

or mutagenic, and it is not a reproductive or developmental toxicant when tested in standard toxicity studies. Animal metabolism and excretion is rapid; there appear to be no special toxicity concerns for a unique plant metabolite; and there is no evidence for endocrine effects. The kidney and liver appear to be the target organs of flufenpyr-ethyl. EPA has not had the opportunity to review the toxicity studies on flufenpyr-ethyl and has not established toxic endpoints. For chronic oral exposure, Valent has chosen the NOAEL from the second rat reproduction study of 100 ppm (5 mg/kg/day nominal) as the toxic endpoint. There is no study with flufenpyr-ethyl that showed toxicity that could be associated with a single, or acute, oral exposure. Therefore no acute endpoint could be identified, and no acute oral risk analyses are performed.

1. *Acute toxicity.* The acute toxicity of technical grade flufenpyr-ethyl is low by all routes. Flufenpyr-ethyl produces minimal toxicity following acute oral, dermal or inhalation exposures. The technical material is essentially non-irritating to the eye, is not irritating to the skin and does not cause dermal sensitization in guinea pigs. Flufenpyr-ethyl technical will be classified as Toxicity Class IV.

2. *Genotoxicity.* Flufenpyr-ethyl does not present a genetic hazard. Flufenpyr-ethyl technical was negative in the following tests for mutagenicity: Ames assay with and without S9, *in vitro* mammalian cell gene mutation assay using L5178Y/TK⁺ mouse lymphoma cells, and the *in vivo* mouse bone marrow micronucleus test.

3. *Reproductive and developmental toxicity.* Developmental toxicity studies have been performed in rats and rabbits, and multigenerational effects on reproduction were tested in rats.

i. *Rats.* In the developmental toxicity study conducted with rats, technical flufenpyr-ethyl was administered by gavage at levels of 0, 100, 300, and 1,000 mg/kg/day during gestation days 6 through 19. There were no adverse maternal or fetal effects observed. The NOAEL for both maternal and developmental toxicity was found to be 1,000 mg/kg/day, the highest dose tested.

ii. *Rabbits.* Flufenpyr-ethyl technical was tested in a developmental toxicity study in rabbits at doses of 0, 100, 300 and 1,000 mg/kg/day during gestation days 6 through 28. Maternal mortality occurred at the two highest doses tested but the deaths at 300 ppm were not considered to be the result of systemic toxicity. In surviving animals and their fetuses, there were no adverse effects.

Based on these results, the maternal toxicity NOAEL was 300 mg/kg/day and the developmental toxicity NOAEL was 1,000 mg/kg/day.

A second developmental toxicity study was conducted to confirm the maternal NOAEL at dose levels of 0, 100, 200, 300 or 1,000 mg/kg/day during gestation. Again, maternal mortality occurred, but at all dose levels. Detailed examination of these animals showed in the majority of cases the cause of death to be test material aspiration into the lungs. The cause of death for several animals at the high dose could not be determined. Their deaths were therefore attributed to systemic toxicity. There were no other adverse effects in the surviving dams or fetuses. The NOAEL for this study (and overall for both rabbit developmental toxicity studies) were found to be 300 mg/kg/day (maternal) and 1,000 mg/kg/day (developmental).

iii. *Reproduction.* In the rat reproduction study, flufenpyr-ethyl technical was administered in the diet at levels of 0, 200, 2,000, and 20,000 ppm for 2-generations. Parental toxicity was observed at all dose levels, although the effects at the low dose were minimal. Parental toxicity was exhibited by dose-related microscopic changes in the kidney in high dose F₀ animals, in all treated F₁ males, and in high dose F₁ females. There were also 2 high dose F₁ males that died possibly as a result of treatment. Midzonal cytoplasmic vacuolation of the hepatocytes was also observed in the liver of all groups of treated animals in both generations. Based on the results of this study, the NOAEL for parental toxicity was considered to be less than 200 ppm. The NOAEL for reproductive and neonatal toxicity was considered to be 20,000 ppm.

A second 1-generation reproduction study was performed to establish a clear NOAEL for adult kidney lesions using the dose levels of 20, 50 and 100 ppm. The results of the study indicate that the NOAEL for histological changes in the kidneys of F₁ male rats was 100 ppm. No other treatment related findings were noted at any dose level indicating 100 ppm as the NOAEL for treatment and reproductive effects evaluated in the study.

A mechanistic study was also conducted to investigate the reproducibility and reversibility of the kidney lesions observed in the initial 2-generation reproduction study. In the first study, the effects observed at 200 ppm in the F₁ males, basophilic tubules and interstitial inflammation, were minimal but slightly increased in incidence and severity and a slight

increase in interstitial fibrosis of the cortex was also observed. In this mechanistic study, using dose levels of 0 and 2,000 ppm, the NOAEL for histological changes in the kidneys of F₀ and F₁ male rats and reproductive effects was 2,000 ppm. The histological changes seen in the kidneys in the original study was not reproducible.

4. *Subchronic toxicity.* Subchronic oral toxicity studies conducted with flufenpyr-ethyl in the rat, mouse and dog indicate a low level of toxicity.

i. *Rats.* Pure (99.4%) flufenpyr-ethyl was tested in rats at dose levels of 0, 600, 2,000, 6,000, and 20,000 ppm in the diet for 13 weeks. Effects observed included urinary incontinence, increased food and water consumption, slight hematological and blood biochemistry changes, decreased spleen weights, an increase in the incidence and severity of basophilic tubules of the kidneys and slight to mild diffusely distributed vacuolation in the liver. Based on these results, the NOAEL was 2,000 ppm (134.2 mg/kg/day) for the males and 20,000 ppm (1,509.6 mg/kg/day) for the females.

In an additional study, flufenpyr-ethyl technical was tested in rats at dose levels of 0, 1,000, 10,000, and 20,000 ppm in the diet for 13 weeks. Effects observed included urinary incontinence, increased food and water consumption, and mild urinalysis, hematological and blood biochemistry changes. Thymus weights were slightly increased. Diffusely distributed hepatic vacuolation was seen in the high dose males. Based on these findings, the NOAEL was 10,000 ppm (595.2 mg/kg/day) in the males and 20,000 ppm (1,377.5 mg/kg/day) in the females.

ii. *Mice.* In a 4-week study, CD-1 mice were fed pure flufenpyr-ethyl at dose levels of 0, 300, 1,000, 3,000, and 7,000 ppm. Effects were slight anemia, changes in blood biochemistry, increased liver and thymus weights, and enlarged liver. Centrilobular hepatocellular hypertrophy and vacuolation and increases in the severity and incidence of hepatic focal and single cell necrosis were observed. Based on these findings, the NOAEL was 300 ppm (44.9 mg/kg/day) for males and 1,000 (210.5 mg/kg/day) for females. In a 13-week study, flufenpyr-ethyl technical was administered to mice at dose levels of 0, 300, 1,000, 3,000, and 7,000 ppm. Slight anemia and blood biochemistry changes were noted. Liver weights were increased and ovary weights were decreased. Histopathological findings included: Hepatocellular fatty vacuolation. The NOAEL for this study in both sexes was