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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES,
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

DATE: 07-January-2004

SUBJECT: **Health Risk Assessment for Spiroxamine Use in/on Grapes, Hops, and Imported Bananas.** PC Code: 120759. TXR No: 0051053.
DP Barcodes: D284789, D284790, D286351, D287717, D293509.
Case Nos: 295510, 295590.
Submission Nos: S623839, S627632.
Petition Nos: 0F6122 - grapes,
3E6518 and 3E6783 - hops,
3E6538 - bananas
Product Nos: 3125-LLN, 3125-LLR
Trade Names: KWG 4168 300 CS, Impulse® EC 800, Prosper 500 EC (KWG 4168 500 EC)

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cc: Shaja Brothers/Robert Forrest (RD)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary and occupational exposure assessments, as needed, to estimate the risk to human health that will

03/04/

result from proposed uses of the fungicide 8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine (spiroxamine) and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety (a.k.a. the aminodiol moiety), calculated as parent equivalent, in/on grapes, hops and bananas.

A summary of the findings and an assessment of human health risk resulting from the uses of spiroxamine are provided in this document. The risk assessment was provided by Meta Bonner (RAB3), the occupational/residential exposure assessment by Jack Arthur (RAB3), the dietary exposure assessment by Nancy Dodd (RAB3), the hazard characterization by Ayaad Assaad (RAB3), and the drinking water assessment by Dirk Young of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration

Provided that data needs are met for conditional registration as described below, the residue chemistry and toxicological databases support the establishment of permanent tolerances for residues of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent, in/on the following raw agricultural commodities (RACs):

Sponsor	Crops	Tolerance (ppm)
Bayer Corp.	Grape	1.0
Bayer Corp	Hop, dried cones	50.0
Bayer Corp.	Banana	3.0

Provided the following data needs are met, HED recommends for conditional registrations for banana, grape, and hop:

Residue Chemistry

Banana, Grape, and Hop

•Modify the confirmatory method to use more than single-ion monitoring or conduct an interference study.

•Send the analytical reference standard for *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane to the National Pesticide Standards Repository.

Banana

• Revise the Section F to correct the commodity definition from "banana, whole fruit" to "banana" and to correct the tolerance expression by replacing "aminodiol" with "*N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane".

Grape

• Submit a revised Section F to: 1) correct the commodity definition from "grape, fruit" to "grape"; 2) propose a tolerance for "spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent"; and 3) delete the proposed tolerance for raisins.

Hop

• Submit a revised Section F to correct the tolerance expression for hop, dried cones by replacing "aminodiol" with "*N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane".

HED recommends that conversion of conditional registration to unconditional registration be considered for banana, grape, and hop upon submission of the following data:

Residue Chemistry

Banana, Grape, and Hop

•A successful method validation for Bayer AG Method No. 00407 must be conducted by EPA's laboratory.

Banana

•Storage stability data are needed on bananas stored frozen for 6 months.

•Information regarding soil types and temperature recordings for the banana field trials should be submitted if available.

Grape

• Unless BEAD indicates that a regional registration for use in CA only is appropriate, four more field trials (two from Region 1 and two from Region 11) are needed.

Hop

• Submitted wheat metabolism studies must be reviewed by the Agency to satisfy a requirement for metabolism studies on three dissimilar crops which show similar metabolic routes.

•Additional storage stability information is needed to support the hop field trials which were conducted in Germany.

Toxicology

• Two-Generation Reproduction Study - Rat.

Labels

• The interim REI of 24 hours appearing on the proposed spiroxamine label, KWG 4168 300 CS, should be increased to 48 hours based on spiroxamine's rating of Toxicity Category I for primary skin irritation.

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1.0 EXECUTIVE SUMMARY

Spiroxamine is a new broad spectrum fungicide proposed for use on grapes, hops (US-grown and imported), and imported bananas to control powdery mildew infesting grapes and hops and black Sigatoka (*Mycosphaerella fijiensis*) infesting bananas. It belongs to a new class of pesticides known as spiroketalamines. There are presently no established tolerances for residues of spiroxamine in/on plant and livestock commodities.

Proposed Uses

Bananas, Grapes, and Hops

Detectable residues of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety are expected to occur in grapes, grape juice, raisins, dried hop cones, and bananas as a result of the uses proposed by Bayer Corporation (on bananas, grapes and imported hops) and IR-4 (on hops grown in the US). Multiple foliar spray applications will be made (twelve on imported bananas, two on grapes, four on hops in the US, and two on imported hops). The proposed seasonal application rates are 3.42 lb ai/A with a 0-day preharvest interval (PHI) for imported bananas, 0.70 lb ai/A with a 28-day PHI for grapes, 1.4 lb ai/A with a 12-day PHI for hops in the US, and 1.50 kg ai/ha (1.34 lb ai/A) with a 10-day PHI for imported hops.

Hazard Assessment

Technical spiroxamine has a moderate to high acute toxicity; it is a Category III by the oral route, II by the dermal, IV by inhalation and eye irritation, but caused severe dermal irritation (Category I). Spiroxamine is also a skin sensitizer. Spiroxamine is a strong irritant and many of its toxic effects and clinical signs are related to its irritant properties. Subchronic studies show that the target organ of spiroxamine toxicity is the liver and that mucous membranes of the esophagus and forestomach were keratinized and hyperplastic due to the strong irritant properties of spiroxamine. There was no evidence (quantitative/qualitative) of increased susceptibility following in utero exposure to rats and rabbits in developmental studies; however, the issue of susceptibility could not be determined because of the lack of an acceptable two-generation reproductive study. There is evidence of mild spiroxamine-induced neurotoxicity from the acute neurotoxicity study, but no neurotoxicity was seen in the subchronic neurotoxicity study. Spiroxamine is "not likely" to be a human carcinogen based on the lack of evidence of malignancy in both the rat and the mouse. Spiroxamine has no mutagenicity potential, based on several *in vivo* and *in vitro* studies. In rat metabolism and pharmaco-kinetics studies, absorption of spiroxamine began immediately after administration with peak plasma concentrations at 1.5-2 hours post-dose and renal excretion accounted for the majority of the radioactivity.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

On October 7, 2003, the HIARC evaluated the toxicology endpoint selection for spiroxamine with regard to the acute and chronic Reference Doses (RfDs) and for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to spiroxamine was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. The HIARC determined that no special FQPA safety factor (i.e., 1X) is required. However, because the 2nd generation data, in the two-generation rat reproductive toxicity study, were insufficient to provide a susceptibility assessment, HIARC concluded that a 3X uncertainty factor for data base deficiencies (3X UF_{DB}) should be added. This factor is applicable only to the chronic RfD.

An acute oral neurotoxicity study was used to select the dose and endpoint for establishing the acute RfD (aRfD) of 0.1 mg/kg/day for the general population. No suitable study was identified in the toxicology data base for the subpopulation of females 13-50 years old. The acute RfD (aRfD) was calculated by dividing the No-Observed-Adverse-Effect-Level (NOAEL) of 10 mg/kg/day from this study by an uncertainty factor (UF) of 100 [10X for interspecies extrapolation, 10X for intraspecies variation]. The Lowest-Observed-Adverse-Effect-Level (LOAEL) for this study (30 mg/kg/day) was based on clinical signs (piloerection and slight to moderate gait incoordination) and FOB effects (decreased forelimb grip strength and foot splay) in males on Day 0-1 of treatment. Since the acute Population-Adjusted-Dose (aPAD) is equal to the aRfD divided by the FQPA SF (1X), the aPAD is equal to the aRfD (0.1 mg/kg/day).

The dog chronic oral toxicity study was used to select the dose and endpoint for establishing the cRfD of 0.0083 mg/kg/day and because the FQPA SF is 1X, the cPAD is also 0.0083 mg/kg/day. The NOAEL of 75 ppm (2.5 mg/kg/day) and the LOAEL of 1000 ppm (equivalent to 28.03/25.84 mg/kg/day [M/F]) was based on hepatocytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males. A 300-fold uncertainty factor (10x for interspecies extrapolation, 10x for intraspecies variations, and 3X UF_{DB}) was applied to the NOAEL.

The dermal absorption factor is 52.5% at 8 hours. A dermal prenatal toxicity study in rats was used for identifying the dermal short- and intermediate-term exposure endpoints of 5 mg/kg/day based on decreased body weight gains at 20 mg/kg/day (LOAEL). For the dermal long-term endpoint, the chronic oral toxicity study in dogs was used to set the endpoint of 2.5 mg/kg/day based on hepatocytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males at a LOAEL of 28.03 mg/kg/day. This dose, endpoint, and study were selected to address the concern for hepatotoxicity following repeated oral doses; a 53% dermal absorption factor should be used in route-to-route extrapolation.

Since there are no residential uses, toxic endpoints were not selected for short- or intermediate-term incidental oral exposures.

A rat non-guideline inhalation toxicity study was used for dose and endpoint selection for evaluating short- and intermediate-term risks; the NOAEL is 23.6 mg/kg/day. The LOAEL of 140.5 mg/kg/day was based on decreased body weights and body weight gains, increased incidences of clinical signs of toxicity and dermal irritation, thymic atrophy, and toxicity to the skin, respiratory system, and liver. The dose/endpoint is derived from a study conducted via the appropriate route of concern and used for short- and intermediate-term inhalation exposure durations. For the inhalation long-term endpoint, the chronic oral toxicity study in dogs was used to set the endpoint of 2.5 mg/kg/day based on hepatocytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males at a LOAEL of 28.03 mg/kg/day. This dose, endpoint, and study were used for long-term exposure risk assessment to address concern for hepatotoxicity following repeated exposure. Absorption via inhalation is assumed to be equivalent to oral absorption.

Residential Exposure Estimates

This is not required because no residential uses are proposed or expected.

Dietary Exposure Estimates

The HED Metabolism Assessment Review Committee (MARC) determined in a meeting on 10/15/03 that the residues of concern in plants are spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent. HED expects to recommend for tolerance levels of 1.0 ppm in/on grape, 3.0 ppm in/on banana, and 50.0 ppm in/on hop, dried cones. No rotational crop tolerances are needed since grapes, bananas, and hops are not typically rotated. No livestock tolerances are needed since no significant livestock feed items are associated with uses on grapes, bananas, and hops.

Spiroxamine acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.33), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The analyses were performed to support Section 3 requests for spiroxamine on bananas, grapes, and hops.

Acute Dietary Exposure Results and Characterization

The acute assessment was a partially refined deterministic assessment. Tolerances were used for the nonblended and partially blended raw agricultural commodities (i.e., 3.0 ppm for

bananas and 1.0 ppm for grapes). For the processed commodities of grapes, the highest average field trial (HAFT) value of 0.613 ppm was used as the residue value, which was computer-multiplied by the processing factors (adjustment factors #1) of 0.67x for grape juice and 1.3x for raisins. For the blended commodity hops, the average residue value from the field trials for imported hops (16 ppm) was used. Percent crop treated data were not used. The acute dietary analyses for spiroxamine show that residues are below HED's level of concern for the US population and all population subgroups listed. Exposure at the 95th percentile was 7.4% of the aPAD for the general US population and 31% of the aPAD for children aged 1-2 years, the most highly exposed population subgroup.

Chronic Dietary Exposure Results and Characterization

The chronic assessment was a partially refined deterministic assessment. Average residue values from the field trials were used for bananas, grapes, and hops (i.e., 1.13 ppm for unbagged bananas, 0.17 ppm for grapes, and 16 ppm for imported hops.) The tolerance level for grapes (1.0 ppm) was used for grape leaves and wine. For the processed commodities of grapes, the average value of 0.17 ppm was used as the residue value, which was computer-multiplied by the processing factors (adjustment factors #1) of 0.67x for grape juice and 1.3x for raisins. Percent crop treated data were not used. The chronic dietary analyses for spiroxamine show that residues are below HED's level of concern for the US population and all population subgroups. Exposure was 8.3% of the cPAD for the general US population and 29% of the cPAD for children aged 1-2 years, the most highly exposed population subgroup.

Drinking Water Exposure Estimates

EFED provided the tier 2 estimated environmental concentrations (EECs) for spiroxamine in drinking water when spiroxamine is used according to proposed labeling for hops and grapes. To simulate these two uses, EFED used a standard Oregon hops scenario and a standard California grape scenario. The hops scenario is the more vulnerable of the two proposed spiroxamine uses. For surface water, the acute EEC value is 17.8 ppb and chronic value is 14.0 ppb. Ground water concentrations were estimated with the SciGrow model, which estimates the groundwater concentration to be 0.27 ppb. The parent spiroxamine, compared to its metabolites, is relatively persistent in both soil and water. Therefore, the drinking water assessment was conducted on the parent only and is not likely to underestimate exposure levels.

