

to a mean daily test substance intake of at least 1,175 and 1,388 mg/kg bwt for males and females, respectively.

A rat developmental toxicity (teratogenicity) study was conducted with dose levels of 0, 100, 315 and 1,000 mg mesosulfuron-methyl/kg bwt.

Treatment did not cause lethality or effects on body weight. There were no clinical signs of toxicity. Pregnancy indices were unaffected. No treatment-related effects were observed in fetuses upon external, internal or skeletal evaluation. Therefore, the no observed effect level (NOEL) for both maternal and embryo-fetal toxicity was the limit dose of 1,000 mg/kg. Mesosulfuron-methyl was not teratogenic in rats.

The rabbit developmental toxicity (teratogenicity) study was conducted with dose levels of 0, 100, 315 and 1,000 mg mesosulfuron-methyl/kg body weight/day. No treatment-related deaths or clinical signs were seen. There were no effects on body weight development. No treatment-related effects were observed in fetuses upon external, internal or skeletal examination. Therefore, the NOAEL for maternal and developmental toxicity was the limit dose of 1,000 mg/kg. Mesosulfuron-methyl was not teratogenic in the rabbit. In reproductive and developmental toxicity studies, mesosulfuron-methyl gave no evidence of reproductive, embryo-fetal or neonatal toxicity. Therefore, the potential for reproductive toxicity-related to mesosulfuron-methyl is low.

4. *Subchronic toxicity.* In a 90-day rat feeding study, groups of 10 male and 10 female Wistar rats were fed diets containing either 0, 240, 1,200, 6,000 or 12,000 ppm of mesosulfuron-methyl. The administration of mesosulfuron-methyl up to the limit dose of 12,000 ppm was well tolerated. There were no mortalities and no adverse clinical findings. Body weight gains and feed consumption were comparable in all groups. There were no adverse behavioral, neurological or ophthalmoscopic findings. There were no effects on organ weights or histopathology. The NOAEL for this study was considered to be 12,000 ppm, corresponding to a daily substance intake of 907.5 mg/kg bwt in males and 976.5 mg/kg in females.

In a 90-day feeding study in mice, mesosulfuron-methyl was administered at dietary concentrations of 0, 140, 1,000, and 7,000 ppm. Leukocyte counts were slightly lower in males at 1,000 and 7,000 ppm. However, since there were no corresponding histopathology findings, in particular no compensatory effect in the bone marrow and no adverse clinical effects associated with

this finding, the NOAEL was 7,000 ppm mesosulfuron-methyl, equivalent to daily intakes of 1,238 mg/kg bwt/day in males and 1,603 mg/kg bwt/day in females.

Groups of 4 male and 4 female beagle dogs were administered mesosulfuron-methyl at dietary concentrations of 0, 2,000, 10,000, and 20,000 mg/kg bwt/day for 13 consecutive weeks. Mesosulfuron-methyl at concentrations of up to 20,000 ppm did not affect the general health status, behavior, body weight development or food consumption in dogs. No adverse effects were seen in hematology or biochemistry at any dose. There were no treatment-related changes in organ weights or histopathology. The NOAEL was 20,000 ppm (equating to 648 mg/kg bwt/day for males and 734 mg/kg bwt/day for females).

5. *Chronic toxicity.* A 1-year study was conducted in beagle dogs at doses of 1, 400, 4,000 and 16,000 ppm in the diet. There were no treatment-related effects noted other than non-specific signs of stomach irritation in some high dose dogs. The NOAEL was considered to be 16,000 ppm, equivalent to 574 mg/kg of body weight per day.

The oncogenic potential of mesosulfuron-methyl was examined in bioassays with rats and mice over dietary exposure periods of 24 months and 18 months, respectively.

Dietary administration of technical mesosulfuron-methyl to groups of 80 male and 80 female Wistar rats at concentrations of 0, 160, 1,600 or 16,000, ppm (corresponding to a daily substance intake of up to 865 mg/kg bwt for males and 1,056 mg/kg bwt for females) did not cause clinical symptoms or changes in hematology or biochemistry. All neoplastic and non-neoplastic lesions noted in the study were considered to be incidental findings commonly noted in rats of this strain and age and not related to treatment. The NOAEL for the daily administration of technical mesosulfuron-methyl for 12 or 24 months to male and female Wistar rats is 16,000 ppm.

Groups of 60 male and 60 female CD-1 mice were given dietary concentrations of 0, 80, 800, or 8,000 ppm technical mesosulfuron-methyl for up to 78 weeks. Mesosulfuron-methyl was not tumorigenic and did not cause non-neoplastic lesions. Leukocyte counts were increased in males and females at 8,000 ppm and in males at 800 ppm. However, as there were no indications for any adverse clinical or morphological effects related to the increased leukocyte values (and decreased values were seen in the 90-

day study), 800 ppm is considered to be the NOAEL in the 18-month study. The NOAEL is based on lower body weight gains in females at the high dose level. This is equivalent to a mean achieved intake of 103 and 130 mg test substance/kg bwt/day in males and females, respectively.

Mesosulfuron-methyl is expected to be classified as "Not Likely" to be a carcinogen based on the lack of carcinogenic findings in rats and mice.

6. *Animal metabolism.* Following a single oral administration of either 10 or 1,000 mg/kg mesosulfuron-methyl to rats, 95.1% of the dose was found in the excreta 24 hours post-dosing. Fecal excretion was predominant, while only 12.8% and 1.3% of the low and high dose, respectively, were found in the urine. The predominant excretion product was unchanged mesosulfuron-methyl (>68%). The main metabolic pathway was cleavage of the sulfonylurea-bridge leading to the pyrimidine moiety (2-amino-4,6-dihydroxypyrimidine) and the resulting phenyl moiety which further cyclised to 6-methanesulfonamidomethyl-1,2-benzisothiazol-3(2H)-one 1,1-dioxide. Minor metabolic reactions observed were O-demethylation of the intact molecule at the pyrimidine moiety, cleavage of the sulfonylurea-bridge to form 4-hydroxy-6-methoxypyrimidin-2-yl-urea, and additional O-demethylation to 4,6-dihydroxypyrimidin-2-yl-urea. In addition, cleavage of the methanesulfonamidomethyl side chain leading to the free amine with further transformation to the alcohol (2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethyl-benzoic acid) was also seen. An additional minor metabolite was a benzoic acid metabolite, formed by hydrolysis of the methyl ester of the parent.

Metabolism studies on mesosulfuron-methyl in ruminants and poultry were performed with application of dose levels which were equivalent to 20 ppm and 10 ppm, respectively. The results showed that mesosulfuron-methyl is predominantly excreted with little systemic distribution and limited metabolism. Residue levels in milk, meat and eggs were extremely low and the elimination from tissues was rapid. No tolerances have been proposed for animal tissues. The metabolic pathway in ruminants and poultry was similar to that in rats.

7. *Endocrine disruption.* No special studies investigating potential estrogenic or endocrine effects of mesosulfuron-methyl have been conducted. However, the standard battery of required studies has been