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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: June 18, 2010.

SUBJECT: **Spiroxamine: Human Health Risk Assessment for Spiroxamine on Imported Artichoke, Asparagus and Fruiting Vegetables (Crop Group 8).**

PC Code: 120759
Decision No.: 409458
Petition No.: 9E7564
Risk Assessment Type: Single Chemical
TXR No.: NA
MRID No.: NA

DP Barcode: D367971
Registration No.: 264-1025
Regulatory Action: Tolerance Assessment
Case No.: NA
CAS No.: 118134-30-8
40 CFR: §180.602

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Recvd in RRC
6/29/2010
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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 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 imported artichokes, asparagus and fruiting vegetables (Crop Group 8). A summary of the findings and an assessment of human health risk resulting from the uses of spiroxamine are provided in this document.

The first and only previous human health risk assessment for spiroxamine was conducted for use on hops and imported grapes and bananas (DP 284789, M. Bonner, updated June 17, 2004). The hazard characterization and toxicity endpoints remain unchanged. However, since the previous risk assessment, an acceptable/guideline multigeneration reproductive toxicity study has been submitted which suffices to remove the database uncertainty factor (UF_{DB}) of 3X. The Food Quality Protection Act (FQPA) safety factor is now reduced to 1X.

The risk assessment and hazard characterization were provided by Sheila Healy, the residue chemistry data review by Debra Rate (ARIA) and the dietary assessment by Cassi Walls. The drinking water assessment was provided by Chuck Peck of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Spiroxamine is a broad spectrum postemergence fungicide proposed for new use on imported artichoke, asparagus and fruiting vegetables (Crop group 8) to control powdery mildew and rust. Spiroxamine belongs to the class of pesticides known as spiroketalamines; its fungicidal mode of action is sterol biosynthesis inhibition. Use on hops (50 ppm) is currently registered in the U.S. and tolerances are established for imported grapes (1.0 ppm) and imported bananas (3.0 ppm).

Proposed Uses
In PP#9E7564, Bayer CropScience is requesting the establishment of tolerances for spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent, in/on imported asparagus (0.7 ppm), artichoke (0.05 ppm) and fruiting vegetables (Crop Group 8, 1.2 ppm).

Impulse 800EC and Prosper 500EC are applied foliarly at a maximum seasonal rate of 0.80 lb ai/A for artichoke and pepper (Peru); 1.34-1.67 lb ai/A for asparagus (Mexico and Peru); and 0.96 lb ai/A for tomato and pepper (Mexico). Preharvest intervals (PHIs) range from 3 days for artichokes, peppers and tomatoes to 21 days for asparagus. The submitted Good Agricultural Practices (GAP) summary is adequate to allow evaluation of the residue data relative to the uses in Mexico and Peru. However, the specimen foreign labels (translated) did not include all pertinent use pattern information and restrictions on use of adjuvants.

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 and causes severe dermal irritation (Category I). Spiroxamine is also a skin sensitizer. Many of spiroxamine's toxic effects and clinical signs are related to its irritant properties. Subchronic studies show that the target organ of spiroxamine toxicity is the liver. Additionally, 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 in rat or rabbit developmental and reproduction studies. The acute neurotoxicity study showed minimal signs of neurotoxicity (piloerection and slight to moderate gait incoordination) and FOB (functional observational battery) effects (decreased forelimb grip strength and foot splay) in males, and 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 tumorigenicity in both the rat and the mouse. Spiroxamine has no mutagenic or clastogenic potential, based on several *in vivo* and *in vitro* studies. In rat metabolism studies, absorption of spiroxamine began immediately after administration with peak plasma concentrations at 1.5-2 hours post-dose; renal excretion accounted for the majority of the radioactivity.

Drinking Water
Based on the existing uses on hops, EFED completed an amended drinking water assessment for spiroxamine using screening-level exposure models, PRZM and EXAMS. Changes to the previous Tier II Drinking Water Assessment (DP 286353, June 17, 2003) include: adsorption

coefficients from all of the American and foreign soil studies were used; the aerobic soil metabolism half-life increased slightly due to a previous miscalculation; and a wider range of start dates was evaluated and a different start date selected. Consequently, the acute and chronic surface water concentrations are slightly decreased, estimated to be 19 and 15 µg/L, respectively and the ground water concentration decreased to 0.035 µg/L based on the maximum proposed application rate for spiroxamine applied to hops.