Aggregate Exposure Scenarios and Risk Conclusions

For Aggregate Exposure Risk Assessment, worker inhalation and dermal risks can be combined by the reciprocal MOE method because the endpoint effect of concern is the same for both routes. Residential aggregation is not required for spiroxamine, since residential uses were not proposed. A cancer aggregate risk assessment was not performed because spiroxamine shows no evidence of carcinogenicity.

For the proposed uses, human health aggregate risk assessments were conducted for the following exposure scenarios: acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Short-term aggregate risk assessments were not necessary because there are no residential use sites for spiroxamine. Intermediate- and long-term aggregate risk assessments were not performed because, based on the current use patterns, HED does not expect exposure durations that would result in intermediate- or long-term exposures. The EEC values are less than the lowest drinking water level of comparison (DWLOC) value of 59 ug/L (the population subgroup Children 1-2 years old) determined for the chronic scenario. Therefore, the EECs do not exceed HED's level of concern. **All aggregate exposure and risk estimates do not exceed HED's level of concern for the scenarios listed above.**

Occupational Exposure Estimates

For occupational handlers, the daily dermal exposure was compared to the NOAEL of 5 mg/kg/day from a prenatal (dermal) toxicity study in rats and the daily inhalation exposure was compared to the 23.6 mg/kg/day NOAEL from a subacute inhalation toxicity study in rats to estimate the risks from short- and intermediate-term exposures. Because the toxicity endpoints are similar for dermal and inhalation exposures, risks from these two routes are combined by the reciprocal MOE approach to provide a total risk. Chronic exposures are not expected for handlers. The target MOE for occupational handlers is 100. Total MOEs range from 104 (applying by open cab airblast sprayer, wearing baseline clothing, plus gloves) to 570 (applying by closed cockpit aircraft, wearing baseline clothing). **Therefore, handler risks DO NOT exceed HED's level of concern when handlers wear the personal protective equipment (PPE) and clothing listed on the proposed spiroxamine labels (i.e., long-sleeved shirt, long pants, waterproof gloves, and shoes plus socks).**

Because the use pattern proposed for spiroxamine involves foliar applications, there is a potential for short- and intermediate-term occupational postapplication exposure to scouts, harvesters and other field workers. The spiroxamine technical product has a Toxicity Category IV for Acute Inhalation and Primary Eye Irritation. However, for Acute Dermal and Primary Skin Irritation, the Toxicity Categories are II and I, respectively. Per the Worker Protection Standard (WPS), a 48-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category I. Therefore, **the interim REI of 24 hours appearing on the proposed spiroxamine label, KWG 4168 300 CS, is not in compliance with the WPS, and should be 48 hours.** Further, an assessment of postapplication risks to toxicity endpoints (systemic) identified by the HIARC, indicate that REIs longer than 48 hours are needed, depending upon the activity involved. Estimates of the short-/intermediate-term postapplication exposure from various agricultural activities with spiroxamine-treated crops were compared to the NOAEL of 5 mg/kg/day from a prenatal (dermal) toxicity study in rats to determine appropriate REIs. Chronic postapplication exposure is not expected. **Resulting REIs ranged from the day of treatment (i.e., day 0) for low exposure activities, such as irrigation,**

weeding and scouting, to 28 days for the very high exposure activity of cane turning of table grapes.

Recommendations for Tolerances

Provided that the data needs described in Sections 8.1 and 8.2 are met, the chemistry and toxicology data bases would support the establishment of the following permanent tolerances for residues of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety:

banana	3.0 ppm
grape	1.0 ppm
hop, dried cones	50.0 ppm.

The data needs described in Sections 8.1 and 8.2 concern the following topics for a conditional registration:

- residue analytical methods for bananas, grapes, and hops
- revised Section F for bananas, grapes, and hops.

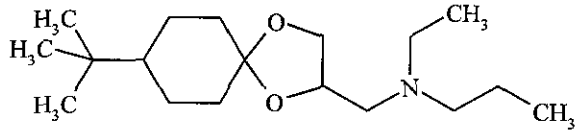
The data needs described in Sections 8.1 and 8.2 concern the following topics for continued registration:

- EPA method validation for bananas, grapes, and hops
- storage stability data for bananas and hops
- supporting crop field trial information for bananas
- additional crop field trials for grapes, pending a deferral to BEAD
- review of wheat metabolism studies for hops.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Chemical Identity and Structure

IUPAC Name: 8-*tert*-butyl-1,4-dioxaspiro[4,5]decan-2-ylmethyl(ethyl)(propyl)amine
CAS Name: 8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine
CAS Registry No.: 118134-30-8
Chemical Class: Fungicide
Empirical Formula: $C_{18}H_{35}NO_2$
Molecular Structure:



2.2 Physical and Chemical Properties of Spiroxamine

Spiroxamine exists as diastereomers A and B at a ratio of 50.68% and 44.22%, respectively. Both diastereomers are pesticidally active. There is no significant potential for formation of an impurity of special concern, such as chlorinated dioxins, nitrosamines, or hexachlorobenzene.

TABLE 2.2. Physicochemical Properties

Parameter	Value
Boiling point/boiling range	329°C @ 1013.25 hPa
pH	9.9 (suspension of 1 g in 50 ml water)
Density	0.93 g/ml @ 20°C
Water solubility (20°C)	>200 g/L for both diastereomers at pH 3. 470 mg/L and 340 mg/L for diastereomers A and B, respectively, at pH 7. 14 mg/L and 10 mg/L for diastereomers A and B, respectively, at pH 9.
Solvent solubility (g/L at 20°C)	>200 g/L in any of 11 organic solvents, which are: n-hexane, toluene, dichloromethane, 2-propanol, 1-octanol, polyethyleneglycol, ethanol, acetone, dimethylformamide, ethyl acetate, and acetonitrile.
Vapor pressure at 20°C	Diastereomer A: 4.0×10^{-5} hPa. Diastereomer B: 5.7×10^{-5} hPa.
Dissociation constant (pK_a)	pK = 7.9 @ 20°C in aqueous system containing 40% 2-propanol.

TABLE 2.2. Physicochemical Properties	
Parameter	Value
Octanol/water partition coefficient Log(K_{OW})	Diastereomer A: 610 (log P_{ow} = 2.79) at pH 7 @ 20°C. Diastereomer B: 960 (log P_{ow} = 2.98 at pH 7 @ 20°C.
UV/visible absorption spectrum	Does not show a maximum absorbance in the range of 200 to 400 nm.

2.3 Physical/Chemical Properties Characterization

Technical spiroxamine is a liquid. It is soluble in water, with solubility decreasing with increasing pH. It is soluble in organic solvents. Because the technical grade of the active ingredient (TGAI) is alkaline (pH 9.9), the TGAI is a skin sensitizer. The TGAI induces local irritation by all routes of administration. Local irritation is considered the cause for most of its toxic effects and clinical signs. The vapor pressure is very low (4.0-5.7 x 10^{-5} hPA), indicating that re-entry can occur relatively soon after application. The TGAI is formulated as emulsifiable concentrates and diluted in water for multiple applications as foliar sprays.

3.0 HAZARD CHARACTERIZATION

The existing toxicological database for spiroxamine supports the establishment of permanent tolerances for residues of spiroxamine in/on the RACs resulting from the proposed uses.

3.1 Hazard Profile

Spiroxamine is a fungicide that acts as an inhibitor of the sterol-biosynthesis in target fungi. Spiroxamine has strong irritant properties. Acute studies showed irritation. However, the toxicity categories were higher in the acute studies because the study design allows for a single dose and the interval of 14 days which resulted in the probable resolution of some inflammation processes. Subchronic and chronic studies show clear irritation characterized by hyperkeratosis in the esophagus and forestomach.

Acute toxicity

Spiroxamine has a moderate to low acute toxicity by the dermal (category II), oral (category III) and inhalation (category IV) routes. It is highly irritating to the skin (category I) but not to the eye (category IV), and it is a skin sensitizer. Acute toxicity of spiroxamine is presented in Table 3.1.1 below, followed by the toxicity profile of spiroxamine in Table 3.1.2.

Table 3.1.1. Acute Toxicity Data on Spiroxamine Technical.

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100/ Acute oral toxicity	45090125	LD50 (M) = > 595 mg/kg LD50 (F) = > 500 mg/kg	III
870.1200/ Acute dermal toxicity	45090128	LD_{50} (M) = > 1600 mg/kg LD_{50} (F) = > 1068 mg/kg	II
870.1300/ Acute inhalation toxicity	45090130	LC_{50} (M) = >2.772 mg/L LC_{50} (F) = >2.029 mg/L	IV
870.2400/ Acute eye irritation	45090132	Non Irritant	IV
870.2500/ Acute dermal irritation	45090132	Severely irritating	I
870.2600/ Skin sensitization	45090205	Sensitizer	N/A

Subchronic toxicity

Subchronic studies show that the target organ of spiroxamine toxicity is the liver. Subchronic studies were characterized by slight to mild hepatotoxicity, with associated elevation in liver enzymes, since the target organ of spiroxamine toxicity is clearly the liver. Effects in rats were seen at the LOAEL of 54.9 mg/kg/day (males) and in dogs at the LOAEL of 16.19 mg/kg/day (males). Toxicity to the liver was also noted in the 28-day inhalation toxicity study in rats at the LOAEL of 140.5 mg/kg/day. Mucous membranes of the esophagus and forestomach were keratinized and hyperplastic due to the strong irritant properties of spiroxamine.

Chronic toxicity

Long term administration of spiroxamine in the dog resulted in hepatocytomegaly, cataracts, and liver discoloration. In the rat, it resulted in an increased mortality in females, decreased body weights and body weight gains in both sexes, and increased esophageal hyperkeratosis in both sexes, while in the mouse, chronic administration resulted in uterine nodules, hyperplasia in the adrenal gland of males, hyperkeratosis in the esophagus, forestomach, and tongue of females, and acanthosis in the pinnae and tails of females.

Developmental and Reproduction

In rats, developmental effects entailed delayed ossification. Developmental effects were not seen in rabbits. There was no evidence of increased susceptibility of the young animals following exposure to spiroxamine in any developmental toxicity studies in the database. However, in the 2-generation reproduction study in rats, susceptibility could not be assessed because of the lack of data regarding the second generation.

Neurotoxicity

There was evidence of mild spiroxamine-induced neurotoxicity characterize by piloerection and slight to moderate gait incoordination, and FOB effects of decreased forelimb grip strength and

foot splay in males in the acute neurotoxicity study. No neuropathology was seen in either the acute or subchronic toxicity studies in rats and no neurotoxicity was detected in the subchronic study.

Carcinogenicity
Spiroxamine has no carcinogenic potential, as indicated in both the rat and the mouse carcinogenicity studies. It is "not likely" to be a human carcinogen based on the lack of evidence of carcinogenicity in both the rat and the mouse.

Mutagenicity
Spiroxamine has no mutagenicity potential, based on several *in vivo* and *in vitro* studies.

Metabolism
In rat metabolism and pharmacokinetics studies, oral absorption of spiroxamine was at least 60-70% and began immediately after administration with peak plasma concentrations at 1.5-2 hours post-dose at 1 mg/kg, and delayed to 8 hours at 100 mg/kg. More than 97% of the recovered radioactivity was excreted via urine and feces within 48 hours in all dose groups and more than 80% within 24 hours. Renal excretion accounted for the majority of the radioactivity (1.8:1 urine:feces on average).

