

3. *Reproductive and developmental toxicity.* Data from developmental toxicity studies in the rat and rabbit and a two-generation reproduction study in the rat have been considered. In rabbit (0, 50, 100, 250, 500 mg/kg/day) and rat (0, 30, 300, 1,000 mg/kg/day) teratology studies there was no evidence of teratogenicity. Maternal toxicity was seen at 500 mg/kg/day and 250 mg/kg/day as evidenced by deaths and premature sacrifices. For the control (50, 100, and 250 mg/kg) groups, pre-implantation losses, number of implantation sites, and post-implantation losses were not affected by treatment. The findings after fetal post mortem examination and fetal visceral examination revealed no treatment related effects. Similarly, there were no skeletal malformations in this study and the incidence of anomalies and variations were not affected by treatment. In conclusion, the no observed adverse effect levels (NOAEL) for maternal toxicity was 100 mg/kg/day and the NOAEL for fetal toxicity was 250 mg/kg/day. There was no indication of embryotoxic, fetotoxic or teratogenic potential for trifloxysulfuron-sodium in rabbits.

In the rat teratology study, 300 and 1,000 mg/kg/day caused maternal toxicity consisting of reduced body weight and food consumption. Developmental toxicity was secondary to maternal toxicity and consisted of slightly reduced fetal body weights and an increase in minor skeletal anomalies and variations. The NOAELs for maternal and developmental toxicity were both 30 mg/kg/day. Trifloxysulfuron-sodium was not embryotoxic, fetotoxic or teratogenic in rats when tested under the conditions of this study.

In a rat multigeneration study, trifloxysulfuron-sodium technical was administered in feed at concentrations of 0, 500, 1,000, 8,000 or 12,000 ppm. The dose in mg/kg/day spans a wide range over the duration of the study as animals gain weight and go through gestation and lactation. The ranges are 24–70, 48–137, 400–1,133, 608–1,755 for males and 32–100, 60–199, 500–1,557, 792–2,374 for females at the 500, 1,000, 8,000, and 12,000 ppm dietary level, respectively.

Trifloxysulfuron-sodium had no effect on reproductive parameters. Parental body weight gain and food consumption were reduced at 12,000 ppm in both sexes and at 8,000 ppm in males only. In addition, there was an increased relative liver weight and an increased incidence of hepatocellular hypertrophy at 12,000 ppm in both sexes of adults and at 8,000 ppm in adult males only.

Offspring body weights were reduced in males and females greater than or equal to 8,000 ppm.

In conclusion, the NOAEL for systemic toxicity in both sexes and both generations was 1,000 ppm. The mean dose in mg/kg/day for all weekly means for both sexes, both generations, all time points at this dietary level was 83.4 mg/kg/day. There were no effects on the reproductive parameters and the NOAEL for reproductive toxicity was >12,000 ppm. Offspring effects were observed only at dose levels that produced parental toxicity. Thus, there is no evidence that developing offspring are more sensitive than adults to the effects of trifloxysulfuron-sodium, and it is concluded, that trifloxysulfuron-sodium does not cause developmental or reproductive toxicity.

4. *Subchronic toxicity.* Trifloxysulfuron-sodium technical was evaluated in a number of subchronic studies. In a 3-month rat feeding study the NOAEL was 65.7 mg/kg with hematologic and liver effects noted. In a 3-month mouse feeding study, the NOAEL was 67.9 mg/kg. Effects seen were adaptive liver effects. In a 3-month feeding study in dogs the NOAEL was 19.6 mg/kg and hematopoietic and liver effects were seen. In a 28-day dermal (rat) study, the NOAEL was 100 mg/kg. In this study only body weight effects were noted, and only occurred at 1,000 mg/kg.

5. *Chronic toxicity.* Trifloxysulfuron-sodium technical was not oncogenic in rats or mice. In a 12-month feeding study in dogs fed diets containing trifloxysulfuron-sodium that resulted in average (sexes combined) daily test substance intakes of 0, 1.67, 6.71, 15.0, 48.2 or 122 mg/kg/day, all animals survived. In life observations, food consumption, eye and neurological examinations, and urine profiles were not affected by treatment. Macroscopic and microscopic examinations revealed no findings that were considered to be treatment related and indicative of systemic toxicity.

The body weight gain was decreased by 16% in males at 122 mg/kg/day. The 33% decrease at 48.2 mg/kg/day was mainly due to one male that gained significantly less weight than the other animals of this group. There was a tendency for a decrease in the erythrocyte count, hemoglobin concentration and hematocrit for both sexes at 122 mg/kg/day at the end of treatment, and for males throughout the treatment period. In female dogs treated with 48.2 and 122 mg/kg/day, the mean absolute and relative liver weights were increased, and a tendency for an

increase in relative liver weight was noted for males at the same dose levels.

The maximum tolerance dose (MTD) was achieved at 122 mg/kg/day based on the decrease in the body weight gain in males at 48.2 and 122 mg/kg/day. Administration of trifloxysulfuron-sodium to dogs for 12 months caused a tendency for decrease in red blood cell parameters in both sexes at 122 mg/kg/day. There was neither histopathological nor functional evidence for compound related neurotoxicity. Based on the effects at 48.2 and 122 mg/kg/day, the NOAEL was established at 15.0 mg/kg/day for males and 14.9 mg/kg/day for females.

In an 18-month oncogenicity study, mice were fed diets containing trifloxysulfuron-sodium that resulted in average (sexes combined) daily test substance intakes of 0, 5.84, 24.3, 116, and 836 mg/kg/day. Treatment had no adverse effect on appearance or behavior. Survival in treated animals was comparable to controls. There were no effects on organ weights, and there were no macroscopic or microscopic findings indicative of treatment-related systemic toxicity. Trifloxysulfuron-sodium was not carcinogenic in the mouse. Body weight gain in females at 836 mg/kg/day was decreased by 21% compared to controls after 3 months and 16% after 18 months. Food consumption was decreased in this group by 8%. The MTD was achieved at 836 mg/kg/day based on a decrease in body weight gain of greater than 15% throughout the study. Trifloxysulfuron-sodium was not carcinogenic in the mouse. Based on the findings at 836 mg/kg/day, the NOAEL for chronic toxicity was established at 121 mg/kg/day for males and 112 mg/kg/day for females.

In a 2-year chronic toxicity and carcinogenicity study, rats were fed diets containing trifloxysulfuron-sodium that resulted in average (sexes combined) daily test substance intakes of 0, 2.08, 22.0, 91.0 or 464 mg/kg/day. Clinical signs, survival, eye examinations, blood chemistry, urinalysis, and water consumption were not adversely affected by treatment. Survival in high dose females was greater than 80%, than in controls of 60%. There were no treatment-related findings at the 12-month interim or terminal necropsy.

A treatment-related decrease in body weight gain (17% decrease compared to controls) was seen in both females and males at 464 mg/kg/day (10,000 ppm), which was considered to be the maximum tolerated dose (MTD). Overall food consumption was decreased by 6% in males or 9% in females at 464 mg/kg/day. At the interim and terminal