

List of Subjects

Environmental protection, Agricultural commodities, Feed additives, Food additives, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: November 26, 2003.

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Acting Director, Registration Division, Office of Pesticide Programs.

Summary of Petition

The petitioner summary of the pesticide petition is printed below as required by FFDCA section 408(d)(3). The summary of the petition was prepared by the petitioner and represents the view of the petitioner. The petition summary announces the availability of a description of the analytical methods available to EPA for the detection and measurement of the pesticide chemical residues or an explanation of why no such method is needed.

Bayer CropScience

PP 3E6783

EPA has received a pesticide petition (PP 3E6783) from Bayer CropScience, 2 T.W. Alexander Drive, P.O. Box 12014, Research Triangle Park, NC 27709 proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of Spiroxamine, 8-(1,1-Dimethylethyl)-N-ethyl-N-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine in or on the raw agricultural commodity hop, dried cone - import at 50.0 parts per million (ppm). EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* A hop plant metabolism study has been conducted, and the nature of the residue is adequately understood. An animal metabolism study is not required since the proposed crop to be treated with Spiroxamine is not fed to livestock.

2. *Analytical method.* A method to determine the total residues of Spiroxamine using gas chromatography has been submitted to the EPA. In addition, Spiroxamine has been evaluated using the multi-residue

methodologies as published in the FDA Pesticide Analytical Manual, Volume I.

3. *Magnitude of residues.* Eight field trials were conducted on fields in typical hop-growing regions in Germany to assess the residue levels of Spiroxamine, 8-(1,1-dimethylethyl)-N-ethyl-N-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine, in/on hops following foliar applications. A formulation containing Spiroxamine (KWG 4168 500 EC) was applied in two spray applications as an emulsifiable concentrate formulation containing 500 grams (g) active ingredient/liter(L), with an application rate of 1.5 liters/hectare (L/ha) and 3,000 L of water/ha. This corresponded to a total applied amount of the active ingredient of 0.750 kilograms (kg)/ha. The applications were carried out at growth stages 75–79 and 77–81, respectively (corresponding to a 9–10 day interval between applications).

Duplicate composite samples of hop cones were collected at a 10-day preharvest interval (PHI) from each plot. In addition, single samples were collected on day 0 and, in four of the trials, on days 6 and 13 after treatment. Hop cones were analyzed both fresh and, on days 10 and 13, after kiln drying. The highest total residue value of Spiroxamine (defined as parent and metabolites converted to aminodiol equivalents) in dried hop cones was 30 ppm (highest individual value)/24.5 ppm (highest average value [HAFT] from two samples in a single trial) at a 10-day PHI. The total Spiroxamine residues in hop cones appeared to decline with time. Note: The residue trials submitted with this petition are being submitted as a national submission in Germany in the European Union (EU). The European procedure for calculating a maximum residue limit (MRL) differs from the procedure used in the USA. Although no final decision has yet been made by the European authorities at the present time, an evaluation of the dried hop cone data according to EU principles leads to an MRL proposal equivalent to 50 ppm total residues of Spiroxamine. In order to avoid possible trade conflicts, it is proposed that the U.S. tolerances be harmonized with the expected EU-MRL.

Samples from two of the above field trials were also processed into beer (four individual processing trials). Average total residues for the dried hop cones prior to processing in these trials were 9.5 and 16 ppm, respectively. In beer, the total residues of Spiroxamine were below the level of detection (i.e., <0.05 ppm) in all four trials.

B. Toxicological Profile

1. Acute toxicity—KWG 4168

(Spiroxamine) Technical. The acute oral LD₅₀ in male rats was 595 milligrams/kilogram (mg/kg) and in female rats was >500 but <560 mg/kg. The acute dermal LD₅₀ in rats was >1,600 and 1,068 mg/kg for males and females, respectively. The 4-hour inhalation LC₅₀ in rats was 2.772 and 1.982 milligrams/liter (mg/L) for males and females, respectively. Irritation studies in rabbits revealed Spiroxamine was severely irritating to the skin while not irritating to the eye. Spiroxamine exhibited a skin-sensitizing potential in guinea pigs in both the Magnusson/Kligman maximization test and 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 two 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 NOAELs were 20 ppm (equal to 2.13 milligrams per kilogram of bodyweight per day (mg/kg bw/day)) and 80 ppm (equal to 9.19 mg/kg bw/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 bw/day and in a supplemental study at doses of 0 and 150 mg/kg bw/day. Severe maternal toxicity occurred at 150 mg/kg bw/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 bw/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