Table 3.1.2. Toxicology Profile for Spiroxamine Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 **90-Day oral toxicity rodents (rats) (a.i.)**	45254104,45090231, 45090232 (1992-1995) Acceptable/Guideline Doses:0, 25, 125, 625 ppm M: 0, 1.9, 9.3, 54.9/ mg/kg/day F: 0, 2.7, 13.2, 75.1 mg/kg/day	NOAEL = M: 9.3, F: 13.2 mg/kg/day LOAEL = M: 54.9, F: 75.1 mg/kg/day based on decreased body weights and body weight gains in both sexes, hyperkeratosis and hyperplasia/hypertrophy in the esophagus of both sexes and hyperkeratosis in the forestomach of males. Minimal to marked hyperkeratosis in the tongue of both sexes. Slight multifocal hyperplasia in the urinary bladder of both sexes. Minimal to slight hyaline droplet degeneration in the liver in males.
870.3100 **90-Day oral toxicity rodents (rats)** (Metabolite KWG 4168 N-oxide)	45254116 & 45254128 (1998-2000) Acceptable/Guideline Doses: 0, 25, 125, 625 ppm M: 0, 1.7, 8.8, 45.0 mg/kg/day F: 0, 1.9, 9.7, 53.6 mg/kg/day	NOAEL = M: 8.8, F: 9.7 mg/kg/day LOAEL = M: 45.0, F: 53.6 mg/kg/day based on hyperkeratosis in the esophagus and forestomach.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3150 90-Day oral toxicity in nonrodents (dogs)	45090209, 45254101 (1991-1994) Acceptable/Guideline Doses: 0, 25, 750, 1500 ppm M:0, 0.66, 20.02, 42.76 mg/kg/day F: 0, 0.78, 21.29, 43.69 mg/kg/day Supplementary study for 15 weeks (MRID 45090210): Doses of 0, 150, 250, or 500 ppm M: 0, 4.84, 9.16, 16.19 mg/kg/day F: 0, 5.45, 8.92, 15.05 mg/kg/day	NOAEL = M: 16.19, F: 15.05 mg/kg/day LOAEL = M: 20.02, F: 21.29 mg/kg/day based on decreased albumin in females, increased absolute and relative liver weights in males, and increased diffuse hepatocytomegaly in males.
870.3200 21/28-Day dermal toxicity (rabbit)	45090211 (Rabbit) (1995) Acceptable/Guideline Doses: 0, 0.5, 1 and 5 mg/kg/day Supplemental Study No. T5055456 Doses: 0, 0.05, 0.2 mg/kg/day	NOAEL = 0.2 mg/kg/day LOAEL = 0.5 mg/kg/day based on erythema at the application site.
870.3465 28-Day inhalation toxicity (rats)	45090302, 45090301, 45254107 (1990-1997) Acceptable/None-Guideline Doses: 0, 14.3, 87.0, and 518.4 mg/m^3 (Analytical Concentration)	NOAEL = 23.6 mg/kg/day (0.087 mg/L) LOAEL = 140.5 mg/kg/day (0.518 mg/L) based on decreased body weights and body weight gains, increased incidences of clinical signs of toxicity and dermal irritation, thymic atrophy, and toxicity to the skin, respiratory system, and liver.
870.3700a Prenatal (oral) developmental in rodents (rats)	45254103, 45090219, 45254115, and 45090220 (1992-1995) Acceptable/Guideline Doses: 0, 10, 30, or 100 mg/kg/day	Maternal NOAEL = 30 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weights, body weight gains, and food consumption. Developmental NOAEL = 30 mg/kg/day LOAEL = 100 mg/kg/day based on increased incidence of delayed skeletal development (incomplete ossification) of the os interparietal (fetal and litter incidences) and os parietale (fetal incidences).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a Prenatal (dermal) developmental in rodents (rats)	45090217, 45090218, and 45090216 (1993) Acceptable/Guideline Doses: 0, 5, 20, or 80 mg/kg/day	Maternal (Systemic) NOAEL 5 = mg/kg/day LOAEL (Systemic) = 10 mg/kg/day based on decreased body weight gains. Maternal (Dermal) NOAEL <5 = mg/kg/day LOAEL (Dermal) = 5 mg/kg/day based on very slight erythema and/or slight scaling of skin. Developmental NOAEL = 20 mg/kg/day LOAEL = 80 mg/kg/day based on the increased fetal and litter incidence of incomplete/non-ossification of the os occipital and the increased non-ossification of the left distal phalanx of digit #4 of the forelimb.
870.3700b Prenatal developmental in nonrodents (rabbits)	45090221, 45254105 (1995-2000) Acceptable/Guideline Doses: 0, 5, 20, or 80 mg/kg/day	Maternal NOAEL = 20 mg/kg/day LOAEL = 80 mg/kg/day based on mortality, clinical signs of toxicity (encrusted mouth, anal prolapse, and little/soft feces), decreased body weight gains, and decreased food consumption. Developmental NOAEL = 80 mg/kg/day LOAEL: Not Achieved
870.3800 Reproduction and fertility effects (rats)	45090222 and 45254102 (1993) Unacceptable /Guideline Doses: 0, 20, 80, or 300 ppm M: 0, 2.5, 10.8, 44.8 mg/kg/day F: 0, 2.7, 11.9, 48.8 mg/kg/day	Parental/Systemic NOAEL = M: 2.5, F: 2.7 mg/kg/day LOAEL = M: 10.8, F: 11.9 mg/kg/day based on decreased food consumption during lactation and on increased incidences of esophageal hyperkeratosis in females. Reproductive NOAEL = M: 44.8, F: 48.8 mg/kg/day LOAEL = Not achieved. Offspring NOAEL (tentative) = M: 10.8, F: 11.9 mg/kg/day LOAEL (tentative) = M: 44.8, F: 48.8 mg/kg/day based on decreased litter size and pup weight and increased clinical signs of toxicity in the F1 generation.
870.4100a Chronic toxicity rodents (rats)	**See 870.4200 Carcinogenicity rats MRID # 45254111**	

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity dogs	45090214 (1995) Acceptable/Guideline Doses:0, 25, 75, 1000, 2000 ppm M: 0, 0.66, 2.47, 28.03, 56.88 mg/kg/day F: 0, 0.76, 2.48, 25.84, 52.39 mg/kg/day	NOAEL = M: 2.47, F: 2.48 mg/kg/day LOAEL = M: 28.03, F: 25.84 mg/kg/day based on hepato/ cytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males.
870.4200 Carcinogenicity rats	45090213 (1994) Acceptable/Guideline Doses: 0, 10, 70, or 490 ppm M: 0, 0.61, 4.22, 32.81 mg/kg/day F: 0, 0.77, 5.67, 43.04 mg/kg/day	NOAEL = M: 4.22, F: 5.67 mg/kg/day LOAEL = M: 32.81, F: 43.04 mg/kg/day based on increased mortality in females, decreased body weights and body weight gains in both sexes, and increased esophageal lesions in both sexes. No evidence of carcinogenicity.
870.4300 Carcinogenicity mice	45254111 (1997) Acceptable/Guideline Doses: 0, 160, or 600 ppm Males: 0, 41.0,149.8 mg/kg/day Females: 0, 46.6, 248.1 mg/kg/day	NOAEL = M: 41.0, F: 64.6 mg/kg/day LOAEL = M: 149.8, F: 248.1 mg/kg/day based on uterine nodules, hyperplasia in the adrenal gland of males, hyperkeratosis in the esophagus, forestomach, and tongue of females, and acanthosis in the pinnae and tails of females. No evidence of carcinogenicity.
870.4300 Carcinogenicity mice	45090215 (1995) Acceptable/Guideline Doses: 0, 20, 160, 480 ppm Males: 0, 4.5, 36.7, 59.3 mg/kg/day Females: 0, 7.8, 59.5, 102.6 mg/kg/day	NOAEL = M:36.7, F:59.5 mg/kg/day LOAEL = M: 59.3, F: 102.6 mg/kg/day based on skin desiccation, hyperkeratosis, acanthosis, and acantholysis in the esophagus, tongue, tail, and/or pinnae. No evidence of carcinogenicity.
Gene Mutation 870.5100 Ames Test	45090223 (11/16/90) Acceptable/Guideline (a.i.)	Negative, ± S9 up to cytotoxic 1000 µg/plate.
Cytogenetics 870.5395	45090225 (03/22/91) Acceptable/Guideline (a.i.)	Negative, at clinically toxic i.p. dose.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Mammalian Cells in Culture 870.5300	45090224 (09/26/91) Acceptable/Guideline (a.i.)	Negative, ± S9 up to cytotoxic /precipitation 200 µg/mL.
Chromosome Aberrations 870.5375	45090226 (06/30/95) Acceptable/Guideline (a.i.)	Negative, ± S9 up to cytotoxic doses.
Unscheduled DNA Synthesis 870.5550	45090227 (01/16/91) Acceptable/Guideline (a.i.)	Negative, ± S9 up to severe cytotoxicity.
870.6200a Acute neurotoxicity screening battery	45090206 (1994) Acceptable/Guideline Doses:0, 10, 30, 100, 220 mg/kg	NOAEL = 10 mg/kg LOAEL = 30 mg/kg based on clinical signs (piloerection and slight to moderate gait incoordination) and FOB effects (decreased forelimb grip strength and foot splay) in males.
870.6200b Subchronic neurotoxicity screening battery	45090212 (1995) Acceptable/Guideline Doses: 0, 35, 155, 700 ppm M: 0, 2.4, 10.6, 48.5 mg/kg/day F: 0, 2.5, 11.1, 50.6 mg/kg/day	NOAEL = M: 10.6, F: 11.1 mg/kg/day LOAEL = M: 48.5, F: 50.6 mg/kg/day based on decreased body weight gain, food consumption (males), and hyperkeratosis in the stomach, esophagus, and tongue.
870.7485 Metabolism and pharmacokinetics (rats)	45090228 (1995) Acceptable/Guideline Doses: 1, 100 mg/kg [Cyclohexyl-1-^{14}C] KWG 4168	Absorption was at least 60-70% and began immediately after administration with peak plasma concentrations at 1.5-2 hours post-dose at 1 mg/kg, and delayed to 8 hours at 100 mg/kg. More than 97% of the recovered radioactivity was excreted via urine and feces within 48 hours in all dose groups and more than 80% within 24 hours. Renal excretion accounted for the majority of the radioactivity (1.8:1 urine:feces on average).
870.7600 Dermal penetration (rats)	45254129 (1994) Acceptable/Guideline Doses: 25, 2.5, 0.25 mg [1,3-dioxolane-4-^{14}C] KWG 4168	Dermal Absorption Factor: 52.5% at 8 hours.

3.2 FQPA Considerations

On October 7, 2003, the HED HIARC evaluated the potential for increased susceptibility of infants and children from exposure to spiroxamine according to the February 2002 OPP 10X guidance document. The HIARC concluded that an additional 3X database uncertainty factor be applied due to the lack of an acceptable 2-generation reproduction study. There are no concerns or residual uncertainties for prenatal toxicity. On this basis the HIARC concluded that the special FQPA Safety Factor be reduced to 1X (Memo, A. Assaad, 11/14/2003; TXR NO. 0052237). Likewise, the spiroxamine risk assessment team evaluated the quality of the exposure data; and, based on these data, agreed that the special FQPA SF could be reduced to 1X. The recommendation is based on the following:

•There are no concerns for residual uncertainty for prenatal toxicity in the available developmental studies. However, susceptibility could not be assessed for postnatal toxicity due to the lack of an acceptable 2-generation reproduction study. The HIARC determined that a 3X database uncertainty factor is required for the lack of an acceptable 2-generation reproduction study.

•A 3X (as opposed to 10X) was determined to be sufficient because the available data from the 1-generation shows offspring effects occurring at doses higher than the dose that caused parental effects and the dose (2.5 mg/kg/day) used for driving the chronic RfD is approximately 3-fold lower than the offspring NOAEL (10.8 mg/kg/day). The HIARC determined that the 3X UF_{DB} should be applied only to the chronic dietary risk assessment because the required study (2-generation reproduction toxicity study) could provide an endpoint applicable to chronic exposure scenario, but not for an acute exposure scenario.

•There was no evidence for quantitative or qualitative susceptibility following oral or dermal exposures to rats *in utero* or oral exposure to rabbits *in utero*.

•Following oral exposures to rats, developmental effects (skeletal variations) were seen only in the presence of maternal toxicity. Following dermal exposure to rats, developmental toxicity occurred at doses higher than those causing maternal toxicity.

•Since conservative assumptions were used in the water models where environmental fate data are lacking, the dietary drinking water exposure assessment will not underestimate the potential risks for infant and children.

•The acute and chronic dietary food exposure assessment utilizing partially refined inputs and 100% crop treated data will not underestimate the potential risks to infants and children.

•The are no residential uses; therefore, residential exposure assessment was not

considered.

3.3 Dose-Response Assessment

On October 7, 2003, the HIARC evaluated the toxicology database for spiroxamine with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational exposure/ risk assessments. The doses and toxicological endpoints selected for various exposure scenarios are discussed below and summarized in Table 3.3.

Acute Dietary Endpoint: No suitable study was identified in the toxicology database for the category of Females 13-50 years old. An acute oral neurotoxicity study was used to select the dose and endpoint for establishing the aRfD of 0.1 mg/kg/day (based on a NOAEL of 10 mg/kg) for the general population. A LOAEL of 30 mg/kg was based on clinical signs (piloerection and slight to moderate gait incoordination) and FOB effects (decreased forelimb grip strength and foot splay) in males. This endpoint was selected from an oral single exposure study by the oral route and the effects were observed day 0-1 post-dosing; thus, this study is considered appropriate for acute dietary exposure for all populations. A 100-fold uncertainty factor (10X interspecies and 10X intraspecies) was applied.

