

kg/day and the maternal toxicity no observed adverse effect level (NOAEL) is 4.7 mg/kg/day (82% of 5.7 mg/kg/day based on concentration analysis). The developmental toxicity NOAEL is 13.0 mg/kg/day based on observed decreased fetal body weight and increased incomplete ossification in selected bones at 30.0 mg/kg/day LOAEL.

New Zealand white rabbits (19 or 20/group) were orally dosed with 0, 1.5, 5, or 15 mg/kg/day pyridaben from day 6 through 19 of gestation. Maternal toxicity was evidenced by a dose-dependent decrease in body weight gain and food consumption at all dose levels. There was also increased incidences of abortions and clinical signs (few feces) in the 15 mg/kg/day group. There was no evidence that the chemical had a developmental effect at any of the tested levels. The maternal NOAEL was <1.5 mg/kg/day and the Maternal LOAEL was 1.5 mg/kg/day based on decreases in body weight gain and food consumption at all dose levels. No developmental toxicity was observed at any dose level. Therefore, the NOAEL for developmental toxicity is greater than or equal to 15 mg/kg/day.

In a standard two-generation reproduction study, CD rats were administered pyridaben in the diet at doses of 0, 10, 28 or 80 ppm. The Parental/Systemic NOAEL is 28 ppm (2.20 and 2.41 mg/kg/day for males and females, respectively). The parental/systemic LOAEL is 80 ppm (6.31 and 7.82 mg/kg/day for males and females, respectively) based on decreased body weights, body weight gains and food efficiency. There was no effect on reproductive parameters on the dose levels tested. The reproductive NOAEL is \geq 80 ppm in males and females. The reproductive LOAEL is >80 ppm in males and females.

4. *Subchronic toxicity.* In a 21-day dermal study, rats received repeated topical applications of pyridaben (98% pure) to about 10% of the body surface area at dosages of 30, 100, 300 and 1,000 mg/kg for 21 days. The treatment produced body weight decreases in the 300 mg/kg/day females and in the 1,000 mg/kg/day males and females. The NOAEL was 100 mg/kg/day and the LOAEL was 300 mg/kg/day based on decreased body weight gain in females. The toxicology endpoints from this study were selected by the Agency for short- and intermediate-term dermal risk assessments.

5. *Chronic toxicity.* In a 12-month chronic feeding study in dogs pyridaben was administered in capsules at dosages of 0, 1.0, 4.0, 16.0 or 32.0 mg/kg/day. All animals survived until the end of the study and there were no treatment-

related changes in hematology, clinical chemistry, or urinalysis parameters. The NOAEL was determined to be <1.0 mg/kg/day and the LOAEL was \leq 1.0 mg/kg/day based on increased incidences of clinical signs (thinness, dehydration, diarrhea, emesis, soft stool, ptialism, and relaxed nictitans) in treatment groups of both sexes and decreased body weight gain in females at 1.0 mg/kg/day.

In a follow-up study, Pyridaben was administered in capsules to beagle dogs at dosages of 0 and 0.5 mg/kg/day for 1 year. The NOAEL was determined to be <0.5 mg/kg/day for males and females and the LOAEL was \leq 0.5 mg/kg/day for males and females based on an increased incidence of clinical signs in both treated sexes and decreased weight gain in the treated females.

Pyridaben was administered in the diet to CD-1 mice at dosages of 0, 2.5, 8.0, 25 or 80 ppm for 78 weeks. There was no evidence of a carcinogenic effect of the chemical. The NOAEL was determined to be 25 ppm (2.78 mg/kg/day) for males and females and a LOAEL of 80 ppm (8.88 and 9.74 mg/kg/day for males and females, respectively). The LOAEL was determined to be 80 ppm for males and females based on decreased body weight gain, decreased food efficiency and changes in organ weights and histopathology (males).

Pyridaben was administered in the diet to groups of Wistar rats for 104 weeks at doses of 0, 4, 10, 28 or 80 ppm to assess carcinogenicity. Additional groups (35 animals/sex/dose) received doses of 0, 4, 10, 28 or 120 ppm for 104 weeks (with an interim sacrifice at 53 weeks) to assess chronic toxicity. There was no treatment-related neoplastic or non-neoplastic pathology in either phase of the study. The NOAEL was determined to be 28 ppm in males (1.13 mg/kg/day) and 28 ppm (1.46 mg/kg/day) in females. The LOAEL was determined to be 120 ppm (5.00 mg/kg/day) in males and 120 ppm (6.52 mg/kg/day) in females based on decreased body weight gain in males and females and decreased ALT levels in males in the chronic toxicity phase. There was no evidence of a carcinogenic effect of this chemical.

6. *Animal metabolism.* In an acceptable rat metabolism study by the oral route, pyridaben was mainly eliminated in the feces where 80–97% of the administered dose was excreted regardless of the dose or site of label (pyridazinone or benzyl ring). Nearly 20% of the excreted residue in the feces was unmetabolized parent compound and there was some evidence of glucuronide conjugate(s) in the bile. The

plasma levels following a single low oral dose (3 mg/kg) peaked at 23 hours while peak levels at the high dose (30 mg/kg) were at approximately 24 hours post-dose due, at least in part, to enterohepatic circulation (nearly 22–30% of an administered radioactive dose is excreted in bile within a period of 24 hours). Residual radioactivity was at or near background levels for most tissues by 72 to 168 hours. Generally, there seemed to be increased distribution to fat over time and, compared to other tissues, fat seemed to have relatively more residual radioactivity. Several metabolites, totaling up to 20–30, were resolved in urine and feces and some were structurally identified.

7. *Metabolite toxicology.* The nature of the residue in animals is adequately understood. The residue of concern is pyridaben and its metabolites PB-7, 2-tert-butyl-5-[4-(1-carboxy-1-methylethyl)benzylthio]-4-chloropyridazin-3(2H)-one and PB-9, 2-tert-butyl-4-chloro-5-[4-(1,1-dimethyl-2-hydroxyethyl)benzylthio]-chloropyridazin-3(2H)-one as specified in 40 CFR 180.494.

8. *Endocrine disruption.* The most common toxicity endpoint across the various studies and test species was decreased body weight/decreased body weight gain followed by decreased feed consumption and/or feed efficiency. These effects were observed in the 13-week feeding study in mice, in a 13-week rat study, in two 13-week dog studies, in a 21-day rat dermal study, in a 28-day inhalation toxicity study in rats, in two 1-year feeding studies in dogs, in a 78-week feeding/carcinogenicity study in mice, in a developmental toxicity study in rats, in two developmental studies in rabbits, and in a 2-year feeding carcinogenicity study in rats. The LOAELs were always based on decreases in body weight gain/body weight decreases or decreases in food consumption. Other effects were sporadic and involved changes in certain clinical chemistry values or increases or decreases in organ weights. Thus, there is no indication that effects on the endocrine system were responsible for any of the observed effects.

C. Aggregate Exposure

1. *Dietary exposure.* Assessments were conducted to evaluate the potential risk due to chronic and acute dietary exposure of the U.S. population to residues of pyridaben (BAS 300 I). Commodities (crops and animal products) specified in 40 CFR 180.494 and all new/updated crop tolerances were included in the dietary assessment (citrus, pome fruit, stone fruit, grapes,