Dietary Exposure (food and drinking water)
Acute and chronic aggregate exposure and risk assessments were conducted using DEEM-FCID™. The modeled exposure estimates for the acute assessment are based on tolerance level residues, assuming 100% of the crops were treated and include the highest Estimated Drinking Water Concentration (EDWC) relevant to the scenario (surface water). Additionally, experimental processing factors, where available, were assumed for both registered and requested foreign crop uses. The resulting acute risk estimate for the U.S. population was 11% of the aPAD (acute Population Adjusted Dose) and the highest exposed population was Children 1-2 years which occupied 36% of the aPAD.

A chronic dietary assessment was conducted assuming that 100% of crops with the requested uses and currently registered uses of spiroxamine are treated and that all treated crops contain residues at tolerance levels. In addition, experimental processing factors, where available, were assumed for both registered and requested crop uses. Potential residues in drinking water were included in the analyses based on surface water results from the Tier II PRZM-EXAMS Index Reservoir model as these values were higher than the ground water estimates from the SCI-GROW model (D376551 C. Peck, April 21, 2010). No population subgroups exceed HED's level of concern: the U.S. population occupied 13% of the chronic Population Adjusted Dose (cPAD), while the most highly exposed population subgroup, Children 1-2 years old, occupied 40% of the cPAD. As all dietary risk estimates were less than 100% of the a/cPAD, no risks of concern were identified.

Residential Exposure
This document only presents the assessment of the proposed new agricultural uses of spiroxamine. There are no existing residential uses and none are being requested at this time; therefore, no residential risk assessment has been conducted.

Aggregate Exposure Scenarios and Risk Conclusions
As there are no existing or proposed residential uses, and subsequently no expected residential exposure, aggregate risk is considered in the dietary (food and drinking water) exposure and risk assessment.

Occupational Exposure Estimates
This document only presents the assessment of the proposed new foreign agricultural uses of spiroxamine. No domestic crop uses are being requested at this time; therefore, no occupational risk assessment has been conducted.

Environmental Justice Considerations
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, nondietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Recommendations for Tolerances
With the exception of a revised Section F to list correct commodity definitions, there are no human health risk issues that would preclude the establishment of tolerances for residues of spiroxamine, including its metabolites and degradates, in or on the commodities in the table below. Although there are no recommended revisions to the petitioned for tolerance levels, in accordance with HED's Interim Guidance on Tolerance Expressions (5/27/09, S. Knizner), the tolerance expression for spiroxamine should be revised to state:

Compliance with the tolerance levels specified below is to be determined by measuring only the sum of spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as the stoichiometric equivalent of spiroxamine, in or on the commodity.

Table 1. Tolerance Summary for Spiroxamine.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Artichoke	0.7	0.7	*Artichoke, globe*
Asparagus	0.05	0.05	
Vegetable, fruiting, group 8	1.2	1.2	*Vegetables, fruiting, crop group 8*

NOTE TO RD: The petitioner should be notified of the new 40 CFR requirement for an immunotoxicity study, the need for revisions to the Prosper® EC 500 label from Peru, as well as the outstanding residue chemistry deficiencies associated with the spiroxamine registration on domestic hops. Refer to Section 9.0 for details.

2.0 Ingredient Profile

2.1 Summary of Proposed Uses

Bayer CropScience currently markets an 800 g/L emulsifiable concentrate (EC) and a 500 g/L EC formulation of spiroxamine for the control of powdery mildew and rust on artichoke, asparagus, pepper, and tomato grown in Peru and/or Mexico. The products are applied foliarly at a maximum seasonal rate of 0.80 lb ai/A for artichoke (Peru); 1.34-1.67 lb ai/A for asparagus (Mexico and Peru); 0.80 lb ai/A for pepper (Peru), and 0.96 lb ai/A for tomato and pepper (Mexico). Preharvest intervals are 3 days for artichoke, peppers and tomatoes and 21 days for asparagus. The submitted GAP Summary is adequate to allow evaluation of the residue data relative to the uses in Mexico and Peru; however, the specimen foreign labels (translated) did not include all pertinent use pattern information and restriction on use of adjuvants.

Tolerances are currently established [40 CFR §180.602(a)] for the combined residues of the fungicide spiroxamine (8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine) and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent, in/on banana (import) at 3.0 ppm; grape (import) at 1.0 ppm; and hop, dried cones at 50 ppm.