Chronic Dietary Endpoint: The cRfD of 0.0083 mg/kg/day is based on a NOAEL of 2.5 mg/kg/day based on hepatocytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males at a LOAEL of 28.03 mg/kg/day in a chronic oral toxicity study in dogs. A 300-fold uncertainty factor (10X for interspecies extrapolation, 10X for intraspecies variations, and 3X UF_{DB} for the lack of an acceptable 2-generation reproduction study) was applied.

Carcinogenicity: Characterized as "not likely" to be a human carcinogen based on lack of increased tumor incidence in the rat and mouse carcinogenicity studies.

Incidental Oral: Since there are no residential uses, endpoints were not selected for incidental oral exposure.

Dermal Penetration: A dermal penetration study in rats identified a dermal absorption factor of 52.5% at 8 hours.

Dermal Exposure: For the dermal short- and intermediate terms a dermal prenatal toxicity study in rats was used to set the endpoint of 5 mg/kg/day (maternal NOAEL), based on decreased body weight gains at 20 mg/kg/day (LOAEL). The duration and the route of administration are appropriate for risk assessment since the study was conducted by dermal application of the test material. The database contains a 21-day dermal toxicity study in the rabbit (MRID 45090211) with a much lower NOAEL (0.2 mg/kg/day); however, this study was not used because the only

effect seen was erythema at the site of application (the only dermal effect); no systemic effects were observed in this study. For the dermal long-term endpoint, the chronic oral toxicity study in dogs was used to set the endpoint. The NOAEL is 2.5 mg/kg/day, based on the LOAEL of 28.03 mg/kg/day (see chronic exposure). This dose, endpoint, and study were selected to address the concern for hepatotoxicity following repeated oral dose; a 53% dermal absorption factor should be used in route-to-route extrapolation.

Inhalation Endpoint: For short- and intermediate-term inhalation, a subchronic inhalation study in the rat was used to set the endpoint. The NOAEL is 23.6 mg/kg/day, based on decreased body weights and body weight gains, increased incidences of clinical signs of toxicity and dermal irritation, thymic atrophy, and toxicity to the skin, respiratory system, and liver, at 140 .5 mg/kg/day (LOAEL). This study is appropriate for the route and duration of exposure concerns. For the inhalation long-term endpoint, the chronic oral toxicity study in dogs was used to set the endpoint of 2.5 mg/kg/day (NOAEL) based on the LOAEL of 28.03 mg/kg/day (see chronic exposure). This dose, endpoint, and study were used for long-term exposure risk assessment to address concern for hepatotoxicity following repeated exposure. Absorption via inhalation is assumed to be equivalent to oral absorption.

MOE for Occupational Risk Assessments: For **occupational exposure short-, intermediate-, and long-term inhalation** and **dermal** exposure risk assessments, a MOE of 100 is adequate. This is based on the conventional uncertainty factor of 100X, which includes the 10X for intraspecies extrapolation and 10X for interspecies variation. No residential uses are proposed for spiroxamine at the present time.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.3.

Table 3.3. Summary of Toxicological Doses and Endpoints for Spiroxamine.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	No suitable study was identified in the toxicology database.		
Acute Dietary (General population including infants and children)	NOAEL = **10** mg/kg UF = **100** **Acute RfD = 0.1** mg/kg	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = **0.1** mg/kg	**Acute neurotoxicity in rats.** LOAEL = 30 mg/kg based on clinical signs (piloerection and slight to moderate gait incoordination) and FOB effects (decreased forelimb grip strength and foot splay) in males on Day 0-1.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All populations)	NOAEL= **2.5** mg/kg/day UF = **300** **Chronic RfD** = **0.0083** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD FQPA SF = **0.0083** mg/kg/day	**Chronic oral toxicity study in dogs.** LOAEL = 28.03/25.84 mg/kg/day [M/F] based on hepatocytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males.
Short and Intermediate-Term Incidental Oral Exposure	**No Residential Uses are Proposed for Spiroxamine**		
Dermal Exposure: Short and Intermediate-Term	Dermal NOAEL = **5** mg/kg/day	**Residential** LOC for MOE = **N/A** **Occupational** LOC for MOE = **100**	**Prenatal Toxicity study in Rats (Dermal)** The maternal LOAEL (systemic) is 20 mg/kg/day based on decreased body weight gains.
Dermal Exposure: Long-Term	Oral NOAEL= **2.5** mg/kg/day (53% Dermal Absorption Factor)	**Residential** LOC for MOE = **N/A** **Occupational** LOC for MOE = **100**	**Chronic oral toxicity study in dogs.** LOAEL = 28.03/25.84 mg/kg/day [M/F] based on hepatocytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males.
Short-Term Inhalation (1 to 30 days)	Inhalation NOAEL= 0.087 mg/L= **23.6** mg/kg/day	**Residential** LOC for MOE = **N/A** **Occupational** LOC for MOE = **100**	28-day Inhalation Toxicity Study in Rats. LOAEL = 0.518 mg/L= **140.5** mg/kg/day based on decreased body weights and body weight gains, increased incidences of clinical signs of toxicity and dermal irritation, thymic atrophy, and toxicity to the skin, respiratory system, and liver.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Inhalation (1 to 6 months)	Inhalation NOAEL= 0.087 mg/L= **23.6** mg/kg/day	**Residential** LOC for MOE = **N/A** **Occupational** LOC for MOE = **100**	**Subchronic Inhalation Toxicity Study in Rats.** LOAEL = 0.518 mg/L= **140.5** mg/kg/day based on decreased body weights and body weight gains, increased incidences of clinical signs of toxicity and dermal irritation, thymic atrophy, and toxicity to the skin, respiratory system, and liver.
Long-Term Inhalation (>6 months)	Oral NOAEL= **2.5** mg/kg/day (100% Oral Absorption Factor)	**Residential** LOC for MOE = **N/A** **Occupational** LOC for MOE = **100**	**Chronic oral toxicity study in dogs.** LOAEL = 28.03/25.84 mg/kg/day [M/F] based on hepatocytomegaly, cataracts, and decreased albumin in males and females; liver discoloration and decreased triglycerides in females; and increased alanine aminotransferase in males.
Cancer (oral, dermal, inhalation)	"Not likely" to be a human carcinogen based on the lack of evidence of carcinogenicity in the rats and mice.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no-observed-adverse-effect-level, LOAEL = lowest-observed-adverse-effect-level, PAD = population-adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable.

3.4 Endocrine Disruption

Evidence of spiroxamine endocrine disruption was not indicated in the studies reviewed. EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, spiroxamine may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Proposed Uses

Spiroxamine is a new broad spectrum fungicide proposed for use on grapes, hops (US-grown and imported), and imported bananas to control powdery mildew infesting grapes and hops and black Sigatoka (*Mycosphaerella fijiensis*) infesting bananas. It belongs to a new class of pesticides known as spiroketalamines. Spiroxamine is a fungicide that acts as an inhibitor of the sterol-biosynthesis in target fungi.

Proposed Uses- Bananas, Grapes, and Hops

Bayer Corporation proposed uses on bananas, grapes and imported hops. IR-4 proposed uses on hops grown in the US. Multiple foliar spray applications will be made (twelve on imported bananas, two on grapes, four on hops in the US, and two on imported hops). The proposed seasonal application rates are 3.42 lb ai/A with a 0-day preharvest interval (PHI) for imported bananas, 0.70 lb ai/A with a 28-day PHI for grapes, 1.4 lb ai/A with a 12-day PHI for hops in the US, and 1.50 kg ai/ha (1.34 lb ai/A) with a 10-day PHI for imported hops.

Table 4.1. Summary of Directions for Use of Spiroxamine.

Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate, lb ai/A (kg ai/ha)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate, lb ai/A (kg ai/ha)	PHI (days)	Use Directions and Limitations
Banana						
Impulse® EC 800	Foliar broadcast spray; ground and aerial equipment	0.285 (0.320 kg ai/ha)	12[1]	3.42 (3.84 kg ai/ha)	0	Apply to control black Sigatoka (Mycosphaerella fijiensis). Applications may be made in 2.1-6.1 gal/A (20-57 L/ha) of an oil water emulsion. Applications may be made at 4-8 day intervals between odd and even numbered applications and at 18-24 day intervals between even and odd numbered applications.
Grape						
KWG 4168 300 CS Foliar Fungicide (EPA Reg. No. 3125-LLN)	Postemergence, foliar and broadcast, ground and aerial equipment	0.35	2	0.70	28	Use limited to CA. Up to two applications may be made to control powdery mildew in the period from shoot emergence until 28 days before harvest, with a minimum 28-day retreatment interval.
Hop in US						
KWG 4168 300 CS Foliar Fungicide (EPA Reg. No. 3125-LLN)	Postemergence foliar spray, ground equipment	0.35	4	1.4	12	The first application should be made when powdery mildew first appears and subsequent applications may be made at a 12-day retreatment interval. Apply in a minimum of 50 gal spray/A to obtain thorough coverage.
Hop in Germany						

Prosper 500EC, also known as KWG 4168 500 EC (Reg. No. 4337-60)	Postemergence foliar spray, ground equipment	0.31-0.67 (0.350-0.750 kg ai/ha)	2	1.34 (1.500 kg ai/ha)	10	Apply according to warning system, or when first symptoms of powdery mildew (*Sphaerotheca humuli*) are visible. Repeat at a spray interval of 6-10 days. Apply as a good coverage foliar spray. Use 0.7-1.5 liters product per ha in 1,400-3,000 liters water/ha, depending on the crop growth stage. Never use less than 600 liters water/ha (159 gal/A).

[1] An examination of the foreign labels show that they are consistent with the use directions described in Section B of the petition package. It is noted, however, that the foreign labels (excluding Mexico) do not specify a maximum seasonal rate or maximum number of applications. The Section B and the draft Mexican label specify a maximum of 12 applications.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Nature of the Residue - Plants

The nature of the residue in grapes and bananas is adequately defined. HED's Metabolism Assessment Review Committee (MARC) determined in a meeting on 10/15/03 that the residues to be included in the tolerance expression and risk assessment for plants are spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent.

Grapes and Bananas: Two metabolism studies, one using [cyclohexyl-1-^{14}C]spiroxamine and the other using [1,3-dioxolane-4-^{14}C]spiroxamine, were submitted for each crop. Metabolism of spiroxamine in grapes and bananas is similar. Spiroxamine was highly metabolized in both grapes and bananas, and the metabolic pathway and identified metabolites were in good agreement between the two radiolabeled test substances in both crops. The major metabolic process involved the cleavage of the ketal structure yielding the aminodiol and *tert*-butylcyclohexanone, which was further reduced to the corresponding alcohol, *tert*-butylcyclohexanol. The aminodiols remained unconjugated in grapes and bananas, while the hydroxylated cyclohexyl moieties (*tert*-butylcyclohexanol and diol metabolites) were completely conjugated. The major residues in both grapes and bananas were spiroxamine, *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane (also known as aminodiol), and *conjugated tert*-butylcyclohexanol. The grape metabolism studies provided data which suggest that only minor

translocation of residues occurred from the leaves to the fruit.

Hop: No plant metabolism data on hops were submitted. For a conditional registration of spiroxamine on hops and for establishment of a tolerance without a US registration, the grape metabolism data may be translated to support uses on hops. As a condition of registration and for continued importation, additional plant metabolism data are needed. In lieu of metabolism studies on hops (one for [cyclohexyl-1-^{14}C]spiroxamine and one for [1,3-dioxolane-4-^{14}C]spiroxamine), metabolism studies on three dissimilar crops which show similar metabolic routes would be adequate to support use on hops. Metabolism studies on grapes and bananas have been reviewed; the wheat metabolism studies have been submitted and are currently under review.

Nature of the Residue - Livestock

The proposed uses of spiroxamine on bananas, grapes, and hops do not trigger the requirements for livestock metabolism data because bananas, grapes and its processed commodities, and hops are currently not considered to be significant livestock feed items.

Residue Analytical Methods-Plants

A proposed enforcement method (Bayer AG Method No. 00407) for analysis of spiroxamine and its metabolites containing the aminodiol moiety in plants has been submitted. The method will be adequate for establishment of tolerances and conditional registrations when the confirmatory method is modified to use more than single-ion monitoring or an interference study is conducted, and when the analytical reference standard for *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane is sent to the National Pesticide Standards Repository. As a condition of registration (for continued registration) and for continuation of importation of bananas and hops, a method validation for Bayer AG Method No. 00407 must be conducted by EPA's laboratory.

