due to a disruption in the thyroid-pituitary status. This chemical has been classified as a Group C chemical (possible human carcinogen) and a non-linear methodology (MOE) was applied for the estimation of human cancer risk. The estimated MOE does not exceed the Agency's level of concern and therefore, EPA has a reasonable certainty that no harm will result from exposures to residues of pyrimethanil."

6. *Animal metabolism*. Pyrimethanil is rapidly metabolized and excreted from lactating dairy cows. The observed total radioactive residues in edible tissues and milk were as follows: Milk - maximum residue of 0.069 ppm; liver - 0.363 ppm; kidney 0.249 ppm and muscle 0.017 ppm. The metabolic pathway is similar to that of plants involving hydroxylation of the phenyl and pyrimidine rings as well as hydroxylation of the methyl