As uses on artichoke, asparagus and fruiting vegetables do not include any regulated livestock feedstuffs, issues pertaining to livestock metabolism, analytical methods and storage stability data for animal commodities and residues in livestock commodities are not germane to the current petition. Nor are rotational crop studies required for this petition.

A summary of the proposed new spiroxamine uses is presented in Table 2.1 below.

Table 2.1. Summary of Directions for Use of Spiroxamine[1]

Applic. Timing, Type, and Equip.	Country	Formulation [conc; type]	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
Artichoke							
Broadcast foliar, during flowering	Peru	Prosper® 500 EC [500 g/L EC]	0.27 [0.30]	3	0.80 [0.90]	3	Retreatment interval (RTI) of 7 days, spray volume of 400-600 L/ha
Asparagus							
Broadcast foliar, vegetative development	Peru	Prosper® 500 EC [500 g/L EC]	0.335 [0.375]	4	1.34 [1.5]	21	RTI of 10 days, spray volume of 400-600 L/ha

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Broadcast foliar, vegetative development – flowering	Mexico	Impulse® 800 EC [800 g/L EC]	0.335 [0.375][2]	5	1.67 [1.875] [2]	21	RTI of 10 days, spray volume of 300-600 L/ha
Peppers							
Broadcast foliar, fruit development	Peru	Prosper® 500 EC [500 g/L EC]	0.27 [0.30]	3	0.80 [0.90]	7	RTI of 7 days, spray volume of 400-600 L/ha
Peppers (Hot and Bell)							
Broadcast foliar Flowering – fruit set	Mexico	Impulse® 800 EC [800 g/L EC]	0.32 [0.36]	3	0.96 [1.08]	3	RTI of 7 days, spray volume of 300-600 L/ha
Tomato							
Broadcast foliar, flowering – fruit set	Mexico	Impulse® 800 EC [800 g/L EC]	0.32 [0.36]	3	0.96 [1.08]	3	RTI of 7 days, spray volume of 300-600 L/ha

[1] The use pattern information was obtained from the GAP Summary in Section B of the petition with slight modifications.

[2] Based on a maximum single application rate of 0.47 L/ha (product), the calculated single application rate would be 0.335 lb ai/A [0.376 kg ai/ha], with a maximum seasonal rate of 1.68 lb ai/A [1.88 kg ai/ha] which is slightly higher than the rates presented in the GAP Summary.

2.2 Chemical Identity and Structure

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. The structure and nomenclature of spiroxamine are reported in Appendix B.

2.3 Physical and Chemical Properties of Spiroxamine

Technical spiroxamine is a liquid. It is soluble in water; solubility is inversely proportional to pH. It is soluble in organic solvents. Because the technical grade of the active ingredient (TGAI) is alkaline (pH 9.9), it is a skin sensitizer. Spiroxamine induces local irritation by all routes of administration. Local irritation is considered the cause for most of its toxic effects and clinical signs. The physiocochemical properties are reported in Appendix B.

3.0 Hazard Characterization/Assessment

3.1 Hazard Dose Response Characterization

A comprehensive Hazard Characterization and Executive Summaries may be found in the assessment for spiroxamine as a new active ingredient (DP 284789, A. Assaad, June 17, 2004). Since the last risk assessment, new data requirements implemented December 2007 and made effective December 2009 have rendered the spiroxamine toxicology database incomplete for lack of an immunotoxicity study (OPPTS 870.7800). Additionally, an acceptable guideline reproductive toxicity study has been submitted which suffices to remove the previous UF_{DB} of 3X; the FQPA safety factor is now 1X.

The toxicology database for spiroxamine is considered adequate to support the establishment of permanent tolerances for residues of spiroxamine in/on the RACs resulting from the proposed uses. A brief summary of the toxicological findings is discussed below in 3.1.2., Toxicological Effects.

3.1.1 Database Summary

3.1.1.1 Studies Available and Considered

With the exception of a newly require immunotoxicity study, the toxicology database contains the full suite of guideline studies including a dermal developmental toxicity study in the rat , a neurotoxicity screening battery, a dermal toxicity study in the rabbit, dermal penetration and a 28-day inhalation toxicity study in rats. A recently submitted acceptable/guideline 2-generation reproductive toxicity study in the rat fulfills a prior database deficiency. A previously submitted 2-generation reproductive toxicity had been classified as unacceptable/guideline because of unacceptable lactation indices (35 – 73%) in all treatment groups (including control) of the F2 generation. Because of such high rates of mortality in the F2 study groups, only the F1 generation could be assessed for susceptibility. Similar adverse effects and endpoints were observed in both studies.