Using the common moiety method (Bayer AG Method No. 00407), spiroxamine residues are converted to a single analyte, *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane (also known as aminodiol), which is derivatized to and measured as the di-trimethylsilyl derivative. All spiroxamine residues containing the aminodiol moiety are quantitated by gas chromatography/mass selective detector (GC/MSD) operated in a single-ion mode. The data-collection method used for the quantitation of residues in grape commodities from the field trial, processing, and storage stability studies is identical to the proposed enforcement method. Minor modifications were made for analysis of bananas and hops.

Table 4.2.1.1. Summary of Analytical Method in Plants.	
Matrix	banana, grape, raisin, grape juice, and hop
Method ID	Bayer AG Method No. 00407 (MRID 45090426)
Type	enforcement and data collection
Analytes (method detects)	spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety (a.k.a. aminodiol moiety), calculated as parent equivalents
Instrumentation	gas chromatography/mass selective detection (GC/MSD) operated in the single-ion-monitoring mode (measuring fragment-ion m/z 100).
Extraction	Residues in/on crops samples are extracted with acetone and/or acetone:water. The extract is acidified and heated at reflux which hydrolyzes residues of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety to aminodiol. Residues are evaporated to an aqueous remainder, and the co-extractives are removed by extraction with dichloromethane and ethyl acetate. The aqueous phase (which contains aminodiol residues) is cleaned up by chromatography on a polystyrene-divinyl benzene column and silylated to the di-trimethylsilyl (di-TMS) derivative for analysis.
ILV[2]	A successful ILV was conducted on grapes.
Radiovalidation (Extraction Efficiency)	Radiovalidation (extraction efficiency) was determined for grapes. The extraction efficiency was 89.3%.[1]
LOD[2]	0.002 ppm in grape juice; 0.005 ppm in/on grapes, raisins, banana fruit, and dried hop cones
LOQ[2]	0.02 ppm in grape juice; 0.05 ppm in/on grapes, raisins, banana fruit, and dried hop cones

[1] Extraction efficiency = (% total radioactive residues [TRR] extractable by the residue method) ÷ (% TRR extractable as determined in the metabolism study) x 100.

[2] ILV = independent laboratory validation, LOQ = limit of quantization, LOD = limit of detection.

Residue Analytical Methods-Livestock Commodities

No analytical method was submitted for livestock commodities. An analytical method for livestock commodities is not required since no livestock feed items are currently associated with the proposed uses on banana, grape, and hop.

Multiresidue Methods

FDA Multiresidue Protocol D (for non-fatty food) appears to be suitable for the analysis of spiroxamine (parent) in grapes. Spiroxamine was completely recovered (>80%) from grapes using Protocol D (without cleanup). Spiroxamine was not recovered (<30%) from the Florisil column cleanup test under Protocol E (for non-fatty food).

Storage Stability

Grape: Adequate storage stability data are available for grapes and its processed fractions. Residues of spiroxamine and its metabolite aminodiol are stable under frozen storage conditions (<-20°C) in grapes stored up to 585 days (19.2 months), grape juice stored up to 574 days (18.9 months), and raisins stored up to 529 days (17.4 months). The storage intervals for the residue samples were 61-302 days (2.0-9.9 months) for grapes, 280 days (9.2 months) for grape juice, and 271 days (8.9 months) for raisins.

Banana: No storage stability data were submitted for bananas. Until storage stability data on bananas stored frozen for 6 months can be provided, the storage stability data on grapes may be translated to bananas. The maximum storage interval of whole banana samples, from harvest to analysis, was 169 days (5.6 months).

Hop: Adequate storage stability data were submitted for hops grown in the US. The storage stability data show that residues of spiroxamine and its metabolite aminodiol are stable in/on dried hop cones stored frozen for up to 226 and 231 days, respectively. The maximum storage interval of US dried hop samples was 264 days (8.7 months).

Additional storage information is needed for imported hops. For MRIDs 46052804 and 46052805, dates of sampling and extraction were reported; dates of analysis should also be reported to verify that the samples were stored for ~19 months and ~6 ½ months, respectively. For MRID 46052804, storage stability data are needed for spiroxamine its metabolites containing the aminodiol moiety on dried hops for 19 months (or longer if the dates of analysis so indicate).

Crop Field Trial Data

A summary table of the results of the crop field trial studies can be found in the Appendix as Table 9.2. Based on the submitted data, residues of spiroxamine are likely to be present in/on samples of raw agricultural and processed commodities following foliar treatments.

Banana: The results of the banana field trials support the proposed RAC tolerance level of 3.0 ppm. In the submitted field trial data for bananas, the maximum residues of spiroxamine, as determined by the common moiety method, were 0.464 ppm in/on bagged whole bananas and 2.44 ppm in/on unbagged whole bananas harvested 0-day after the last of 12 applications of the 6.7 lb ai/gal EC formulation at 1X the maximum proposed seasonal rate. The residue decline data showed that residues of spiroxamine appear to decrease with increasing sampling PHI's. Washing and removing the peels from treated whole banana samples and measuring residues in the pulp reduced the total spiroxamine residues by average reduction factors of 8.2x (bagged samples) and 12.0x (unbagged samples).

Grape: The submitted CA residue data indicate that residues in CA from the proposed use on grapes will not exceed 1.0 ppm in grapes. In the submitted field trial data for grapes, the maximum residues of spiroxamine, as determined by the common moiety method, were 0.634 ppm in/on grape samples harvested 26-29 days following the last of two applications of the 2.5 lb ai/gal EC formulation at 1.0x the maximum proposed seasonal rate.

Hop: The results of the US and German hop field trials support the proposed RAC tolerance level of 50.0 ppm. The US tolerance of 50.0 ppm was proposed to harmonize with the European Community's proposed MRL of 50.0 ppm.

The maximum residues of spiroxamine, as determined by the common moiety method, were 10.90 ppm in/on treated samples of dried hop cones harvested 12-14 days after the last of four applications in the US of the 2.5 lb ai/gal EC formulation at 1.0X the maximum proposed seasonal rate. No residue decline data were submitted with the US studies.

Pending submission of the requested storage stability data, the available residue data for hops grown in Germany indicate that the maximum residues of spiroxamine, as determined by the common moiety method, were 30.0 ppm in/on treated samples of dried hop cones harvested 10 days after the last of two applications of the KWG 4168 500 EC formulation at 1.0X the maximum proposed seasonal rate. Residues in green hop cones in the German studies generally declined from 0 to 13 days.

Processed Food/Feed

Banana: There are no processed commodities from banana.

Grape: The submitted grape processing data are adequate and indicate that residues of spiroxamine may concentrate slightly in raisins (average processing factor of 1.3x) and decrease in juice (average processing factor of 0.67x) processed from grapes bearing detectable residues of spiroxamine. The processing study indicates that residues in grape juice and raisins from the proposed use on grapes will not exceed 1.0 ppm, which is the proposed tolerance level for grape; therefore, tolerances on juice and raisin are not required.

Hop: The raw agricultural commodity is defined as hop, dried cones. There are no processed commodities for hop.

Confined Accumulation in Rotational Crops

The proposed uses of spiroxamine on bananas, grapes, and hops do not trigger the requirements for confined and field rotational crop studies because bananas, grapes, and hops are typically not rotated with other crops.

Meat, Milk, Poultry, and Eggs

No livestock feeding studies have been conducted and no livestock tolerances have been proposed; none are required. There are currently no significant livestock feed items associated with the proposed uses of spiroxamine on bananas, grapes, or hops. Therefore, data pertaining to magnitude of the residue in meat, milk, poultry, and eggs are not required for the purpose of these petitions. The proposed uses on bananas, grapes, and hops fall under 40 CFR §180.6(a)(3).

International Harmonization

There are currently no Codex, Canadian, or Mexican MRLs or tolerances for spiroxamine. A proposal for registration of spiroxamine on hops in the European Community (Germany) with a maximum residue limit (MRL) of 50.0 ppm is concurrent with the proposal for US registration of spiroxamine on hops with a tolerance of 50.0 ppm. The US tolerance of 50.0 ppm was proposed to harmonize with the European Community's proposed MRL. International harmonization is not an issue at this time.

4.2.2 Dietary Exposure Analyses

Partially refined acute and chronic dietary risk assessments for spiroxamine were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 1.33), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to support Section 3 requests for spiroxamine on bananas, grapes, and hops. Tolerance level residues, average residues from field trial data, the concentration/reduction factors from processing studies, and 100% crop treated information were used. The acute (at the 95th percentile) and chronic dietary exposures were below HED's level of concern for the US population and all population subgroups. A cancer dietary risk assessment was not conducted because spiroxamine has no carcinogenic potential; it is "not likely" to be a human carcinogen based on the lack of evidence of carcinogenicity in both the rat and mouse carcinogenicity studies.

The highest exposed group for both acute and chronic assessments was children 1-2 years old. The CEC analysis indicated that bananas are the major residue contributor for the highest

exposed population group, children 1-2 years old. Data on projected market share or percent crop treated (% of imported bananas that are treated x % of total bananas that are imported) would further refine HED's exposure and risk estimates. For the chronic assessment, the residue level used for bananas was the average calculated for unbagged bananas, which had higher residues than bagged bananas. An average including both bagged and unbagged bananas would be lower. For the acute and chronic assessments, the residue level used for hops was the average residue of imported hops since residues on imported hops were higher than on US-grown hops. An average residue for hops including both US-grown hops and imported hops would be lower.

The results of the acute and chronic assessments are presented in Table 4.2.2.

Table 4.2.2. Summary of Dietary Exposure and Risk for Spiroxamine

Population Subgroup*	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.007352	7.4	0.00069	8.3	N/A[1]	N/A
All Infants (< 1 year old)	0.026898	27	0.001498	18	N/A	N/A
Children 1-2 years old	0.031173	**31**	0.00237	**29**		
Children 3-5 years old	0.021778	22	0.001287	16		
Children 6-12 years old	0.011131	11	0.00053	6.3		
Youth 13-19 years old	0.004913	4.9	0.00022	2.7		
Adults 20-49 years old	0.006017	6	0.00062	7.5		
Adults 50+ years old	0.006501	6.5	0.0007	8.5		
Females 13-49 years old	0.006156	6.2	0.0005	6.0		

[1] Not applicable.

4.2.2.1 Acute Dietary Exposure Analysis

The acute assessment was a partially refined deterministic assessment. Tolerances were used for the nonblended and partially blended raw agricultural commodities (i.e., 3.0 ppm for bananas and 1.0 ppm for grapes). For the processed commodities of grapes, the highest average field trial (HAFT) value of 0.613 ppm was used as the residue value, which was computer-multiplied by the processing factors (adjustment factors #1) of 0.67x for grape juice and 1.3x for raisins. For the blended commodity hops, the average residue value from the field trials for imported hops (16 ppm) was used. Data on projected market share or percent crop treated were not used. The acute dietary analyses for spiroxamine show that residues are below HED's level of concern for

the US population and all population subgroups. Exposure at the 95th percentile was 7.4% of the aPAD for the general US population and 31% of the aPAD for children aged 1-2 years, the most highly exposed population subgroup.

4.2.2.2 Chronic Dietary Exposure Analysis

The chronic assessment was a partially refined deterministic assessment. Average residue values from the field trials were used for bananas, grapes, and hops (i.e., 1.13 ppm for unbagged bananas, 0.17 ppm for grapes, and 16 ppm for imported hops.) The tolerance level for grapes (1.0 ppm) was used for grape leaves and wine. For the processed commodities of grapes, the average value of 0.17 ppm was used as the residue value, which was computer-multiplied by the processing factors (adjustment factors #1) of 0.67x for grape juice and 1.3x for raisins. Data on projected market share or percent crop treated were not used. The chronic dietary analyses for spiroxamine show that residues are below HED's level of concern for the US population and all population subgroups. Exposure was 8.3% of the cPAD for the general US population and 29% of the cPAD for children aged 1-2 years, the most highly exposed population subgroup.

