

post-treatment. In a dermal irritation study in rabbits, mild erythema and/or edema was observed at 72 hours post-treatment with all irritation resolving by 14 days post-treatment. Prosper 300 did not have the potential to induce dermal sensitization in guinea pigs under conditions of the Buehler patch test.

2. *Genotoxicity.* The genotoxic action of spiroxamine was studied in bacteria and mammalian cells with the aid of various *in vitro* test systems (Salmonella microsome test, forward mutation assay, cytogenetic study with Chinese hamster ovary cells and unscheduled DNA synthesis test), and in one *in vivo* test (micronucleus test). None of the tests revealed any evidence of a mutagenic or genotoxic potential of spiroxamine. The compound did not induce point mutations, DNA damage or chromosome aberrations.

3. *Reproductive and developmental toxicity.* In a reproduction study using rats, spiroxamine was administered for 2 generations at dietary concentrations of 20, 80, or 300 ppm. Reproductive effects such as reduced litter size at birth and clinical signs of toxicity occurred at the high dose in conjunction with maternal toxicity. The parental and reproductive no observed effect levels (NOELs) were 20 ppm (equal to 2.13 mg/kg body weight/day (bwt/day) and 80 ppm (equal to 9.19 mg/kg bwt/day), respectively.

In a developmental toxicity study in rats, spiroxamine was administered by oral gavage at dose levels of 0, 10, and 25 mg/kg bwt/day and in a supplemental study at doses of 0 and 150 mg/kg bwt/day. Severe maternal toxicity occurred at 150 mg/kg bwt/day resulting in the deaths of 21 of 25 animals. Embryotoxicity (palatoschisis and omphalocele) was observed at the high dose in conjunction with the severe maternal toxicity. The two lower dose levels did not reveal any maternal or developmental toxicity. The results of these studies showed that the dose of 150 mg/kg bwt/day was too high to obtain unequivocal results with respect to embryotoxicity and teratogenicity.

In another oral developmental toxicity study in rats, spiroxamine was administered by gavage during gestation at doses of 0, 10, 30, or 100 mg/kg bwt/day. Developmental toxicity occurred in conjunction with distinct maternal toxicity at the highest dose tested. The maternal NOEL was 30 mg/kg bwt/day based on reduced body weight gain and feed intake at 100 mg/kg bwt/day. The NOEL for developmental toxicity was 30 mg/kg bwt/day based on delayed ossification, slightly reduced fetal weights and three cases of palatoschisis at 100 mg/kg bwt/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 bwt/day and in a supplemental study at doses of 0 and 80 mg/kg bwt/day. The maternal NOEL was 20 mg/kg bwt/day based on clinical findings, reduced body weight gain, reduced food intake and lethality at 80 mg/kg bwt/day. The NOEL for developmental toxicity was 20 mg/kg bwt/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 NOELs for systemic and local maternal toxicity were 5 and <5 mg/kg, respectively. The NOEL 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 bwt/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 NOELs for local and systemic effects were 0.2 and 5 mg/kg bwt/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 NOEL was 20 ppm (equal to 6.2 mg/kg bwt/day) for male mice based on marginally reduced body weight development at 80 ppm. The NOEL for female mice was 80 ppm (equal to 28.5 mg/kg bwt/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 NOEL was <60 mg/kg bwt/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 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 NOEL 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 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 NOELs from these studies were 500 (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 NOEL 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 NOEL 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 percent of the dose was excreted