

sacrifices, mean carcass weights were lower in males (9% and 13%, respectively) and females (17% and 12%, respectively) for the 464 mg/kg/day group. At terminal sacrifice, the testes to body weight ratio was increased by 19% in the 464 mg/kg/day group.

Microscopical examination revealed a non-dose responsive increase in the incidence of kidney tubular atrophy in the two top dose groups of female rats, and an increase in Leydig cell hyperplasia in high dose males only. Both treatment-related lesions occurred late in age/treatment, and were not seen in animals sacrificed in the initial year of the study. Neither lesion showed an increase in severity (only incidence) or a progression of the lesion. Both lesions are commonly seen in high incidence in aged control rats; 26% of control females showed renal tubular atrophy, and 22% of control males showed Leydig cell hyperplasia. The control incidence in 10 studies was less than 10%, suggesting that the animals in this study were particularly susceptible to this lesion. There were no data from other measured parameters in this study that suggest kidney or testis as target organs, therefore indicating that these lesions are high-dose, long-term effects.

In conclusion, the MTD was reached or exceeded at 464 mg/kg/day for the 2-year rat feeding study. The NOAEL in males was 82.6 mg/kg/day based on the increased incidence of Leydig cell hyperplasia, and 23.7 mg/kg/day in females based on the increased incidence of kidney tubular atrophy. There was no evidence of a carcinogenic effect after 2 years of treatment with trifloxysulfuron-sodium in rats.

6. *Animal metabolism.* Metabolism in rats proceeded primarily via three concurrent metabolic pathways (typical sulfonylurea chemistry: Oxidative o-demethylation, hydroxylation of the pyrimidine ring and Smiles rearrangement of the sulfonylurea. Hydrolysis of the sulfonylurea and oxidative O-demethylation are minor pathways in the rat. Parent compound was the major residue in the rat. The metabolite pattern in urine and feces extracts of dogs is similar to that of rats. Trifloxysulfuron-sodium was the major component detected in extracts of urine and feces for dogs, as in the rats. In hens and goats, the metabolite profile was very similar to that observed in the rat.

7. *Metabolite toxicology.* The metabolism profile for trifloxysulfuron-sodium supports the use of an analytical enforcement method that accounts for parent trifloxysulfuron-sodium. Other metabolites are considered of equal or lesser toxicity than parent compound.

8. *Endocrine disruption.*

Trifloxysulfuron-sodium does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system. There is no evidence that trifloxysulfuron-sodium has any effect on endocrine function in development or reproduction studies. Furthermore, histological investigation of endocrine organs in chronic dog, mouse, and rat studies did not indicate that the endocrine system is targeted by trifloxysulfuron-sodium.

9. *Neurotoxicity.* In an acute range finding neurotoxicity study in which rats received a single oral dose of 2,000 or 3,500 mg/kg trifloxysulfuron-sodium, there were no effects on clinical signs, body weight and food consumption, or parameters in an abbreviated functional observational battery (FOB). Therefore, the time to peak effect for FOB and motor activity testing was based on a blood kinetic study. In this study, trifloxysulfuron-sodium induced peak plasma levels at 1–2 hours post-dose, and levels were almost zero at 24 hours.

In an acute neurotoxicity study in rats, trifloxysulfuron-sodium was administered by gavage at 0 or 2,000 mg/kg. Mortality, body weight development and food consumption were not affected by treatment. Neither clinical signs nor changes in observation and functional test conducted as part of the FOB were observed. Reduced horizontal and vertical motor activity were observed in males and females only at the time of peak effect (1–2 hours post-dosing). There were no persistent signs of toxicity and no histopathological evidence of neurotoxicity.

In a second acute neurotoxicity study in rats, trifloxysulfuron-sodium was administered by gavage at 0, 200, 600 and 2,000 mg/kg. Mortality, body weight development and food consumption were not affected by treatment. There were no effects on clinical signs or on parameters in the FOB. During the peak plasma period (1–2 hours post-dosing), motor activity parameters of the males were comparable to the control while females tended to be slightly less active. Based on the results of this study, Trifloxysulfuron-sodium was devoid of neurotoxic effects. Due to the slightly reduced motor activity in top dose females, the NOAEL was established at 600 mg/kg.

In a 90-day subchronic neurotoxicity study in rats, trifloxysulfuron-sodium was not neurotoxic when administered in the diet for 13 weeks at concentrations resulting in average daily test substance intakes of 0, 112, 472, or 967 mg/kg/day for males or 0, 134, 553 or 1,128 mg/kg/day for females. There

were no treatment-related deaths or clinical signs. Effects on body weight development and food consumption indicated systemic toxicity in males at doses 472 mg/kg/day and in females at 1,128 mg/kg/day. There were no treatment-related neurobehavioral or motor activity effects, no macroscopic findings, and no microscopic findings in central or peripheral nervous tissue.

In the absence of any functional or morphological changes in the nervous system at any of the dose levels tested, trifloxysulfuron-sodium is considered devoid of neurotoxic potential when administered to rats for 90 days. Based on body weight effects, the NOAEL was established at 112 mg/kg/day for male rats and 553 mg/kg/day for female rats.

C. *Aggregate Exposure*

1. *Dietary exposure.* Dietary exposure from trifloxysulfuron-sodium potentially exists through both food commodities and drinking water. Each exposure pathway is addressed below.

i. *Food.* Chronic dietary exposure to trifloxysulfuron-sodium was estimated based on proposed tolerance-based residue values and the assumption that 100% of all planted acres were treated. The assessment included cotton, processed cotton fractions, sugarcane and associated processed commodities, citrus, almonds and tomatoes. Chronic exposure for all populations was compared to a reference dose (RfD) of 0.15 milligrams/kilogram/body weight/day (mg/kg/bwt/day) based on a no observed adverse effect level (NOAEL) of 14.9 mg/kg/bwt/day from a 1-year study in dogs and a 100X uncertainty factor. The analysis was conducted using the dietary exposure evaluation model (DEEM™) and the USDA's 1994–96 Continuing Survey of Food Intake by Individuals (CSFII). Secondary residues in animal commodities were not considered in this evaluation since calculations showed that transfer from livestock and poultry was minimal and would result in residue levels significantly below current analytical method capabilities. Chronic exposure to trifloxysulfuron-sodium was found to be essentially zero with less than 0.1% of the RfD utilized for all populations. These exposure calculations are conservative in that 100% of the crop was assumed as treated and tolerance-based residue levels were entered into the dietary model.

Acute dietary assessments were conducted for trifloxysulfuron-sodium using proposed tolerance-based residue values and the assumption that 100% of all planted acres were treated. The assessment included cotton, processed cotton fractions, sugarcane and