4.3 Water Exposure/Risk Pathway

MARC Conclusion (October 15, 1998): The residues of concern in water are spiroxamine and two degradates: WAK 6301 [a.k.a. KWG-*N*-oxide; 8-(1,1-dimethylethyl)-*N*-ethyl-*N*-oxo-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine] and WAK 5708 [a.k.a. ECW 80511 and ECW 8046; 2-[(ethylpropylamino)methyl]-α,α-dimethyl-1,4-dioxaspiro[4,5]decane-8-acetic acid], calculated as parent equivalents. These metabolites were the only two degradates that appeared at levels greater than 10% of the applied parent, namely 11.8% for WAK 6301 and 10.8% for WAK 5708. The degradateWAK 6301 is more mobile than the parent and its half life in aerobic aquatic system is difficult to estimate, but it is likely to be less than 7 days. No information is available for WAK 5708 and its persistence could not be determined. However, the parent spiroxamine, compared to its metabolites, is relatively persistent in both soil and water, with estimated environmental half-life on the order of months or longer. Therefore, the drinking water assessment was conducted on the parent only and is not likely to underestimate exposure levels.

Dirk Young's memo (June 17, 2003) summarizes the tier 2 estimated environmental concentrations (EECs) for spiroxamine in drinking water when spiroxamine is used according to proposed labeling for hops and grapes. Table 7 summarizes the recommended EECs for use in human drinking water assessments. Actual values in the following Table 4.3 represent EECs derived from use on hops, which produced the highest EECs for the two proposed domestic uses.

Table 4.3. Tier II Drinking water EECs for Drinking Water

Surface Water Acute[a] EEC	Surface Water Chronic[b] EEC	Ground Water EEC
17.8 ppb	14. ppb	0.27 ppb

[a] Acute EEC represents the upper 1-in-10 year peak concentration.
[b] Chronic EEC represents the upper 1-in-10 year mean annual concentration.

EFED simulated two proposed uses of spiroxamine for hops and grapes using a standard Oregon hops scenario and a standard California grape scenario. For surface water calculations EFED used PRZM (3.12 beta) and EXAMS (2.98.04).

For Oregon hops PRZM/EXAMS simulations, spiroxamine was applied in a manner consistent with proposed labels– by aerial application, 4 times per year at maximum rate of 0.352 lb/acre (0.394 kg/ha) with a 12 day interval between applications. Resulting EEC values from PRZM/ EXAMS were reduced by the percent crop area factor of 0.87. Additionally, in order to get a better understanding of the variability caused by application dates, several different beginning application dates during summer months were examined.

For California grapes, spiroxamine was also applied in a manner consistent with proposed labels– by aerial application, 2 times per year at maximum rate of 0.352 lb/acre (0.394 kg/ha) with a 28 day interval between applications. Resulting EEC values from EXAMS were reduced by the percent crop area factor of 0.87. As with the hops calculations above, several different beginning application dates during summer months were examined. From the results, it is clear that the hops scenario is the more vulnerable of the two proposed spiroxamine uses.

Ground water concentrations were estimated with SciGrow, which is EFED's standard model for estimating groundwater concentrations of pesticides. According to standard EFED guidance, the following model inputs were used: an application rate of 0.352 lb/acre applied four times per year, a mean soil half life of 136 days, and the minimum Koc of 657 ml/g.

4.4 Residential Exposure/Risk Pathway

There are no current or proposed residential use sites for spiroxamine; therefore, a residential risk assessment was not performed.

4.5 Off Target Non-Occupational Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for spiroxamine.

The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Human health aggregate exposure /risk assessments were conducted for the following exposure scenarios: acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Residential aggregation is not required for spiroxamine, since residential site uses were not proposed; therefore, short-term aggregate risk assessments were not necessary for spiroxamine. Intermediate- and long-term aggregate risk assessments were not performed because, based on the current use patterns, HED does not expect exposure durations that would result in intermediate- or long-term exposures. Further, a cancer aggregate risk assessment was not performed because spiroxamine shows no evidence of carcinogenicity.

Since HED does not have ground or surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxicity endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate DWLOCs, the dietary food estimates (from DEEM-FCID, Version 1.33) were subtracted from the PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70 kg/2L (US population, adult male, and youth), 60 kg/2L (adult female), and 10 kg/L (infants and children).

For acute and chronic dietary exposure, HED is concerned when estimated dietary risk exceeds 100% of the aPAD and cPAD, respectively. HED's level of concern for residential oral, dermal and inhalation exposures are for MOEs <100.

5.1 Acute Aggregate Risk Assessment (Food and Drinking Water)

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of spiroxamine (food and drinking water). The acute assessment was a partially refined deterministic assessment. The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for the general U.S. population (7.4% of the aPAD) and all other population subgroups. The most highly exposed population subgroup is children 1-2 years old, at 31% of the aPAD. The EECs generated by EFED are less than HED's calculated DWLOCs for acute exposure to spiroxamine in drinking water. Therefore, the acute aggregate risk associated with the proposed use of spiroxamine does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 5.1 summarizes the acute aggregate exposure estimates to spiroxamine residues.

Table 5.1. Acute DWLOC Calculations for Spiroxamine.

Table 5.1. Acute DWLOC Calculations.						
Population Subgroup[1]	Acute Scenario					
	aPAD mg/kg/day	Acute Food Exp mg/kg/day	Max Acute Water Exp mg/kg/day[2]	Ground Water EEC (ppb)[3]	Surface Water EEC (ppb)[3]	Acute DWLOC (µg/L)[4]
U.S. Population	0.1	0.00735	0.092648	0.27	18	3200
All Infants (<1year)	0.1	0.026898	0.073102	0.27	18	730
Children 1-2 years	0.1	0.031173	0.068827	0.27	18	690
Children 3-5 years	0.1	0.021778	0.078222	0.27	18	780
Children 6-12	0.1	0.011131	0.088869	0.27	18	890
Youth 13-19	0.1	0.00491	0.095087	0.27	18	2900
Adults 20-49	0.1	0.00602	0.093983	0.27	18	3300
Females 13+	0.1	0.00616	0.093844	0.27	18	2800
Adults 50+ years	0.1	0.0065	0.093499	0.27	18	3200

[1] Body weights (70 kg adult male; 60 kg adult female; 10 kg child).

[2] Maximum acute water exposure (mg/kg/day) = [(acute PAD (mg/kg/day) - acute food exposure (mg/kg/day)]

[3] The crop producing the highest level was used.

[4] Acute DWLOC(µg/L) = $\frac{\text{[maximum acute water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

5.2 Chronic Aggregate Risk Assessment (Food and Drinking Water)

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of spiroxamine (food and drinking water). There are no proposed uses of spiroxamine that would result in residential exposure. The chronic assessment was a partially refined deterministic assessment. Chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (8.3% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at 29% of the cPAD. The EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to spiroxamine in drinking water. Therefore, the chronic aggregate risk associated with the proposed use of spiroxamine does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 5.2 summarizes the chronic aggregate exposure estimates to spiroxamine residues.

Table 5.2. Chronic DWLOC Calculations for Chronic Exposure to Spiroxamine.

Table 5.2. Chronic DWLOC Calculations.						
Population Subgroup[1]	Chronic Scenario					
	cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[2]	Ground Water EEC (ppb)[3]	Surface Water EEC (ppb)[3]	Chronic DWLOC (µg/L)
U.S. Population	0.0083	0.0007	0.007609	0.27	14	270
All Infants (<1year)	0.0083	0.0015	0.006802	0.27	14	70
Children 1-2 years	0.0083	0.00237	0.00593	0.27	14	60
Children 3-5 years	0.0083	0.00129	0.007013	0.27	14	70
Children 6-12	0.0083	0.0005	0.007774	0.27	14	80
Youth 13-19	0.0083	0.0002	0.008077	0.27	14	240
Adults 20-49	0.0083	0.0006	0.00768	0.27	14	270
Females 13+	0.0083	0.0005	0.007803	0.27	14	230
Adults 50+ years	0.0083	0.0007	0.007598	0.27	14	270

[1] Body weights (70 kg adult male; 60 kg adult female; 10 kg child).

[2]Maximum Chronic Water Exposure (mg/kg/day) = [Chronic PAD (mg/kg/day) - Chronic Dietary Exposure (mg/kg/day)]

[3]The crop producing the highest level was used.

[4] Chronic DWLOC(µg/L) = [maximum chronic water exposure (mg/kg/day) x body weight (kg)] / [water consumption (L) x 10^{-3} mg/µg]

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether spiroxamine has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to spiroxamine and any other substances and spiroxamine does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that spiroxamine has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 OCCUPATIONAL EXPOSURE

An occupational exposure assessment for spiroxamine was prepared in an HED memorandum dated 11/18/2003 (Memo, J. Arthur; D287042).

7.1 Occupational Handler

There is a potential for exposure to spiroxamine during mixing, loading, and application activities. Handler's exposure and risk were estimated for the following scenarios: (1) mixer/loader: open mixing liquid for aerial, (2) mixer/loader: open mixing liquid for groundboom, (3) mixer/loader: open mixing liquid for airblast, (4) aerial application of liquid: closed cab, (5) ground-boom application: open cab, (6) airblast application: open cab, and (7) flagging for aerial applications. Flaggers for aerial application are assessed for 350 acres per day application, because a larger number of acres treated would likely require pilot-activated mechanical flagging or Global Positioning Systems, and not human flaggers.

The minimum level of PPE for handlers is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. Exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) were used with other HED standard values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures.

For handlers, daily dermal and inhalation exposures were calculated separately. The daily dermal exposure was compared to the NOAEL of 5 mg/kg/day from a prenatal (dermal) toxicity study in rats (endpoint: maternal decreased body weight gain) to determine the risk for short-term and intermediate-term dermal exposures. The daily inhalation exposure was compared to the 23.6 mg/kg/day NOAEL from a subacute inhalation toxicity study in rats (endpoint: decreased body weight and body weight gains, increased incidences of clinical signs of toxicity and dermal irritation, thymic atrophy, and toxicity to the skin, respiratory system and liver) to estimate the risk from short- and intermediate-term exposures. Because the toxicity endpoints are similar for dermal and inhalation, exposure from these two routes are combined to provide a total risk, by the reciprocal MOE approach. Chronic exposures are not expected for handlers. The target MOE for occupational handlers is 100. As can be seen in Table 7 below, total MOEs range from 104 (applying by open cab airblast sprayer, wearing baseline clothing, plus gloves) to 570 (applying by closed cockpit aircraft, wearing baseline clothing). **Therefore, handler risks DO NOT exceed HED's level of concern when handlers wear the personal protective equipment (PPE) and clothing listed on the proposed spiroxamine labels (i.e., long-sleeved shirt, long pants, waterproof gloves, and shoes plus socks).**

Table 7. Short- and Intermediate-Term Exposure and Risk Estimates for Occupational Handlers

PHED Scenario Selected from PSEG (8/98)	Personal Protective Equipment	Exposure Route	Application Rate[1]	Acres Treated (acres/ day)	PHED Unit Exposure (mg/lb ai)	PHED Data Confid Level	Absorp Factor[2]	Body Wt (kg)	Daily Dose[3] (mg/kg/day)	Dermal Risk (MOE)[4]	Inhalation Risk (MOE)[4]	Total Risk (MOE)[5]
1. Mix/load : Open Mixing Liquid for Aerial	Long Sleeves, Long Pants	Dermal	0.352 lb ai/acre	350	2.9	High	100%	70	5.1	1	11,000	1
		Inhalation			0.0012	High			0.0021			
1a. Mix/load : Open Mixing Liquid for Aerial	Long Sleeves, Long Pants, **Gloves**	Dermal	0.352 lb ai/acre	350	0.023	High	100%	70	0.04	120	11,000	120
		Inhalation			0.0012	High			0.0021			
2. Mix/load : Open Mixing Liquid for Airblast	Long Sleeves, Long Pants	Dermal	0.352 lb ai/acre	40	2.9	High	100%	70	0.58	9	98,000	10
		Inhalation			0.0012	High			0.00024			
2a. Mix/load : Open Mixing Liquid for Airblast	Long Sleeves, Long Pants, **Gloves**	Dermal	0.352 lb ai/acre	40	0.023	High	100%	70	0.0046	1,100	98,000	1,100
		Inhalation			0.0012	High			0.00024			
3. Apply: Aerial Liquid Closed Cockpit	Long Sleeves, Long Pants	Dermal	0.352 lb ai/acre	350	0.0050	Med	100%	70	0.0088	570	200,000	570
		Inhalation			0.000068	Med			0.00012			
4. Apply: Airblast Open Cab	Long Sleeves, Long Pants	Dermal	0.352 lb ai/acre	40	0.36	High	100%	70	0.072	70	26,000	70
		Inhalation			0.0045	High			0.00091			
4a. Apply: Airblast Open Cab	Long Sleeves, Long Pants, **Gloves**	Dermal	0.352 lb ai/acre	40	0.24	High	100%	70	0.048	100	26,000	100
		Inhalation			0.0045	High			0.00091			
5. Flagging for Aerial Operations	Long Sleeves, Long Pants	Dermal	0.352 lb ai/acre	350	0.011	High	100%	70	0.019	260	38,000	260
		Inhalation			0.00035	High			0.00062			

[1] Maximum application rate is assessed.

