

conjunctiva completely reversible within 7 days.

v. A dermal irritation study on technical grade flufenacet in rabbits did not produced any irritation.

vi. Skin sensitization studies on technical grade flufenacet in guinea pigs have produced equivocal results. A skin sensitization potential was exhibited under the conditions of a maximization test, whereby, there was no skin sensitization potential when tested by the Buehler Topical Closed Patch Technique.

2. *Genotoxicity*. Flufenacet was negative for mutagenic/genotoxic effects in a gene mutation/*in vitro* assay in bacteria, a gene mutation/*in vitro* assay in Chinese hamster lung fibroblasts cells, a cytogenetics/*in vitro* assay in Chinese hamster ovary cells, a cytogenetics/*in vivo* mouse micronucleus assay, and an *in vitro* unscheduled DNA synthesis assay in primary rat hepatocytes.

3. *Reproductive and developmental toxicity*. i. A two-generation rat reproduction study with a parental systemic no observed adverse effect level (NOAEL) of 20 ppm (1.4 mg/kg/day in males and 1.5 mg/kg/day in females) and a reproductive NOAEL of 20 ppm (1.3 mg/kg/day) and a parental systemic lowest observed adverse effect level (LOAEL) of 100 ppm (7.4 mg/kg/day in males and 8.2 mg/kg/day in females) based on increased liver weight in F₁ females and hepatocytomegaly in F₁ males and a reproductive LOAEL of 100 ppm (6.9 mg/kg/day) based on increased pup death in early lactation (including cannibalism) for F₁ litters and the same effects in both F₁ and F₂ pups at the high dose level of 500 ppm (37.2 mg/kg/day in F₁ males and 41.5 mg/kg/day in F₁ females, respectively).

ii. A rat developmental study with a maternal NOAEL of 25 mg/kg/day and with a maternal LOAEL of 125 mg/kg/day based on decreased body weight gain initially and a developmental NOEL of 25 mg/kg/day and a developmental LOAEL of 125 mg/kg/day based on decreased fetal body weight, delayed development (mainly delays in ossification in the skull, vertebrae, sternebrae, and appendages), and an increase in the incidence of extra ribs.

iii. A rabbit developmental study with a maternal NOAEL of 5 mg/kg/day and a maternal LOAEL of 25 mg/kg/day based on histopathological finds in the liver and a developmental NOAEL of 25 mg/kg/day and a developmental LOAEL of 125 mg/kg/day based on increased skeletal variations.

4. *Subchronic toxicity*. i. A 84-day rat feeding study with a NOAEL less than

100 ppm (6.0 mg/kg/day) for males and a NOAEL of 100 ppm (7.2 mg/kg/day) for females and with a LOAEL of 100 ppm (6.8 mg/kg/day) for males based on suppression of thyroxine (T₄) level and a LOAEL of 400 ppm (28.8 mg/kg/day) for females based on hematology and clinical chemistry findings.

ii. A 13-week mouse feeding study with a NOAEL of 100 ppm (18.2 mg/kg/day for males and 24.5 mg/kg/day for females) and a LOAEL of 400 ppm (64.2 mg/kg/day for males and 91.3 mg/kg/day for females) based on histopathology of the liver, spleen and thyroid.

iii. A 13-week dog dietary study with a NOAEL of 50 ppm (1.70 mg/kg/day for males and 1.67 mg/kg/day for females) and a LOAEL of 200 ppm (6.90 mg/kg/day for males and 7.20 mg/kg/day for females) based on evidence that the bio-transformation capacity of the liver has been exceeded, (as indicated by an increase in LDH, liver weight, ALK and hepatomegaly), globulin and spleen pigment in females, decreased T₄ and ALT values in both sexes, decreased albumin in males, and decreased serum glucose in females.

iv. A 21-day rabbit dermal study with the dermal irritation NOAEL of 1,000 mg/kg/day for males and females and a systemic NOAEL of 20 mg/kg/day for males and 150 mg/kg/day for females and a systemic LOAEL of 150 mg/kg/day for males and 1,000 mg/kg/day for females based on clinical chemistry data (decreased T₄ and FT₄ levels in both sexes) and centrilobular hepatocytomegaly in females.

5. *Chronic toxicity*. i. A 1-year dog chronic feeding study with a NOAEL was 40 ppm (1.29 mg/kg/day in males and 1.14 mg/kg/day in females) and a LOAEL of 800 ppm (27.75 mg/kg/day in males and 26.82 mg/kg/day in females) based on increased alkaline phosphatase, kidney, and liver weight in both sexes, increased cholesterol in males, decreased T₂, T₄ and ALT values in both sexes, and increased incidences of microscopic lesions in the brain, eye, kidney, spinal cord, sciatic nerve and liver.

ii. A rat chronic feeding/carcinogenicity study with a NOAEL less than 25 ppm (1.2 mg/kg/day in males and 1.5 mg/kg/day in females) and a LOAEL of 25 ppm (1.2 mg/kg/day in males and 1.5 mg/kg/day in females) based on methemoglobinemia and multi-organ effects in blood, kidney, spleen, heart, and uterus. Under experimental conditions the treatment did not alter the spontaneous tumor profile.

iii. In a mouse carcinogenicity study the NOAEL was less than 50 ppm (7.4

mg/kg/day) for males and the NOAEL was 50 ppm (9.4 mg/kg/day) for females and the LOAEL was 50 ppm (7.4 mg/kg/day) for males and the LOAEL was 200 ppm (38.4 mg/kg/day) for females based on cataract incidence and severity. There was no evidence of carcinogenicity for flufenacet in this study.

6. *Animal metabolism*. A rat metabolism study showed that radio-labeled flufenacet was rapidly absorbed and metabolized by both sexes. Urine was the major route of excretion at all dose levels and smaller amounts were excreted via the feces.

7. *Metabolite toxicology*. A 55-day dog study with subcutaneous administration of thiadone (flufenacet metabolite) supports the hypothesis that limitations in glutathione interdependent pathways and antioxidant stress result in metabolic lesions in the brain and heart following flufenacet exposure.

8. *Endocrine disruption*. EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other effect. The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects. Based on the toxicological findings for flufenacet relating to endocrine disruption effects, flufenacet should be considered as a candidate for evaluation as an endocrine disrupter when the criteria are established.

9. *Other studies*. i. An acute rat neurotoxicity study with a NOAEL less than 75 mg/kg/day and a LOAEL of 75 mg/kg/day based on decreased motor activity in males.

ii. A rat subchronic neurotoxicity study with a NOAEL of 120 ppm (7.3 mg/kg/day in males and 8.4 mg/kg/day in females) and a LOAEL of 600 (38.1 mg/kg/day in males and 42.6 mg/kg/day in females) based on microscopic lesions in the cerebellum/medulla and spinal cords.

iii. A rat developmental neurotoxicity dietary study established an overall NOAEL for both dams and offspring of 17.5 ppm. A LOAEL of 80.8 ppm was established based on body weight and