3.1.1.2 Mode of action

Spiroxamine belongs to the class of pesticides known as spiroketalamines. Spiroxamine's fungicidal activity is due to inhibition of sterol biosynthesis.

3.1.2 Toxicological Effects

Spiroxamine has low acute toxicity via the oral and inhalation routes of exposure and is not irritating to the eye. However, spiroxamine is a skin sensitizer under the conditions of the guinea pig maximization test and a severe dermal irritant.

In the mammalian toxicology database, the primary target organ for spiroxamine exposure is the liver. Subchronic and chronic studies were characterized by hepatomegaly and corresponding elevations in liver enzymes.

Spiroxamine induces local irritation by all routes of administration and local irritation is considered the cause for most of its toxic effects and clinical signs such as: decreased body weight gain and food consumption; keratinized and hyperplastic mucous membranes of the esophagus and forestomach; hyperkeratosis of the tongue, hyperplasia in the urinary bladder; dermal irritation/skin toxicity; sensitization and lung toxicity.

3.1.3 Dose-response

Generally, spiroxamine is not well-tolerated at doses greater than 100 mg/kg/day. Decreased body weight (gain) and food consumption are common endpoints observed across species, duration and gender upon which systemic LOAELs, ranging from approximately 20 - 150 mg/kg/day, are based. Dermal effects are seen at $\leq$ 5 mg/kg/day. Decreased body weight gain and food consumption are attributable to lesions caused by local irritation in the tongue, esophagus and stomach.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

In rat metabolism and pharmacokinetics studies, oral absorption of spiroxamine was approximately 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 80% of the recovered radioactivity was excreted via urine and feces within 24 hours in all dose groups and more than 97% within 48 hours. Renal excretion accounted for the majority of the radioactivity (1.8:1 urine:feces on average).

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicology database used to assess pre- and postnatal exposure to spiroxamine is considered adequate.

3.3.2 Evidence of Neurotoxicity

In the acute neurotoxicity study, minimal clinical signs of neurotoxicity (piloerection and slight to moderate gait incoordination) and FOB effects (decreased forelimb grip strength and foot splay) were observed in males at 30 mg/kg/day. The acute neurotoxicity study was the only study in which evidence of test article-related neurotoxicity was observed. No treatment-related effects were seen at the NOAEL of 10 mg/kg/day. No evidence of neurotoxicity or

neuropathology (including FOB parameters) were seen at doses up to 50 mg/kg/day in the subchronic neurotoxicity study.

In a rabbit developmental toxicity study, hydrocephalus internus with caudal displacement of the ears was observed in one fetus in the main study at the highest dose tested, (80 mg/kg/day). However, in a parallel supplementary study at the same dose and number of animals, no hydrocephalus was detected. In the supplementary study, bilateral retinal folds (a variation) was observed in one fetus. Likewise, this variation was not observed in the original, parallel study. Both of these findings are considered a spontaneous malformation and variation, respectively.

In the 28-day inhalation toxicity study in the rat, a statistically significant decrease in plasma cholinesterase was observed in females but not in males. Examination of the raw data revealed that at the inception of the study, ChE levels were much lower in female rats (25-30%) compared to male rats. Clinical signs observed in the inhalation study were attributed to pulmonary toxicity rather than neurotoxicity as the clinical signs were not consistent with cholinesterase inhibition. There were no reported measures of RBC or brain ChEI in any other study. Since ChEI was observed in only one sex and in only the 28-day inhalation toxicity study, the relevance of this finding is unknown.

A developmental neurotoxicity study is not required at this time.

3.3.3 Developmental Toxicity

Following both oral and dermal exposure to rats, developmental effects (wavy ribs, delayed ossification and cleft palate) were seen only in the presence of maternal toxicity (oral) or at doses greater than the maternal LOAEL (dermal).

At 100 mg/kg, minimal decreases (2-4%) in fetal body weights were observed. Delayed skeletal development was indicated by increased fetal and litter incidences of incomplete ossification of the cranium and sternum and non-ossification of the metatarsals (hind limb) and phalanges of the fore- and hind-limbs. Additionally at this dose, palatoschisis was observed in three fetuses from three litters, and one fetus had a caudal malposition of the left hind leg. These observations were not reported in the historical controls.

