

weights were increased in the F0 and F1 parental males. No adverse reproductive effects were noted at any dose level in the incidence of normal estrous cycle, mating index, fertility and gestation indices, the number of implantation sites, and duration of gestation in F0 and F1 parental animals. For the offspring, it was noted that at 2,000 ppm, the viability index on lactation Day 4 was significantly lower in the F1 pups and body weights were lowered in pups during the latter half of the lactation period. For the F0 and F1 pups of the 80 and 400 ppm groups, there were no treatment-related adverse effects observed for any parameter, i.e. mean number of pups delivered, sex ratio, viability indices on lactation days 0, 4 and 21, clinical signs, body weights and gross pathological findings. The parental NOAEL was 400 ppm (17.0 mg/kg/day) based on the effects on relative liver weight in males at 2,000 ppm. The pup NOAEL was 400 ppm (37.9 mg/kg/day) based on decreased viability on lactation Day 4 and decreased body weight at 2,000 ppm in the F1 pups. The reproductive NOAEL was 2,000 ppm (86.4 mg/kg/day), the highest dose tested.

4. *Subchronic toxicity.* Subchronic toxicity studies conducted with etoxazole technical in the rat (oral and dermal), mouse and dog indicate a low level of toxicity. Effects observed at high dose levels consisted primarily of anemia and histological changes in the adrenal gland, liver and kidneys.

i. *Rat feeding study:* A 90-day subchronic toxicity study was conducted in rats, with dietary intake levels of 100, 300, 1,000 and 3,000 ppm etoxazole technical. The NOAEL was 100 ppm for males and 300 ppm for females based on increased incidence of hepatocellular swelling at 1,000 ppm and 3,000 ppm.

ii. *Mouse feeding study.* A 90-day subchronic toxicity study was conducted in mice, with dietary intake levels of 100, 400, 1,600, and 6,400 ppm etoxazole technical. The NOAEL was 400 ppm for males and 1,600 ppm for females based on increased alkaline phosphatase activity, increased liver weights, and increased incidence of hepatocellular swelling at 6,400 ppm (both sexes) and at 1,600 ppm in males and enlarged livers in females at 6,400 ppm.

iii. *Dog feeding study.* Etoxazole technical was fed to male and female Beagle dogs for 13 weeks at dietary concentrations of 200, 2,000, and 10,000 ppm. The NOAEL was 200 ppm (5.3 mg/kg/day) based on clinical signs, clinical pathology changes, liver weight

effects and histopathological changes at 2,000 and 10,000 ppm.

iv. *Repeated dose dermal study.* A 28-day dermal toxicity study was conducted in rats at dose levels of 30, 100, and 1,000 mg/kg. There were no treatment related changes in any of the parameters monitored. The NOAEL was 1,000 mg/kg, the highest dose tested.

5. *Chronic toxicity.* Etoxazole technical has been tested in chronic studies with dogs, rats and mice. Valent proposes a chronic oral endpoint of 4 mg/kg bwt/day, based on the NOAEL for male rats in a two-year chronic toxicity oncogenicity feeding study.

i. *Dog chronic feeding study.* Etoxazole technical was fed to male and female beagle dogs for one year at dietary concentrations of 200, 1,000, and 5,000 ppm. The NOAEL was 200 ppm (4.6 mg/kg/day for males and 4.79 mg/kg/day for females) based on increased absolute and relative liver weights with corresponding histopathological changes in the liver at 1,000 and 5,000 ppm.

ii. *Rat chronic feeding/oncogenicity study.* Etoxazole was not oncogenic in rats in either of two chronic feeding studies conducted. In the first study, etoxazole technical was fed to male and female Sprague Dawley rats for two years at dietary concentrations of 4, 16, and 64 mg/kg/day. A trend toward decreased body weight gain for males at 64 mg/kg/day in the latter half of the study was observed. Hematology and clinical chemistry changes, increased liver weights and hepatic enlargement at 16 mg/kg/day or above were observed. Testicular masses, centrilobular hepatocellular swelling and testicular interstitial (Leydig) cell tumors occurred at or above 16 mg/kg/day. The interstitial (Leydig) cell tumors were believed to be incidental. The NOAEL was 4 mg/kg/day for males and 16 mg/kg/day for females. Because an MTD level was not achieved in this study, a second study was conducted in which etoxazole technical was fed to male and female Sprague Dawley rats for two years at dietary concentrations of 50, 5,000, and 10,000 ppm. In this study, decreased mortality, bodyweight and food consumption/ efficiency (females) at 10,000 ppm was observed. Hematological, clinical, and histopathological changes of the incisors, and increased liver weights occurred in both sexes at 5,000 and 10,000 ppm.

Centrilobular hepatocellular hypertrophy was observed in both sexes at 10,000 ppm. The interstitial (Leydig) cell tumors observed in the first study, were not observed in the repeat study.

The NOAEL in the repeat study was 50 ppm (1.8 mg/kg/day).

iii. *Mouse oncogenicity study.* Etoxazole was not oncogenic in either of two mouse oncogenicity studies conducted. In the first study, etoxazole technical was fed to male and female CD-1 mice for 18 months at dietary concentrations of 15, 60, and 240 mg/kg/day. Increased liver weights occurred in females at the highest dose tested. Histopathology parameters were altered for males at 240 mg/kg/day. No neoplastic lesions were observed at any dose level. The NOAEL was 60 mg/kg/day. Since the toxicity in this study was minimal and did not meet the definition of MTD, a second study was conducted at dose levels of 2,250 and 4,500 ppm etoxazole. There were no effects in any group on clinical observations, mortality, body weight, food consumption or hematology. Females showed a significant elevation in relative liver weight after 52 weeks of treatment at 4,500 ppm. In histopathology, a significantly higher incidence of centrilobular hepatocellular fatty change was observed in males in the 4,500 ppm group necropsied after 78 weeks of treatment. There were no treatment-related changes in either sex of the 2,250 ppm dose group. No increase in neoplastic lesions were observed in any treated group of either sex. Therefore, it was concluded that the no observed effect level is 2,250 ppm (242 mg/kg/day for the males and 243 mg/kg/day for the females).

6. *Animal metabolism.* The absorption, tissue distribution, metabolism and excretion of etoxazole were studied in rats after single oral doses of 5 or 500 mg/kg, and after 14 daily oral doses at 5 mg/kg. Etoxazole, labeled in both the t-butylphenyl ring and the oxazole ring were used in this study. For both single dose groups, most (94–97%) of the administered radiolabel was excreted in the urine and feces within seven days after dosing. Most of this excretion occurred in the first 48 hours after dosing. Maximum plasma concentrations occurred 2–4 hours after dosing, with half-lives ranging from 53–89 hours at the low dose and 7–44 hours at the high dose. Plasma levels were significantly lower in females. Concentrations of radioactivity were significantly higher in the tissues of male rats compared to females. The highest concentrations occurred at 3 hours after dosing and were greatest in the gastrointestinal tract and tissues such as liver and kidneys, which are responsible for metabolism and excretion. By 168 hours, the concentration in most tissues was below