

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, 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-day 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.

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.

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 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 substituents. Further metabolic reactions occur including cleavage of the phenyl ring to produce substituted pyrimidines. The major metabolite was AE C614276 (46% of the kidney residues, 63% of the milk residues resulting from hydroxylation of the phenyl ring. Hydroxylation of the pyrimidinyl ring of pyrimethanil resulted in formation of minor amounts of AE C614277. Hydroxylation of the methyl groups of pyrimethanil resulted in formation of minor amounts of AE C614278. Hydroxylation of the methyl groups of AE C614276 resulted in formation of minor amounts of AE C614800.

7. *Metabolite toxicology*. The primary residue of concern in both crop and animal commodities is pyrimethanil. In the animal metabolism, since major metabolites are produced following the oral administration of pyrimethanil, toxicology data for metabolites are completely supported by data obtained for pyrimethanil.

8. *Endocrine disruption*. Chronic, life span, and multi-generational bioassays

in mammals and acute and subchronic studies on aquatic organisms and wildlife did not reveal endocrine effects. Any endocrine related effects would have been detected in this definitive array of required tests. The probability of any such effect due to agricultural uses of pyrimethanil is negligible.

C. Aggregate Exposure

1. *Dietary exposure*. Tolerances are proposed under 40 CFR part 180 for pyrimethanil in or on tree nuts, bulb vegetables, grapes, stone fruits (except cherries), pome fruit, tuberous and corm vegetables, strawberries, and tomatoes. An import tolerance for wine grapes has been approved by the EPA. A petition for registration of pyrimethanil on bananas is pending at EPA. There are no residential uses proposed for pyrimethanil. Therefore, potential human risk scenarios cover aggregate exposure from food residues and drinking water.

i. *Food*. Refined estimates of acute dietary exposure from potential pyrimethanil residues on the proposed crops are all well under 100% of the acute reference dose (aRfD) at the 99.9th percentile. The most highly exposed sub population of children (1–6) utilizes 7.9% of the RfD, while the U.S. population utilizes 3.4%. These potential dietary exposures were estimated in a Tier 3 Monte Carlo risk assessment using the DEEM™ software, Version 7.76 (Novigen Sciences, Inc.). The 1994–96, 1998 Continuing Survey of Food Intake by Individuals (CSFII) consumption data from Department of Agriculture (USDA) was used which includes the Supplemental Children's Survey (1998). Residue values included in the assessment were distributions of the field trial values incorporating percent crop treated (PCT) as zeroes for all non-blended and partially blended items. Blended items were included as the average residue and adjusted for PCT. These PCT values are the anticipated market share of pyrimethanil for the crops at market maturity (5 years). Concentration factors derived from processing studies were included where appropriate. Secondary residues for meat and milk were included in the assessment. These were calculated using theoretical dietary burdens from sensible diets for beef and dairy cattle and tissue to feed ratios from the ruminant feeding study.

Refined chronic dietary exposure estimates resulting from the proposed uses of pyrimethanil are well within acceptable limits for all population subgroups examined. The most highly exposed group of children (1–6) utilized 0.3% of the RfD with the U.S.