

1,000 ppm (128.4 mg/kg/day for males and 155.7 mg/kg/day for females).

iii. *Dogs.* Flufenpyr-ethyl technical was administered for 13 weeks via capsule to Beagle dogs at levels of 0, 100, 300 or 1,000 mg/kg/day. The effects were very minimal. Only small nonsignificant decreases in body weight and slightly elevated alkaline phosphatase values were noted. In the absence of other effects, the NOAEL in both sexes was determined to be 1,000 mg/kg/day.

iv. *Dermal.* A 21-day dermal toxicity study in rats with flufenpyr-ethyl technical did not produce any signs of dermal or systemic toxicity at 1,000 mg/kg/day, the highest dose tested.

5. *Chronic toxicity.* Flufenpyr-ethyl technical has been tested in chronic studies with dogs, rats and mice.

i. *Rats.* In a 104-week combined chronic/oncogenicity study in rats, flufenpyr-ethyl technical was administered at dose levels of 0, 100, 1,000, 10,000, or 20,000 ppm in the diet for 24 months. Urinary incontinence, increased food and water consumption, changes in urinalysis, hematological and blood biochemistry changes were observed but the effects were not toxicologically significant. No neoplastic lesions were observed. The NOAEL was found to be 20,000 ppm (777.5 mg/kg/day for males and 1024 mg/kg/day for females).

ii. *Mice.* In a 78-week oncogenicity study with mice, flufenpyr-ethyl technical was administered at dose levels of 0, 350, 3,500, and 7,000 ppm. Male animals exhibited slight anemia. Females had increased liver and kidney weights (week 53 only). Slight to moderate hepatocellular fatty vacuolation and necrosis were observed. There were no increases in incidence of pre-neoplastic or neoplastic lesions. Based on these results, the NOAEL was 350 ppm for both sexes (39.9 mg/kg/day for males and 43.7 mg/kg/day for females).

iii. *Dogs.* In a 52-week chronic study, flufenpyr-ethyl technical was administered by capsule to Beagle dogs at dose levels of 0, 50, 200, and 1,000 mg/kg/day. There were very few observations related to treatment. Slightly elevated alkaline phosphatase values were again observed, but they were not accompanied with any other findings and were thus considered not to be an adverse effect. The NOAEL was determined to be 1,000 mg/kg/day, the highest dose tested.

iv. *Carcinogenicity.* Flufenpyr-ethyl is not a carcinogen. Studies with flufenpyr-ethyl technical have shown that repeated high dose exposures produced minimal signs of toxicity,

including slight hematologic, liver and kidney effects, but did not produce cancer in test animals. No oncogenic response was observed in a rat 2-year chronic feeding/oncogenicity study or in a 78-week study on mice. Valent anticipates that the oncogenicity classification of flufenpyr-ethyl will be "E" (no evidence of carcinogenicity for humans).

6. *Animal metabolism.* Following oral administration of ¹⁴C-phenyl-labeled flufenpyr-ethyl to rats at 50 mg/kg, the majority of the radiocarbon is eliminated from the body within 2 days. Approximately half is excreted in the urine and the balance is excreted in the feces. Tissue residues are very low 7 days after administration (<0.09% of the administered dose). The major metabolite was identified as [2-chloro-4-fluoro-5-(5-methyl-6-oxo-4-trifluoromethyl-1,6-dihydropyridazin-1-yl)phenoxy]acetic acid (S-3153-acid) which accounted for 93.2% of the dose. Two other minor metabolites each accounted for less than 5% of the administered radiocarbon. Flufenpyr-ethyl was detected only in feces (0.5%). The major reaction was cleavage of the ester linkage; minor reactions were hydroxylation of the 5-methyl of pyridazine ring and cleavage of the ether linkage between the phenyl group and the carboxymethyl group.

7. *Metabolite toxicity.* Metabolism studies of flufenpyr-ethyl in rats, goats and hens, as well as the fish bioaccumulation study demonstrate that the parent is very rapidly metabolized and eliminated. Because parent and metabolites are not retained in the body, the potential for acute toxicity from *in situ* formed metabolites is low. The potential for chronic toxicity is adequately tested by chronic exposure to the parent at the maximum tolerated dose (MTD) and consequent chronic exposure to the internally formed metabolites. One plant metabolite, S-3153-acid-4-OH was not detected as an animal metabolite. This compound was tested for acute oral toxicity in rats, and for mutagenicity Ames testing with and without mixed function oxidation (S9 mix). The metabolite caused no mortality in rats at 5,000 mg/kg the highest dose tested, and was not mutagenic at up to 5,000 micrograms per plate.

8. *Potential endocrine effects.* No special studies to investigate the potential for estrogenic or other endocrine effects of flufenpyr-ethyl have been performed. However, as summarized above, a large and detailed toxicology data base exists for the compound including studies in all required categories. These studies

include acute, sub-chronic, chronic, developmental, and reproductive toxicology studies including detailed histology and histopathology of numerous tissues, including endocrine organs, following repeated or long-term exposures. These studies are considered capable of revealing endocrine effects. The results of all of these studies show no evidence of any endocrine-mediated effects and no pathology of the endocrine organs. Consequently, it is concluded that flufenpyr-ethyl does not possess estrogenic or endocrine disrupting properties.

C. Aggregate Exposure

1. *Dietary exposure.* A full battery of toxicology testing including studies of acute, chronic, oncogenicity, developmental, mutagenicity, and reproductive effects is available for flufenpyr-ethyl. EPA has not had the opportunity to review the toxicity studies on flufenpyr-ethyl and has not established toxic endpoints of concern for use in risk analyses. 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. The chronic RfD using the standard 100-fold uncertainty factor is 0.05 mg/kg/day, and because there is no evidence of enhances susceptibility of infants and children, the FQPA extra 10-fold uncertainty factor is removed. Thus, the Population Adjusted Dose for chronic oral exposure (cPAD) used in these risk assessments is 0.05 mg/kg/day.

i. *Food—*a. *Acute dietary exposure.* There is no acute oral toxic endpoint identified, and so no acute exposure and risk analysis was performed.

b. *Chronic dietary exposures to flufenpyr-ethyl residues were calculated for the U.S. population and 25 population subgroups.* This Tier I analysis includes residue contribution from the field corn, soybean and sugarcane uses and assumes tolerance-level residues and 100% of the crops treated. The results from several representative subgroups are listed below. For all population subgroups, chronic dietary exposure was below 0.2% of the cPAD. Generally, the Agency has no cause for concern if total chronic exposure to residues contributed by published and proposed tolerances is less than 100% of the cPAD.