[2] For short/intermediate-term dermal risk assessment, the dermal absorption factor of 100% is applied because the endpoint chosen was derived from a dermal toxicity study.

[3] Daily Dose =[Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure(mg/lb ai handled) x Absorption Factor]/Body Weight (70 kg used because toxicity endpoint effect is not gender-specific)

[4] MOE = NOAEL/ Daily Dose. Short-/Intermediate-term Dermal NOAEL= 5 mg/kg/day. Short-/Intermediate-term Inhalation NOAEL= 23.6 mg/kg/day.

[5] Total MOE = $1 \div ((1/MOE_{dermal}) + (1/MOE_{inhalation}))$

7.2 Occupational Postapplication Exposure

The use pattern proposed for spiroxamine involves foliar applications. There is a potential for postapplication exposure to scouts, harvesters and other field workers, and a risk assessment is required. Postapplication risk in residential settings is not anticipated because the proposed use sites are expected to be commercial agricultural sites. To estimate worker postapplication exposures, surrogate transfer coefficients (Tc) were used for applicable agricultural activities. These surrogates are based on data from the Agricultural Re-entry Task Force (ARTF) as presented in the HED Exposure SAC SOP 003.1 (8/7/00). An estimate of the short-/intermediate-term MOEs for postapplication exposure from various agricultural activities following treatment by spiroxamine resulted in REIs ranging from the day of treatment (i.e., day 0) for low exposure potential activities such as irrigation, weeding and scouting, to 28 days for the very high exposure activity of cane turning of table grapes. A summary of the postapplication exposure/risk estimates and resulting REIs is presented in Table 10.

HED's postapplication exposure estimates are based on surrogate data. The unit exposure values are considered to be central tendency. The application rates, treatment variables, etc. used in this assessment are upper percentile values. Therefore, the potential dose is characterized as central to high-end.

The proposed label for spiroxamine has a 24-hour restricted entry interval (REI). The spiroxamine technical product has a Toxicity Category IV for Acute Inhalation and Primary Eye Irritation. However, for Acute Dermal and Primary Skin Irritation, the Toxicity Categories are II and I, respectively. Per the Worker Protection Standard (WPS), a 48-hour REI is required for chemicals classified under Toxicity Category I. Therefore, **the interim REI of 24 hours appearing on the proposed spiroxamine label, KWG 4168 300 CS, should be increased to 48 hours.** Further, an assessment of postapplication risks to toxicity endpoints (systemic) identified by the HIARC, indicate that REIs up to 28 days are needed, depending upon the activity involved.

It should be noted from Table 7.2 that irrigation, hand weeding, and hedging are activities that may be performed within the WPS 48-hour REI. High contact activities such as hand harvesting may be performed at or around the PHI for hops (12 days) and grapes (28 days).

Table 7.2. Exposure and Risk for Occupational Postapplication Activities

Crop Group	Appli-cation Rate (lb ai/A)	Fraction ai Retained on Foliage	Fraction ai Dissipating Daily	Dermal Transfer Coefficient [reference] (cm^2/hr)	Dislodgeable Foliar Residue (ug/cm^2)	Postapplication Day (t)	Daily Dose[2] (mg/kg/day)	Short/Intermed. Term Dermal MOE[3]
Bunch/Bundle (hops)	0.352	0.2	0.1	100: irrigation, weeding (hand), scouting, thinning. [MRID 426891]	0.79	0	0.009	550
				1300: irrigation, scouting. [ARF024]	0.378	7	0.056	89
					0.340	8	0.051	99
					0.306	9	0.045	110
				2000: harvest (hand), harvest (mechanical), stripping, training, pruning (hand), thinning, topping, weeding (hand). [ARF024]	0.248	11	0.057	88
					0.223	12	0.051	98
					0.201	13	0.046	110
Vine/Trellis (grapes - juice and wine)	0.352	0.2	0.1	500: irrigation, weeding (hand), scouting, hedging. [ARF023]	0.790	0	0.045	110
				1000: scouting, training, tying. [ARF023]	0.518	4	0.059	84
					0.466	5	0.053	94
					0.420	6	0.048	100
				5000: harvest (hand), pruning (hand), training, tying, thinning, leaf pulling. [MRID 409856]	0.107	19	0.061	82
					0.096	20	0.055	91
					0.086	21	0.049	100
Vine/Trellis (grapes - table and raisin)	0.352	0.2	0.1	500: irrigation, weeding (hand), scouting, hedging. [ARF023]	See Vine/Trellis (grapes - juice and wine) above.			
				1000: scouting, training, tying. [ARF023]				
				5000: harvest (hand), pruning (hand), training, tying, thinning, leaf pulling. [MRID 409856]				
				10,000: girdling, turning (cane turning), tying (cane turning). [MRID 409856]	0.051	26	0.058	86
					0.046	27	0.052	95
					0.041	28	0.047	110

[1] Dislodgeable Foliar Residue $_{Postapplication\ day}$ (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Retained on the Foliage x (1- Fraction of Residue That Dissipates Daily) postapplication d ay x 4.54E+8 ug/lb x 24.7E-9 A/cm^2

[2] Daily Dose = [Dislodgeable Foliar Residue x Absorption Factor (100%) x 0.001 mg/ug x Dermal Transfer Coefficient x Exposure Time (8 hrs)]/ [Body weight (70 kg)]

[3] MOE = NOAEL/Daily Dose. Short-/Intermediate-Term Dermal NOAEL = 5 mg/kg/day. A dermal absorption factor was not applied because the endpoint chosen for this risk assessment was derived from a dermal toxicity study.

7.3 Incidents

Spiroxamine is a proposed new active ingredient (i.e., not currently on the market), and therefore, there are no reports for spiroxamine in the OPP Incidents Database.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

Data which remain outstanding for banana, grape, and hop are listed below by guideline series.

BANANA

Pending the resolution of Residue Chemistry Deficiencies #'s1 and 3 (below) pertaining to the residue analytical methods and Deficiencies # 6 (below) regarding the tolerance expression, there are no residue chemistry data gaps that would preclude the establishment of the proposed permanent tolerance (without U.S. registration) of 3.0 ppm for residues of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety in/on banana.

For continued importation of bananas, a method validation by EPA's laboratory (Deficiency #2 below) and storage stability data (Deficiency #4 below) are needed. Also, field trial information regarding soil types and temperature recordings (Deficiency #5 below) should be submitted if available.

860.1340 Residue Analytical Methods

1. Modify the confirmatory method to use more than single-ion monitoring or conduct an interference study.

2. A successful method validation for Bayer AG Method No. 00407 must be conducted by EPA's laboratory.

3. Send the analytical reference standard for *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane to the National Pesticide Standards Repository.

860.1380 Storage Stability

4. Storage stability data are needed on bananas stored frozen for 6 months.

860.1500 Crop Field Trials

5. Information regarding soil types and temperature recordings for the banana field trials

should be submitted if available.

860.1550 Proposed Tolerances

6. Revise the Section F in order to correct the commodity definition from "banana, whole fruit" to "banana" and to correct the tolerance expression by replacing "aminodiol" with "*N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane".

GRAPE

Pending the resolution of Residue Chemistry Deficiencies #'s 7 and 9 (below) pertaining to the residue analytical methods and Deficiencies #11 (below) regarding the tolerance expression, there are no residue chemistry data gaps that would preclude a conditional registration and the establishment of the proposed permanent tolerance of 1.0 ppm for residues of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety in/on grape.

As conditions of registration (for continued registration), a method validation by EPA's laboratory (Deficiency #8 below) and either four more field trials or a response from BEAD (Deficiency #10 below) are needed.

860.1340 Residue Analytical Methods

7. Modify the confirmatory method to use more than single-ion monitoring or conduct an interference study.

8. A successful method validation for Bayer AG Method No. 00407 must be conducted by EPA's laboratory.

9. Send the analytical reference standard for *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane to the National Pesticide Standards Repository.

860.1500 Crop Field Trials

10. Unless BEAD indicates that a regional registration for use in CA only is appropriate, four more field trials (two from Region 1 and two from Region 11) are needed.

860.1550 Proposed Tolerances

11. Submit a revised Section F to: 1) correct the commodity definition from "grape, fruit" to "grape"; 2) propose a tolerance for "spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent"; and 3) delete the proposed tolerance for raisins.

HOP

Pending the resolution of Deficiencies #'s13 and 15 (below) pertaining to the residue analytical

methods and Deficiency #17 (below) regarding the tolerance expression, there are no residue chemistry data gaps that would preclude a conditional registration and the establishment of the proposed permanent tolerance of 50.0 ppm for residues of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety in/on hop, dried cones.

As conditions of registration (for continued registration and for continued importation of hops from Germany), EPA review of the submitted wheat metabolism studies (Deficiency #12 below), a method validation by EPA's laboratory (Deficiency #14 below), and storage stability data (Deficiency #16 below) are needed.

860.1300 Nature of the Residue - Plants

12. Submitted wheat metabolism studies must be reviewed by the Agency to satisfy a requirement for metabolism studies on three dissimilar crops which show similar metabolic routes.

860.1340 Residue Analytical Methods

13. Modify the confirmatory method to use more than single-ion monitoring or conduct an interference study.

14. A successful method validation for Bayer AG Method No. 00407 must be conducted by EPA's laboratory.

15. Send the analytical reference standard for *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane to the National Pesticide Standards Repository.

860.1380 Storage Stability

16. Additional storage stability information is needed to support the hop field trials which were conducted in Germany.

860.1550 Proposed Tolerance

17. Submit a revised Section F to correct the tolerance expression for hop, dried cones by replacing "aminodiol" with "*N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane".

8.2 Toxicology

The HIARC determined that the following data gap exist:
Two-generation reproduction study in the rat.

8.3 Labels

The interim REI of 24 hours appearing on the proposed spiroxamine label, KWG 4168 300 CS, is not in compliance with the WPS, and should be increased to 48 hours.

9.0 APPENDIX

9.1. Names and Structures

TABLE 9.1.1. Identification of Compounds from the Grape and Banana Metabolism Studies

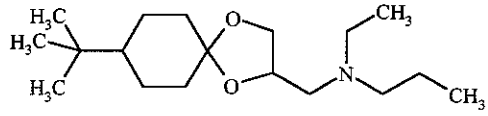
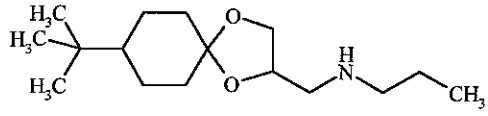
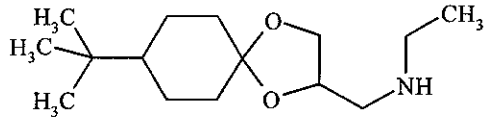
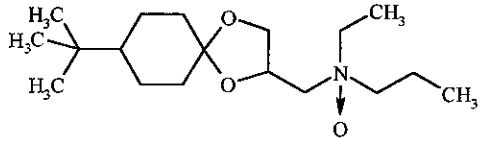
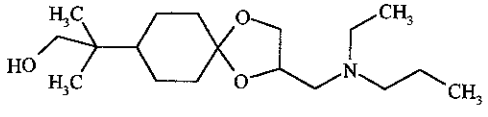
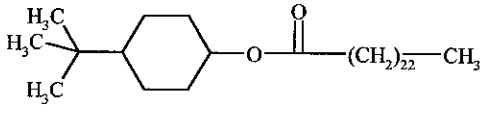
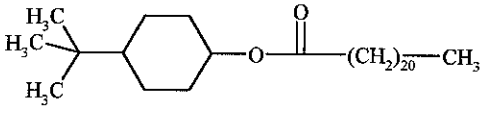
Common name/code	Chemical name	Chemical structure
spiroxamine KWG 4168	8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine	
desethyl-KWG	8-(1,1-dimethylethyl)-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine	
despropyl-KWG	8-(1,1-dimethylethyl)-*N*-ethyl-1,4-dioxaspiro[4,5]decane-2-methanamine	
KWG-*N*-oxide	8-(1,1-dimethylethyl)-*N*-ethyl-*N*-oxo-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine	
hydroxy-KWG	8-(1,1-dimethyl-2-hydroxyethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine	
tetracosanoic acid ester[1]	tetracosanoic acid, 4-*tert*-butylcyclohexyl ester	
docosanoic acid ester[1]	docosanoic acid, 4-*tert*-butylcyclohexyl ester	

