

at doses of 0, 10, 30 or 100 mg/kg bw/day. Developmental toxicity occurred in conjunction with distinct maternal toxicity at the highest dose tested. The maternal NOAEL was 30 mg/kg bw/day based on reduced body weight gain and feed intake at 100 mg/kg bw/day. The NOAEL for developmental toxicity was 30 mg/kg bw/day based on delayed ossification, slightly reduced fetal weights and three cases of palatoschisis at 100 mg/kg bw/day.

In oral developmental toxicity studies in rabbits, Spiroxamine was administered by gavage during gestation at doses of 0, 5, 20 or 80 mg/kg bw/day and in a supplemental study at doses of 0 and 80 mg/kg bw/day. The maternal NOAEL was 20 mg/kg bw/day based on clinical findings, reduced body weight gain, reduced food intake and lethality at 80 mg/kg bw/day. The NOAEL for developmental toxicity was 20 mg/kg bw/day based on marginal developmental toxicity (reduced fetal weight and a slight increased rate of spontaneous malformations) at the highest dose level.

In a dermal developmental toxicity study in rats, Spiroxamine was administered for 6 hours/day during gestation at doses of 0, 5, 20 or 80 mg/kg. Reduced body weight gain occurred in dams at 20 mg/kg and greater. Dose-related skin reactions were observed at all treated doses. Developmental toxicity, such as wavy ribs, occurred in conjunction with maternal toxicity at the highest dose tested. The NOAELs for systemic and local maternal toxicity were 5 and <5 mg/kg, respectively. The NOAEL for developmental toxicity was 20 mg/kg. Spiroxamine did not reveal any teratogenic potential associated with dermal application.

**4. Subchronic toxicity.** In subacute dermal toxicity studies, rabbits were treated with Spiroxamine at doses ranging from 0.05 to 5 mg/kg bw/day for 6 hours/day over a period of 3 weeks. Systemic effects were not observed in these studies. Local irritation, increased skin fold thickness, and histopathological findings of the skin occurred in these studies. The overall NOAELs for local and systemic effects were 0.2 and 5 mg/kg bw/day, respectively.

In a 90-day feeding study, mice were administered Spiroxamine at dietary concentrations of 0, 20, 80, 320 or 1,280 ppm. Effects observed included clinical signs of toxicity, decreased body weight and food consumption, changes in hematological parameters, hyperplastic changes in the epidermis of the auricles and/or tail, and effects on the liver, kidney, and urinary bladder. The NOAEL was 20 ppm (equal to 6.2 mg/

kg bw/day) for male mice based on marginally reduced body weight development at 80 ppm. The NOAEL for female mice was 80 ppm (equal to 28.5 mg/kg bw/day) based on slight morphological findings in the liver at 320 ppm.

In another subchronic mouse study, Spiroxamine was administered by oral gavage at doses of 0, 60, 180 or 240 mg/kg. Effects observed included clinical signs of toxicity, and effects of the liver, urinary bladder and hyperplastic changes in the epidermis of the auricles and tails. Evidence of liver enzyme induction was seen in all treatment groups. The NOAEL was <60 mg/kg bw/day for both males and females.

Spiroxamine was administered to rats in a subchronic feeding study at dietary concentrations of 0, 25, 125 or 625 ppm over a period of 13 weeks. Effects included clinical signs of toxicity, reduced body weight gains, changes in hematological parameters, and effects on the liver, urinary bladder, esophagus and forestomach. The NOAEL for both male and female was 25 ppm (equal to 1.9 and 2.7 mg/kg bw/day, respectively) based on histopathological findings in the esophagus and forestomach at 125 ppm.

In two subchronic feeding studies in dogs, Spiroxamine was administered at dietary concentrations of 0, 25, 750 or 1,500 ppm and at 0, 150, 250 or 500 ppm over a period of 13 weeks. Toxicological effects included changes in clinical chemistries, increased relative liver weights, and histopathological findings in the liver. The overall NOAELs from these studies were 500 ppm (equal to 16.9 mg/kg bw/day) and 750 ppm (equal to 21.29 mg/kg bw/day) for males and females, respectively, based on liver effects.

**5. Chronic toxicity.** In a chronic dog study, Spiroxamine was administered at dietary concentrations of 0, 25, 75, 1,000 or 2,000 ppm for a period of 52 weeks. Effects included ophthalmological findings, changes in clinical chemistries, mild anemia, and histopathological findings (eye and liver). The NOAEL for both sexes was 75 ppm (equal to 2.47 and 2.48 mg/kg bw/day for males and females, respectively) based on eye and liver effects.

Rats were administered Spiroxamine for 2 years at dietary concentrations of 0, 10, 70 or 490 ppm. Effects included reduced body weight gains, a slight increase in mortality and histopathological findings in the esophagus and urinary bladder. The NOAEL for both sexes was 70 ppm (equal to 4.22 and 5.67 mg/kg bw/day for males and females, respectively)

based on esophagus and urinary bladder effects.

The carcinogenicity potential of Spiroxamine was investigated in rats and mice at maximum dietary concentrations of 490 ppm (equal to 32.81 mg/kg bw/day) and 600 ppm (equal to 149.8 mg/kg bw/day), respectively. No evidence of an oncogenic potential of Spiroxamine was found in the long-term studies in rats and mice.

**6. Animal metabolism.** Rats were gavaged with 1 or 100 mg/kg radio-labeled technical Spiroxamine. Seventy percent of the oral low dose was absorbed. Within 48 hours of dosing, over 97% of the dose was excreted in urine and feces. At sacrifice (48 hours post dosing), the radioactivity remaining in the body was below 1% in the low dose groups and approximately 1% and 2% in the male and female rats, respectively, from the high dose group. Concentrations found in tissues and organs were relatively low: i.e., they do not exceed 0.04 micrograms/gram ( $\mu\text{g/g}$ ). The highest concentrations were found in liver, thymus and adrenals. Slightly smaller concentrations were observed in the thyroid, spleen, fat, ovaries and uterus. The main metabolite in all dose groups is Spiroxamine oxidized to the carboxylic acid in the t-butyl-moiety. The identification rate was approximately 77% of the recovered radioactivity in all dose groups.

**7. Metabolite toxicology.** Toxicological studies have been conducted on KWG 4168 N-oxide, a plant and animal metabolite of Spiroxamine. In an acute oral toxicity study on KWG 4168 N-oxide using female rats, the LD<sub>50</sub> was 707 mg/kg. In a subacute toxicity study, rats were administered KWG 4168 N-oxide at dietary concentrations of 0, 30, 150 and 1,000 ppm. The highest concentration resulted in treatment-related effects. The main targets were the epithelia of the digestive tract and the urinary bladder. A mild liver enzyme induction was observed without any correlating gross- or micropathological findings. In a subchronic study, rats were administered KWG 4168 N-oxide at dietary concentrations of 0, 25, 125 and 625 ppm, and KWG 4168 at 625 ppm. Toxic effects were observed at 625 ppm for both test substances. Similar effects included delayed body weight development, changes in clinical chemistries and micropathological findings of the esophagus and stomach. The effects were less pronounced for KWG 4168 N-oxide when compared to KWG 4168 (parent). Effects noted only in animals treated with KWG 4168 included changes in hematological