Fetal and litter incidences of wavy ribs were increased significantly at 80 mg/kg; however, these incidences fell within the range of historical controls. The fetal and litter incidences of significantly increased incomplete/non-ossification of the os occipital and the increased non-ossification of the left distal phalanx of digit #4 of the forelimb were observed at 80 mg/kg, and were outside of the range of historical controls. A tapering mandibula was observed in one fetus at 80 mg/kg but was not observed in the historical controls.

3.3.4 Evidence of Immunotoxicity

The toxicology database is lacking an immunotoxicity study (OPPTS 870.7800) which is a new data requirement under 40 CFR Part 158.500 for registration of a pesticide (food and non-food uses). EPA has evaluated the available toxicity data for spiroxamine and determined that an additional database uncertainty factor is not needed to account for potential immunotoxicity. The reasons follow:

- Spiroxamine does not belong to a class of chemicals that would be expected to be immunosuppressive. Therefore, HED does not believe that conducting a special series 870.7800 immunotoxicity study will result in a NOAEL less than 2.5 mg/kg/day, which is presently used as the cRfD point of departure.

- The most sensitive endpoint in the database is liver toxicity accompanied by body weight and food consumption effects which are likely secondary to test article-related hyperkeratosis of the tongue, esophagus and stomach.

- Thymic atrophy is seen at concentrations of 0.518mg/L (140.5 mg/kg/day) in a 28-day inhalation study. Accompanying hematological effects include: decreased thrombocytes; increased clotting time; decreased lymphocytes; and increased neutrophils. These effects are seen only when inhalation is the route of administration and are likely secondary local (respiratory system) irritation, inflammation and injury.

- An immunotoxicity study in rats and/or mice (OPPTS 870.7800) is required as part of the new 40 CFR §158 Guidelines

3.3.5 Pre-and/or Postnatal Toxicity

There were no treatment-related effects on fertility, viability or lactation indices or other reproductive parameters in either generation of the two-generation reproductive toxicity study. LOAELs (both parental and offspring = 22.2 mg/kg/day) were defined by decreased body weight and gains in both generations and diffuse hyperkeratosis of the esophagus in both sexes of both generations. Delayed balanopreputial separation and vaginal patency was also observed in the F1 and F2 pups at the LOAELs. The LOAEL for reproductive toxicity was not observed.

Based on the available data, including the recently submitted reproductive study in rats (MRID 47526301), there is no concern for pre- or postnatal toxicity. The slight delays in balanopreputial separation and vaginal patency were considered to be a reflection of the decreased body weights, which contributed to a delay in development.

3.3.6.1 Determination of Susceptibility

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

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

There are no susceptibility concerns or residual uncertainties for prenatal toxicity in the available developmental and reproductive toxicity studies:

3.4 Safety Factor for Infants and Children

An uncertainty factor (UF_{DB} = 3X) was retained in the prior risk assessment due to the lack of an acceptable 2-generation reproduction study (for notably high lactation indices which were not related to treatment). Since then, the registrant has submitted an acceptable 2-generation reproduction study (MRID 47526301) in which no susceptibility or direct prenatal toxicity was observed. Similar adverse effects and endpoints were observed in both studies. The spiroxamine risk assessment team evaluated the quality of the current toxicity and exposure data and, based on these data, recommended that the FQPA Safety Factor be reduced to 1X. The recommendation is based on the following:

- With the exception of a required immunotoxicity study, the toxicology database for spiroxamine is complete for the purposes of this risk assessment and the characterization of potential pre- and postnatal risks to infants and children.
- There is no quantitative or qualitative susceptibility to spiroxamine toxicity following oral or dermal exposures to rats *in utero*, oral exposure to rabbits *in utero* or post natal exposure to rats.
- There is no concern for neurotoxicity resulting from exposure to spiroxamine.
- Additionally, the exposure assessment is protective: the acute dietary food exposure assessment utilizes tolerance level residues, the chronic dietary food exposure assessment utilizes average residue levels found in the crop field trials and both assessments assume 100% of crops with requested uses of spiroxamine are treated.
- Also, the drinking water assessment generated EDWCs using models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations. The highest relevant EDWCs were used in the dietary (food and drinking water) exposure assessment.
- By using these screening-level exposure assessments in the acute and the chronic dietary (food and drinking water) assessments, risk is not underestimated.

