

(mouse), 80 mg/kg/day (Wistar rats), 100 mg/kg/day (male Fischer 344 rats), and 500 mg/kg/day (female Fischer 344 rats).

6. *Animal metabolism.* Both fluroxypyr and fluroxypyr MHE have been evaluated in rat metabolism studies. In summary, these studies show that fluroxypyr MHE is rapidly hydrolyzed and the fate of the hydrolysis products, fluroxypyr and 1-methylheptanol, are independent of whether they were given as the ester or the acid. Fluroxypyr, per se, was extensively absorbed and rapidly excreted principally unchanged in the urine; 1-methylheptanol also was rapidly absorbed and rapidly eliminated. Repeated administration of fluroxypyr MHE was not associated with accumulation in tissues. Also, the metabolism and pharmacokinetics of 1-methylheptanol are comparable to that of the methylheptyl portion of fluroxypyr MHE.

7. *Metabolite toxicology.*

Administration of fluroxypyr, as the acid or methylheptyl ester in a variety of toxicological studies, has produced similar effects. The principal response to sufficiently high dosages, whether administered over the short-term or, in some cases, over a lifetime, was nephrosis. Fluroxypyr is an organic acid that is actively excreted into the urine by the kidney. Thus, the target organ and dose response relationship for fluroxypyr toxicity is entirely consistent with the data on the toxicokinetics of fluroxypyr. Metabolism studies have shown that fluroxypyr MHE is rapidly and completely hydrolyzed to fluroxypyr acid and methylheptanol.

8. *Endocrine disruption.* There is no evidence to suggest that fluroxypyr and fluroxypyr MHE have an effect on any endocrine system.

C. *Aggregate Exposure*

1. *Dietary exposure—i. Food.* Tier I dietary risk assessments were conducted for acute, short-term, and chronic exposures. Very conservative assumptions were made in these risk assessments. The dietary exposure assessments were based on all commodities with tolerances for fluroxypyr established at 40 CFR 180.535 together with proposed tolerances for field corn, sweet corn, grain sorghum, and forage grass and hay, including revised tolerances for milk and meat. It was assumed that fluroxypyr residues were present at tolerance or proposed tolerance levels and that 100% of the crops were treated. Potential dietary exposure and risk was estimated using DEEM™ software (Dietary Exposure Evaluation Model,

Version 7.075, Novigen Sciences, Inc., Washington, DC).

Developmental toxicity was not observed in the absence of maternal toxicity and there was no indication of increased susceptibility in young animals to prenatal or postnatal exposure to fluroxypyr in the toxicology studies. Therefore, an additional Food Quality Protection Act (FQPA) safety factor for infants and children was not included in this assessment. Acute dietary risk was assessed using an acute RfD of 1.25 mg/kg/day, based on a maternal NOAEL of 125 mg/kg/day from a rat developmental toxicity study and an uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variation). EPA previously established the maternal NOAEL for this study at 125 mg/kg/day and it was used here for a very conservative assessment of potential developmental toxicity. Pregnant females are estimated to have acute dietary exposure of 0.006582 mg/kg/day, which occupies only 0.53% of the acute RfD. Adverse effects are not expected for exposures occupying 100% or less of the RfD. Therefore, acute dietary exposure and risk are well within acceptable levels.

Chronic dietary exposure estimates along with a short-term oral NOAEL were used to assess short-term dietary exposure and risk. The assessment of chronic dietary exposure and risk is discussed below. The chronic exposure values reported for the total U.S. population and for children 1–6 years old was used to estimate dietary exposure for adults and toddlers, respectively. A 90-day dietary study in rats with a NOAEL of 80 mg/kg/day was selected for establishing a short-term oral toxicity endpoint. A 90-day subchronic study was selected for evaluating risk from short-term oral exposure since the 90-day exposure interval is more appropriate than chronic exposure for assessing short-term risk. Of the 90-day subchronic studies conducted with fluroxypyr, the one selected provided the lowest NOAEL. The short-term oral NOAEL (80 mg/kg/day) was divided by the estimated dietary exposure for adults and toddlers to calculate the respective short-term margins of exposure (MOEs). A conservative Tier I estimate of chronic dietary exposure to fluroxypyr estimated exposure at 0.003160 mg/kg/day and 0.010321 mg/kg/day for the total U.S. population and for children 1–6 years old, respectively. A short-term dietary (food) MOE was calculated by dividing the short-term oral NOAEL (80 mg/kg/day) by the estimated exposure (0.003160 mg/kg/day). The resulting food MOE for adults and toddlers was

calculated to be 25,316 and 7,751, respectively. Since the MOE is substantially greater than 100, risk is estimated to be well within acceptable levels.

Tolerances for fluroxypyr exist for several raw agricultural commodities and as discussed previously, tolerances for additional commodities have been proposed. Chronic dietary exposure to fluroxypyr is possible due to the potential presence of fluroxypyr residue in certain foods. Therefore, a chronic dietary risk assessment was conducted. The assessment used a chronic RfD of 0.8 mg/kg/day based on a NOAEL of 80 mg/kg/day from a combined chronic toxicity and carcinogenicity study in rats and an uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variation). A Tier I chronic dietary exposure and risk assessment was conducted. It was assumed that fluroxypyr residues were present at tolerance or proposed tolerance levels and that 100% of the crops were treated. DEEM™ estimates dietary exposure and the percent of the chronic RfD that is occupied by the input residue values for several population subgroups in the United States. Chronic dietary exposure for the general U.S. population was estimated to be 0.003160 mg/kg/day, which occupies 0.4% of the RfD. Children 1–6 years old comprise the population subgroup predicted to have the highest potential level of dietary exposure. Children 1–6 years old are estimated to have a chronic dietary exposure of 0.010321 mg/kg/day, which occupies 1.3% of the RfD. Adverse effects are not expected for exposures occupying 100% or less of the RfD. Therefore, chronic dietary exposure and risk for both the general U.S. population and children 1–6 years old are well within acceptable levels.

ii. *Drinking water.* There are no established maximum contaminant levels for residues of fluroxypyr in drinking water and health advisory levels for fluroxypyr in drinking water have not been established. Guidance from EPA has indicated that Tier I screening level models, such as GENECC and SCI-GROW, may be used to estimate upper-bound pesticide residues in surface water and ground water when assessing potential exposure through drinking water. Estimated concentrations of a pesticide in surface water or ground water are then compared to a drinking water level of comparison (DWLOC) as a surrogate estimate of exposure and risk. The DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light