

considered in support of the tolerances include the following:

1. A 1-year dog feeding study using doses of 0, 10, 100, 400, and 1,600 ppm (equivalent to doses of 0, 0.34, 3.09, 14.28, and 54.22 milligrams/kilogram (mg/kg) body weight (bwt)/day in males and 0, 0.40, 3.83, 15.68, and 58.20 mg/kg/day in females). The no-observed-effect level (NOEL) is 100 ppm (3.09 mg/kg/day for males and 3.83 mg/kg/day for females) based upon hepatocellular hypertrophy, increases in liver weights, "ballooned" hepatocytes, and increases in alkaline phosphatase, SGPT, and GGT, and possible slight hematological effects. The lowest-observed-effect level (LOEL) is 400 ppm (14.28 mg/kg/day for males and 15.68 mg/kg/day for females).

2. A 2-year chronic feeding/carcinogenicity study in rats using dietary concentrations of 0, 50, 200, and 800 ppm (equivalent to doses of 0, 2.49, 9.84, and 39.21 mg/kg bwt/day in males and 0, 3.23, 12.86, and 52.34 mg/kg bwt/day in females). The NOEL for chronic effects other than carcinogenicity is 2.49 mg/kg/day, and the LOEL is 9.84 mg/kg/day based on testicular atrophy in males. No other significant effects were observed in either sex at the stated dose levels over a 2-year period. In addition, no carcinogenic effects were observed in either sex at any of the dose levels tested. Based on the toxicological findings, the maximum tolerated dose (MTD) selected for testing (based on the 90-day feeding study) was not high enough to fully characterize the compound's carcinogenic potential.

The study was repeated at dose levels of 0 and 2,500 ppm (125 mg/kg/day) in the diet, which approaches the MTD, in order to characterize the carcinogenic potential. At 2,500 ppm, the observed effects included: decreases in absolute and relative testes weights, increases in the incidences of centrilobular to midzonal hepatocellular enlargement and vacuolation in the liver of both sexes, increases in bilateral aspermatogenesis in the testes, increases in the incidence of hypospermia and cellular debris in the epididymides, and increased incidence of arteritis/periarteritis in the testes. In this study, a NOEL could not be established because there were effects at the only dose level tested. Myclobutanil was not oncogenic when tested under the conditions of the study.

3. A 2-year carcinogenicity study in mice using dietary concentrations of 0, 20, 100, and 500 ppm (equivalent to 0, 2.7, 13.7, and 70.2 mg/kg/day in males and 0, 3.2, 16.5 and 85.2 mg/kg/day in females). The NOEL for chronic effects other than carcinogenicity was 20 ppm

(2.7 mg/kg/day in males and 3.2 mg/kg/day in females). The LOEL was 100 ppm (13.7 mg/kg/day in males and 16.5 mg/kg/day in females) based on a slight increase in liver mixed-function oxidase (MFO). Microscopic changes in the liver were evident in both sexes at 500 ppm (70.2 mg/kg/day in males and 85.2 mg/kg/day in females). There were no carcinogenic effects in either sex at any dose level tested. The highest selected dose was satisfactory for evaluating carcinogenic potential in male mice, but was lower than the MTD in females.

The above study was reevaluated since the increase in the MFO at 3 months in females was not considered to be significant enough to establish an LOEL. The LOEL was raised to 500 ppm (70.2 mg/kg/day for males and 85.2 mg/kg/day for females) based on increases in MFO in both sexes, increases in SGPT values in females and in absolute and relative liver weights in both sexes at 3 months, increased incidences and severity of centrilobular hepatocytic hypertrophy, Kupffer cell pigmentation, periportal punctate vacuolation and individual hepatocellular necrosis in males, and increased incidences of focal hepatocellular alteration and multifocal hepatocellular vacuolation in both sexes. The NOEL has been raised to 100 ppm (13.7 mg/kg/day for males and 16.5 mg/kg/day for females).

An 18-month study was conducted with female mice using a dose level of 2,000 ppm, which approaches the MTD, to evaluate the carcinogenic potential in female mice. In this study, a NOEL could not be established because there were effects at the only dose level tested. These effects included: decreases in body weight and body weight gain, increases in liver weights, hepatocellular hypertrophy, hepatocellular vacuolation, necrosis of single hypertrophied hepatocytes, yellow-brown pigment in the Kupffer cells, and cytoplasmic eosinophilia and hypertrophy of the cells of the zona fasciculata area of the adrenal cortex. Myclobutanil was not oncogenic when tested under the conditions of the study.

4. A rabbit developmental toxicity study at dosages of 0, 20, 60, and 200 mg/kg/day administered by oral gavage. The LOEL for maternal toxicity was 200 mg/kg/day, and the maternal toxicity NOEL was 60 mg/kg/day based on reduced body weight and body weight gain during the dosing period, clinical signs of toxicity, and possibly abortions. The LOEL for developmental toxicity is 200 mg/kg/day and NOEL for developmental toxicity is 60 mg/kg/day based on increases in resorptions, decreases in litter size, and a decrease in the viability index.

5. A developmental toxicity study on rats treated with dosages of 0, 31.26, 93.77, 312.58, and 468.87 mg/kg/day. The maternal toxicity LOEL was 312.6 mg/kg/day, and maternal toxicity NOEL was 93.8 mg/kg/day based on clinical signs of toxicity. The developmental toxicity LOEL was 312.6 mg/kg/day, and the developmental toxicity NOEL was 93.8 mg/kg/day based on increased incidences of 14th rudimentary and 7th cervical ribs.

6. A two-generation rat reproduction study with dosage rates of 0, 50, 200, and 1,000 ppm (equivalent to 0, 2.5, 10, and 50 mg/kg/day). The parental (systemic) toxicity LOEL was 200 ppm (10 mg/kg/day) and the parental (systemic) toxicity NOEL was 50 ppm (2.5 mg/kg/day) based on hepatocellular hypertrophy and increases in liver weights. The reproductive toxicity LOEL was 1,000 ppm (50 mg/kg/day), and reproductive toxicity NOEL was 200 ppm (10 mg/kg/day) based on an increased incidence in the number of stillborns and atrophy of the testes and prostate. The developmental toxicity LOEL was 1,000 ppm (50 mg/kg/day), and the developmental toxicity NOEL was 200 ppm (10 mg/kg/day) based on a decrease in pup body weight gain during lactation.

7. A reverse mutation assay (Ames), point mutation in CHO/HGPRT cells, *in vitro* and *in vivo* (mouse) cytogenetic assays, unscheduled DNA synthesis, and a dominant-lethal study in rats, all of which were negative for mutagenic effects.

The Reference Dose (RfD) based on the 2-year rat chronic feeding study (NOEL of 2.49 mg/kg bwt/day) and using a hundredfold uncertainty factor is calculated to be 0.025 mg/kg bwt/day. The theoretical maximum residue contribution (TMRC) from previously established tolerances and tolerances established here is 0.002319 mg/kg bwt/day for the general population and utilizes 9% of the RfD. The percentages of the RfD for the most highly exposed subgroups, nonnursing infants (less than 1 year old) and children (1 to 6 years old), are 58% and 25%, respectively. The TMRC was calculated based on the assumption that myclobutanil occurs at the maximum legal limit in all of the dietary commodities for which tolerances are proposed. Even with this probable large overestimate of exposure/risk, the TMRC is well below the RfD for the population as a whole and for each of the 22 subgroups considered. Thus, the dietary risk from exposure to myclobutanil appears to be minimal for the use on stone fruits.

The nature of the residues is adequately understood and adequate