3.5 Hazard Identification and Toxicity Endpoint Selection

A summary of the toxicological endpoints and doses chosen for the relevant exposure scenarios for human risk assessment is found in Table 3.5.4. Endpoint selection is based on the discussion provided in the June 17, 2004 memo (DP# 284789). The UF_{DB} of 3X has been reduced to 1X subsequent to the submission of an acceptable 2-generation reproduction study (MRID 47526301).

3.5.1 Level of Concern for Risk Assessment

Table 3.5.1. Summary of Levels of Concern for Risk Assessment.			
Route	**Short-Term (1 - 30 Days)**	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	MOE < 100	MOE < 100	NA
Inhalation	MOE < 100	MOE < 100	NA
Residential Exposure			
Dermal	MOE < 100	MOE < 100	NA
Inhalation	MOE < 100	MOE < 100	NA
Incidental Oral	MOE < 100	MOE < 100	NA
Dietary (Food and Water)	Exposure > 100% aPAD (acute, 1-day exposure)	NA	exposure > 100% cPAD (chronic exposure)

3.5.2 Recommendation for Combining Routes of Exposure for Risk Assessments

Under FQPA, HED must consider and aggregate pesticide exposures and risk from three major sources: food, drinking water, and residential exposures. Residential exposure to spiroxamine is not expected (because there are no proposed residential uses); therefore, the aggregate exposure assessment for this chemical involves considering only the contribution from food and drinking water. The common critical effect of hepatotoxicity is observed in studies of subacute to chronic duration. Additionally, spiroxamine induces local irritation by all routes of administration and local irritation is considered the cause for most of its toxic effects and clinical signs.

3.5.3 Classification of Carcinogenic Potential

There was no evidence of carcinogenicity in rats and mice up to the limit dose at 24- and 18-months, respectively. Spiroxamine was determined to be non-mutagenic in bacteria, negative in an *in vivo* mammalian cytogenetics assay, and did not cause unscheduled DNA synthesis in mammalian cells *in vitro*. The cancer classification is "not likely to be carcinogenic to humans," and therefore, there is no concern for cancer risk to humans.

3.5.4 Summary of Toxicological Doses and Endpoints for Spiroxamine for Use in Human Health Risk Assessments

Table 3.5.4. Summary of Toxicological Doses and Endpoints for Spiroxamine for Use in Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population, including infants and children	NOAEL = 10 mg/kg/day	UF_A = 10X UF_H = 10X FQPA = 1X	aRfD = 0.1 mg/kg/day aPAD = 0.1 mg/kg/day	**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.
Acute Dietary (females 13-49 years old)	No hazard identified			
Chronic Dietary – general population, including infants and children	NOAEL = 2.5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA = 1X	cRfD = 0.025 mg/kg/day cPAD = 0.025 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-term (1-30 days) Incidental Oral	No residential uses are proposed			
Intermediate Term (1-6 months) Incidental Oral				
Short-term (1-30 days) Dermal	NOAEL 5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA = 1X	LOC = MOE ≤ 100	**Prenatal Toxicity study in Rats (Dermal)** The maternal LOAEL (systemic) is 20 mg/kg/day based on decreased body weight gains.
Intermediate term (1-6 months) Dermal				
Short term (1-30 days) Inhalation	NOAEL = 23.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA = 1X	LOC = 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.
Intermediate term (1-6 months) Inhalation				
Cancer (oral, dermal, inhalation)	**Classification:** Not likely to be carcinogenic to humans based on negative genotoxicity and carcinogenicity in long term cancer studies in rats and mice.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human

exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable

3.6 Endocrine disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA is issuing test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Spiroxamine is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA Sec. 408(p), the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4.0 Dietary Exposure/Risk Characterization

Reference: *Spiroxamine: Import Tolerance Petition on Artichokes, Asparagus and Fruiting Vegetables (Crop Group 8) (PP# 9E7564). Summary of Analytical Chemistry and Residue Data. D. Rate, DP371636, 3/31/10*

4.1 Pesticide Metabolism and Environmental Degradation

4.1.1 Metabolism in Primary Crops

For the purposes of this tolerance petition, the available grape and banana metabolism studies are considered sufficient to delineate the nature of the residues in plants. The residues of concern remain spiroxamine and its metabolites containing the *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane moiety, calculated as parent equivalent. The outstanding data required to upgrade the wheat metabolism studies will be considered confirmatory for this petition and are required if uses for wheat or another crop which is not similar to banana or grape are proposed.

