

methods for detecting and measuring levels of pyridalyl and its metabolite S-1812-DP have been developed and validated in all appropriate agricultural commodities and respective processing fractions. These analytical methods are suitable for monitoring of food with residues at the levels proposed for the tolerances. Methods have also, been developed and validated for determining pyridalyl and S-1812-DP in animal matrices. The limit of quantitation (LOQ) of pyridalyl in the crop methods are 0.02 ppm in cottonseed, 0.1 ppm in cotton gin trash, and 0.02 ppm in vegetables. The LOQs of pyridalyl in the animal methods are 0.01 ppm in milk, 0.02 ppm in tissues, liver and kidney, and 0.10 ppm in fat.

3. *Magnitude of residues.* Magnitude of residues were conducted in fruiting vegetables tomato and peppers (bell and non-bell), leafy vegetables (head and leaf lettuce, celery, and spinach), head and stem brassica vegetables (broccoli and cabbage), mustard greens, and cotton. Trials were conducted in all of the major use area for each of the crops as specified in the OPPTS Harmonized Guidelines OPPTS 860.1500 with applications at the maximum use rate for each crop. As a result of the field trials, the following tolerances for the residues of pyridalyl are proposed for each of the crop groups, crops or matrices: Cottonseed at 0.4 ppm; turnip greens at 30 ppm; vegetables, leafy, except Brassica, group 4 at 20.0 ppm; brassica, head and stem, subgroup 5A at 5.0 ppm; Brassica, leafy greens, subgroup 5B at 30 ppm; and vegetables, fruiting, group 8 at 1.1 ppm. Tolerances for the residues of pyridalyl plus the metabolite S-1812-DP are proposed for cotton gin by-products at 23.0 ppm. Processing studies were conducted with tomato and cottonseed. No tolerances are proposed for cottonseed and tomato processing commodities since no concentration factor was observed. Tolerances for residues of pyridalyl are also proposed for milk at 0.1 ppm; meat at 0.04 ppm; animal fat at 1.0 ppm; and meat by-products at 0.05 ppm.

B. Toxicological Profile

A full battery of toxicology testing including studies of acute, subchronic, chronic, oncogenicity, developmental, reproductive and genotoxicity effects is available for pyridalyl. The acute toxicity of pyridalyl is low by all routes. Subchronic and chronic studies exhibit no observed adverse effect level (NOAEL) values from a low of 3.4 milligrams/kilogram/day (mg/kg/day) (male rat combined toxicity/oncogenicity study) to 1,000 mg/kg/day (28-day dermal toxicity study).

Pyridalyl is not oncogenic and the weight-of-evidence indicates it is not genotoxic. There are no developmental concerns or reproductive effects.

The lowest acute NOAEL of 50 mg/kg/day is derived from both the maternal and reproductive toxicity endpoint of the rabbit developmental toxicity study.

The lowest chronic NOAEL of 40 ppm (2.8 mg/kg/day in males) is taken from the premating growth period in the 2-generation reproduction study.

1. *Acute toxicity.* The acute toxicity of pyridalyl technical is low by all routes. Pyridalyl was not toxic when administered in limit tests orally, dermally and via inhalation to rats. It is not a skin irritant and is only a mild eye irritant. Pyridalyl was positive in skin sensitization tests. Pyridalyl and its formulated products will be placed into Toxicity Category III.

2. *Genotoxicity.* The genotoxic potential of pyridalyl was studied *in vitro* in bacteria (ames test), in mammalian cells hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and mouse lymphoma L5178Y TK+/-), in the chromosome aberration assay, and *in vivo* in the unscheduled DNA synthesis (UDS) test and the mouse micronucleus test. The test systems assayed did not show any evidence of pyridalyl genotoxicity except the *in vitro* mammalian cytogenetics (chromosome aberration) assay. The weight of the evidence indicates that pyridalyl does not raise significant genotoxicity concerns.

3. *Reproductive and developmental toxicity.* Developmental effects of pyridalyl were studied in rats and rabbits and multigenerational effects on reproduction were studied in rats.

i. *Rat developmental.* In a developmental toxicity study conducted with rats, the maternal NOAEL was 10 mg/kg/day based on the non-acute effects of reduced body weight gain and food consumption. There were no developmental effects, and the developmental NOAEL is 250 mg/kg/day, the highest dose tested (HDT).

ii. *Rabbit developmental.* In a rabbit developmental toxicity study, the acute effects of maternal toxicity and decreased fetal weight was observed at 150 mg/kg/day. The maternal and developmental NOAEL is 50 mg/kg/day.

iii. *Reproduction.* In a rat reproduction study, there were no adverse effects of pyridalyl on reproductive parameters in the absence of parental toxicity. The reproductive, parental and offspring toxicity NOAEL is 40 ppm.

4. *Subchronic toxicity.* Subchronic toxicity studies have been conducted

with pyridalyl in the rat, mouse, and dog.

i. *Rats.* Pyridalyl technical was tested in rats in a 3-month feeding study. Effects included decreased body weight gain, altered blood biochemistry, increased relative liver weight and histopathological changes in the liver, ovary, adrenal and lung. The NOAEL is 100 ppm (5.56 mg/kg/day in males and 6.45 mg/kg/day in females).

ii. *Mice.* A 13-week feeding study in mice was conducted. Effects included decreased body weight gain, hematological and blood biochemical effects, increased liver weight, decreased kidney and ovary weights and histopathological changes in liver, kidney, ovary and adrenal. The NOAEL is 70 ppm in males (8.169 mg/kg/day) and 700 ppm in females (86.78 mg/kg/day).

iii. *Dogs.* A 13-week oral (capsule) toxicity study was conducted in dogs. Effects included decreased body weight gain, clinical signs indicative of respiratory distress, hematological and blood biochemistry effects, increased liver, lung and kidney weights and histopathological alterations of the lung, kidney, adrenal and liver. The NOAEL was 10 mg/kg/day.

iv. *Dermal rat.* A 28-day dermal toxicity study in rats with pyridalyl did not produce any signs of dermal or systemic toxicity at 1,000 mg/kg/day, the highest dose tested (HDT).

5. *Chronic toxicity.* Pyridalyl has been tested in chronic studies with dogs, rats and mice.

i. *Rats.* In a 104-week combined chronic/oncogenicity study in rats, effects included decreased body weight gain, increased frequency of rearing (high dose females only), hematological alterations and histopathological alterations of the spleen. No oncogenicity was found. The NOAEL for this study is 100 ppm (3.4 mg/kg/day in males and 4.1 mg/kg/day in females).

ii. *Mice.* Pyridalyl was administered in the diet to mice for 78-weeks. Effects included decreased body weight gain and food consumption/efficiency, and increased liver and kidney weights. The NOAEL of the study was 50 ppm (5.04 mg/kg/day in males and 4.78 mg/kg/day in females).

iii. *Dogs.* Pyridalyl was administered for 12-months by capsule to dogs. There were alterations in blood biochemistry (alkaline phosphatase and alanine aminotransaminase) and increased liver weights. The NOAEL of the study was 20 mg/kg/day.

iv. *Carcinogenicity.* Pyridalyl did not produce carcinogenicity in chronic studies with rats or mice. Valent anticipates that the oncogenicity