TABLE 9.1.1. Identification of Compounds from the Grape and Banana Metabolism Studies

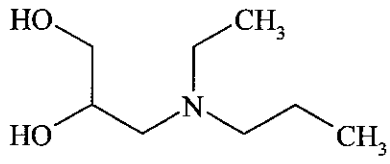
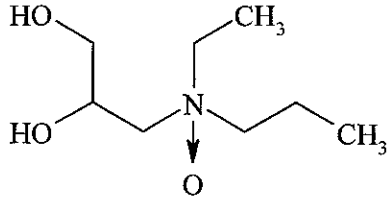
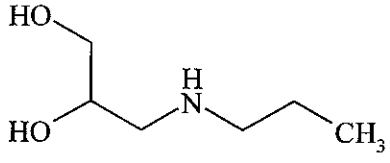
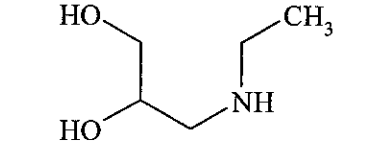
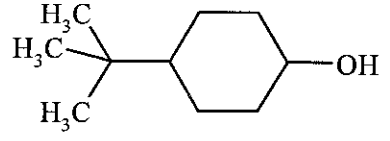
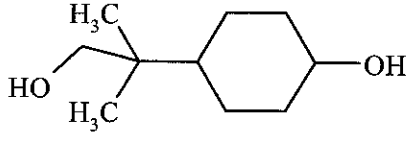
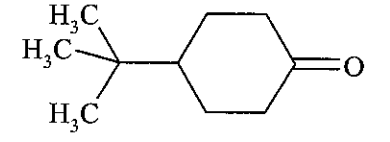
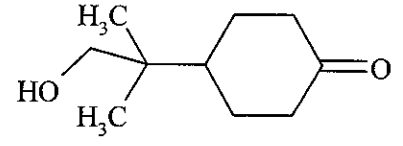
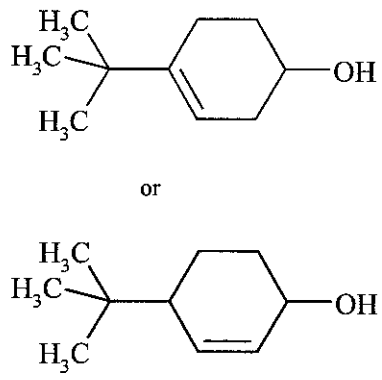
Common name/code	Chemical name	Chemical structure
aminodiol	*N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane	
aminodiol-*N*-oxide	*N*-ethyl-*N*-oxo-*N*-propyl-1,2-dihydroxy-3-aminopropane	
desethyl-aminodiol	*N*-propyl-1,2-dihydroxy-3-aminopropane	
despropyl-aminodiol	*N*–ethyl-1,2-dihydroxy-3-aminopropane	
tert-butylcyclohexanol [2] "cyclohexanol"	4-(1,1-dimethylethyl)cyclohexanol	
diol [2]	4-(1,1-dimethyl-2-hydroxyethyl)cyclohexanol	
tert-butylcyclohexanone[2] "cyclohexanone" "*tert*-butylketone" "ketone"	4-(1,1-dimethylethyl)cyclohexanone	
hydroxyketone [2]	4-(1,1-dimethyl-2-hydroxyethyl)cyclohexanone	

TABLE 9.1.1. Identification of Compounds from the Grape and Banana Metabolism Studies		
Common name/code	Chemical name	Chemical structure
tert-butylcyclohexenol [1,2] "cyclohexenol"	olefin derivative of *tert*-butylcyclohexanol	

[1] Tetracosanoic acid ester, docosanoic acid ester, and *tert*-butylcyclohexenol were reported in the grape metabolism study; they were not reported in the banana metabolism study.
[2] Identified following acid hydrolysis.

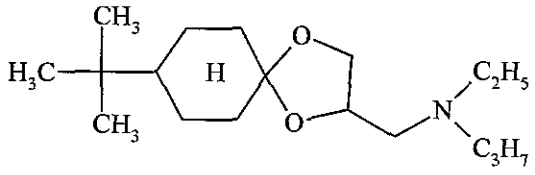
Table 9.1.2. Summary of Known Spiroxamine Degradates in Water/Soil.

Degradate chemical name	Designation	Study Type[1]
8-(1,1-dimethylethyl)-N-ethyl-N-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine –oxide	WAK 6301 (KWG 4168 N-oxide)	aerobic aquatic metabolism **(11.8 %)**, aerobic soil metabolism, hydrolysis, aquatic proteolysis, soil proteolysis, terrestrial field dissipation
[2-[(ethylpropylamino)methyl]-β,β-dimethyl-1,4-dioxaspiro[4,5]decane-8-ethanol]	WAK 5868	aerobic aquatic metabolism, aquatic proteolysis, soil proteolysis
α,α-dimethyl-2-[(propylamino)methyl]-1,4-dioxaspiro[4,5]decane-8-acetic acid	WAK 5756	aerobic aquatic metabolism , aerobic soil metabolism
2-[(ethylpropylamino)methyl]-α,α-dimethyl-1,4-dioxaspiro[4,5]decane-8-acetic acid	WAK 5708	aerobic aquatic metabolism **(10.8 %)**, aerobic soil metabolism
[4-(1,1-dimethylethyl)cyclohexanone]	WAK 5428	aerobic soil, aquatic proteolysis, soil proteolysis
[8-(1,1-dimethylethyl)-N-ethyl-1,4-dioxaspiro[4,5]decane-2-methanamine]	KWG 4669 (despropyl KWG 4168)	aerobic aquatic metabolism, aerobic soil metabolism, hydrolysis, aquatic proteolysis, soil proteolysis, terrestrial field dissipation
[8-(1,1-dimethylethyl)-N-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine]	KWG 4557 (desethyl KWG 4168)	aerobic aquatic metabolism, aerobic soil metabolism, hydrolysis, aquatic proteolysis, soil proteolysis, terrestrial field dissipation
[2-[(ethylamino)methyl]-α,α-dimethyl-1,4-dioxaspiro[4,5]decane-8-acetic acid	BNF 5534	aerobic soil metabolism

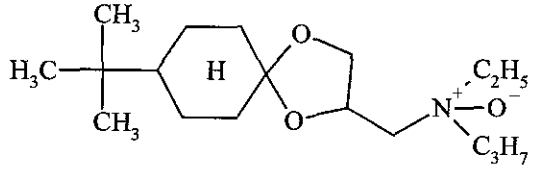
[1] This column contains the type of fate study in which the particular degradate occurred. Only those degradates that occurred in concentrations >10 % are followed by that percentage in parenthesis; otherwise, the amounts are <10%.

Table 9.1.3. Chemical Structures for Spiroxamine and its Degradates in Soil/Water

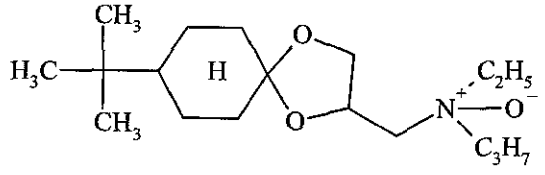
Spiroxamine
KWG 4168



Degradates
WAK 6301 (KWG 4168 N-oxide)



WAK 6301/1



KWG 4669 (despropyl KWG 4168); WAK 6174

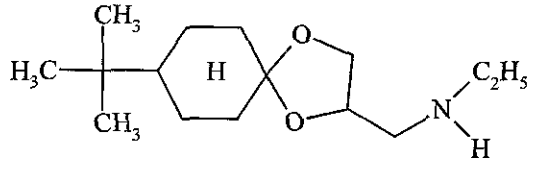
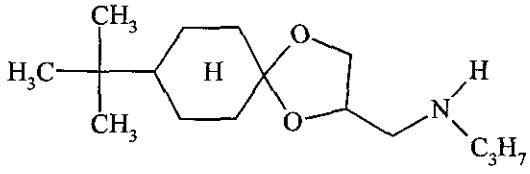
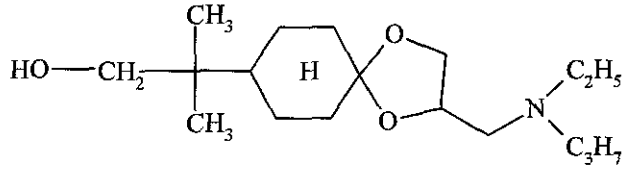


Table 9.1.3. Chemical Structures for Spiroxamine and its Degradates in Soil/Water

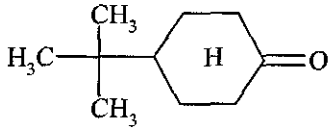
KWG 4557 (desethyl KWG 4168); FHW 0104H



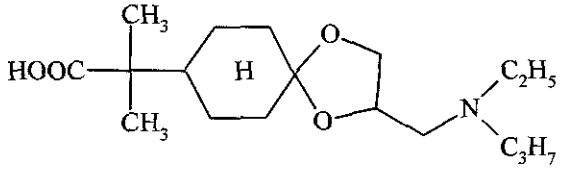
WAK 5868



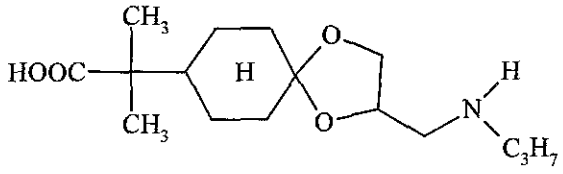
WAK 5428



WAK 5708



WAK 5756



BNF 5534

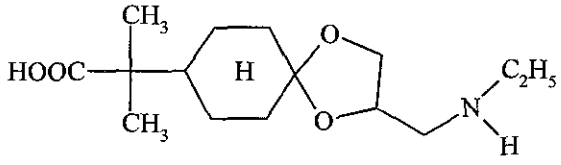


Table 9.2. Summary of Residues from the Crop Field Trials with Spiroxamine.

Commodity	Total Applic. Rate, lb ai/A (kg ai/ha)	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Mean	Std. Dev.	HAFT[1]	Min.	Max.
BANANA (proposed use = 3.42 lb ai/A total application rate, 0-day PHI)									
Whole fruit, bagged	3.272-3.928 (3.667-4.403)	0	spiroxamine[2]	12	0.13	0.14	0.464	<0.05	0.464
Whole fruit, unbagged	3.269-3.928 (3.664-4.403)	0	spiroxamine[2]	12	1.13	0.61	2.44	0.143	2.44
GRAPE (proposed use = 0.70 lb ai/A total application rate, 28-day PHI)									
Fruit	0.687-0.758	26-29	spiroxamine[2]	24	0.176	0.162	0.613	<0.05	0.634
HOP in US (proposed use = 1.4 lb ai/A total application rate, 12-day PHI)									
Hop, dried cones	1.4	12-14	spiroxamine[2]	6	5.21	4.4	10.88	1.95	10.9
HOP in Germany (proposed use = 1.34 lb ai/A total application rate, 10-day PHI)									
Hop, dried cones	1.34 (1.500 kg ai/ha)	10	spiroxamine[2]	16	16	7.1	24	4.8	30

[1] HAFT = Highest Average Field Trial.

[2] The method determined parent and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety (a.k.a. the aminodiol moiety), calculated as parent equivalent.

9.3 References

Spiroxamine. PP#0F06122. Petition for the Establishment of Permanent Tolerances on Grapes. Summary of Analytical Chemistry and Residue Data. D284913, N. Dodd, 12/09/03.

Spiroxamine. PP#3E06518. Petition for the Establishment of a Permanent Tolerance on Hops. Summary of Analytical Chemistry and Residue Data. D287037, D293165, and D293513, N. Dodd, 12/09/03.

Spiroxamine. PP#3E06538. Petition for the Establishment of a Tolerance on Imported Bananas. Summary of Analytical Chemistry and Residue Data. D287862, N. Dodd, 12/09/03.

Spiroxamine. Report of the Metabolism Assessment Review Committee. D296024 and D296025, N. Dodd, A. Assaad, and Dirk Young, 10/15/03.

Spiroxamine Acute and Chronic Dietary Exposure Assessments for the Section 3 Registration Actions on Bananas, Grapes, and Hops. D296034, N. Dodd, 12/08/03.

Spiroxamine 1st-Report of the Hazard Identification Assessment Review Committee. TXR # 0052237, A. Assaad, 11/14/03.

Spiroxamine Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision (or Registration Support) Document. A. Assaad, 11/14/03.

Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Spiroxamine on Hops and Grapes. D287042, J. Arthur, 11/18/03.

Spiroxamine: Drinking water EECs for human health risk assessment. D286353, D. Young, 06/17/03.

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