Metabolism studies have previously been reviewed for spiroxamine on grapes (PP#0F06122) and bananas (PP#3E06538). For each crop, two metabolism studies were conducted: one using [cyclohexyl-1-^{14}C]spiroxamine and one using [1,3-dioxolane-4-^{14}C]spiroxamine. The studies indicated that the metabolism of spiroxamine in grapes and bananas is similar. Spiroxamine was extensively 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. Principal residues identified 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.

Metabolism studies for spring and winter wheat were submitted and reviewed (PP#3E06783). In the spring wheat study, the test substance used was [cyclohexyl-1-^{14}C]spiroxamine. The results showed that spiroxamine was extensively metabolized. Oxidation occurred primarily at the tertiary amine group to form spiroxamine-N-oxide, and to a minor extent at the *tert*-butyl group. Spiroxamine and spiroxamine-N-oxide were the major residues identified in all spring wheat matrices. Desalkylation of the amine and hydroxylation of the *tert*-butyl group occurred. Hydroxylated metabolites were conjugated. Metabolites N-formyl-desethyl-spiroxamine, hydroxy-spiroxamine, desethyl-spiroxamine, and despropyl-spiroxamine were identified in all wheat matrices, conjugates of diol and hydroxy-N-oxide were identified in wheat forage and straw, and two metabolites which were found to hydrolyze to *tert*-butylcyclohexanone were identified in all wheat matrices. In addition, metabolites diol, hydroxyketone, *tert*-butylcyclohexanone, and *tert*-butylcyclohexanol were identified in the hydrolysates of wheat

straw and grain. The spring wheat metabolism study was deemed scientifically acceptable pending submission of storage stability information. Information is needed pertaining to storage durations of the samples from the metabolism study before the Agency can determine whether the submitted storage stability study is adequate to support the wheat metabolism study.

In the winter wheat study, the test substance used was [1,3-dioxolane-4-^{14}C]spiroxamine. The metabolites identified in the winter wheat study were similar to those found in the spring wheat study. Spiroxamine and spiroxamine-N-oxide were the major residues identified in all winter wheat matrices. Other metabolites identified in winter wheat forage and straw were *N*-formyl-desethyl-spiroxamine, despropyl-spiroxamine, hydroxy-spiroxamine and desethyl-spiroxamine (combined), hydroxy-despropyl-spiroxamine and a malonic acid glucoside of hydroxy-*N*-oxide, each ≤10% TRR. Only ~4% TRR in winter wheat grain were identified. The winter wheat metabolism study was deemed as scientifically unacceptable because: (i) metabolite identifications were not confirmed using a second method; (ii) large amounts of radioactivity remained unidentified in wheat matrices (i.e., unidentified and unextractable residues in forage collected 14 days after treatment (DAT) and mature straw; aqueous fractions in wheat grain); and (iii) dates of sample extraction and analysis were not submitted, so storage durations of samples could not be determined. The winter wheat metabolism study can be upgraded if the cited deficiencies can be resolved.

4.1.2 Metabolism in Livestock

There are no livestock feedstuffs associated with the request to establish import tolerances on artichokes, asparagus and fruiting vegetables. Therefore, data requirements for livestock metabolism are not relevant to this tolerance petition.

4.1.3 Analytical Methodology

A common moiety method, GC/MS Bayer AG Method No. 00407, is available for quantitation of total spiroxamine residues of concern in crop commodities and meets the requirements for an enforcement method. Samples of crop commodities that were collected from the magnitude of the residue studies were analyzed for residues of spiroxamine and total spiroxamine including its metabolites containing the aminodiol moiety using LC/MS/MS Method 01089. The method is adequate for data-collection based on acceptable method validation and concurrent method recoveries from fortified grapes, artichokes, asparagus, bell peppers, and tomatoes and its processed commodities.

Enforcement methods: A common moiety method, Bayer AG Method No. 00407, was submitted with the previous spiroxamine petitions on imported bananas (PP# 3E6538), hops (PP#s 3E6518 and 3E6783), and imported grapes (PP# 0F6122). The method involves extraction, acid hydrolysis, solid phase extraction cleanup, and silylation of the aminodiol analyte to its ditri-methylsilyl (di-TMS) derivative for analysis by GC/MS. Residues are reported in parent equivalents; the LLMV is 0.05 ppm. Bayer AG Method No. 00407 adequately fulfills the requirements for an enforcement method. It has successfully been validated by an independent

laboratory and adequate radiovalidation data have been submitted. An adequate confirmatory method, using a column of different polarity, has been included in the method descriptions (DP#310311, N. Dodd, 03/01/2006).

Data-gathering methods: Samples of crop commodities that were collected from the magnitude of the residue studies were analyzed for residues of spiroxamine and total spiroxamine including its metabolites containing the aminodiol moiety using LC/MS/MS Method 01089. Under separate cover (MRID 47724901), Bayer CropScience submitted a complete method description and method validation data using grapes

Method 01089 was adequately validated with grapes. Untreated samples of grape were fortified with spiroxamine or aminodiol at 0.05 and 0.5 ppm. Spiroxamine-fortified samples were analyzed for spiroxamine or as aminodiol using Method 01089; and aminodiol-fortified samples were analyzed for aminodiol. Validation was conducted using both the quantitation and confirmatory mass ion transitions for spiroxamine and aminodiol. The method validation recoveries were adequate, within the acceptable range of 70-120%, for spiroxamine, spiroxamine quantitated as aminodiol, and aminodiol in/on fortified grapes.

In addition, Method 01089 was validated in conjunction with the submitted field trial and processing studies. In these studies, the method was modified to include a cation exchange, solid phase extraction cleanup step prior to analysis for aminodiol. Overall concurrent validation recoveries were acceptable for artichokes, tomato, bell pepper, and tomato paste and puree fortified with spiroxamine at 0.050 and 0.50 ppm, and asparagus fortified with spiroxamine at 0.050-1.0 ppm, each analyzed as spiroxamine and aminodiol. Fortification levels were adequate to bracket residues found in treated samples.

The method monitors two mass ion transitions for both spiroxamine and aminodiol. No radiovalidation data have been submitted for Method 01089; however, the extraction procedures are similar to the available GC/MS enforcement method, without aminodiol residues silylated to the di-trimethylsilyl derivative prior to analysis.

Spiroxamine was analyzed in conjunction with the previous grape petition (PP#0F6122) according to the FDA Multiresidue Method Test Guidelines (PAM Vol. I, Appendix II, 1/94). Protocol D appears to be suitable for the analysis of spiroxamine 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.

4.1.4 Drinking Water Residue Profile

Spiroxamine is a persistent and moderately to slightly mobile chemical according to the Food and Agricultural Organization (FAO) classification scheme (K_d values range from 4.61 to 892.6 mL/kg). There is no evidence of degradation by hydrolysis. Spiroxamine degrades with a half life of several months in soil and aerobic and anaerobic aquatic environments, and is semivolatile

(vapor pressure = 3.6 x 10^{-5} torr). Spiroxamine is fairly stable to aqueous photolysis ($t_{1/2}$ = 50 days), while less stable to soil photolysis ($t_{1/2}$ = 39 days). Field dissipation studies confirmed the low mobility and persistence of spiroxamine, as no spiroxamine leached below 6 inches, yet was observed to linger in the top soil layers at low concentrations for over a year.

There is a potential for spiroxamine to reach surface water through spray drift, as the compound may be applied by ground spray and aerial spray. Because spiroxamine is persistent in surface soils, there is also the potential for it to reach surface water through surface runoff either in solution or adsorbed to the soil. Based on the moderately high adsorption coefficients, it is unlikely that there will be significant contamination of surface water with spiroxamine through subsurface flow

A Tier 2 PRZM/EXAMS assessment based on hops was used to estimate drinking water concentrations derived from surface water sources. For the 1 in 10 year peak, the highest PRZM/EXAMS EDWC for spiroxamine was 19 µg/L based on application to Oregon hops. For the 1 in 10 year annual average, the highest PRZM/EXAMS EDWC was 15 µg/L, also based on application to Oregon hops.

Ground water. In lieu of sufficient groundwater monitoring data for spiroxamine, the Tier 1 groundwater screening model SCI-GROW was used to estimate concentration of spiroxamine in groundwater sources. Hops applications with an annual use rate of 1.41 lbs ai/A/year was used in the modeling and resulted in a groundwater EDWC of 0.035 µg/L.

Table 4.1.4. Tier II Estimated Drinking Water Concentrations (EDWCs) Resulting from Applications of Spiroxamine.

Use	Surface water (PRZM/EXAMS)			Ground water (SCIGROW)
	1-in-10 year acute (µg/L)	**1-in-10 year chronic (µg/L)**	**30- year average (µg/L)**	**Screening concentration (µg/L)**
Hops	19	15	12	0.035

4.1.5 Food Residue Profile

Reference: *Spiroxamine: Import Tolerance Petition on Artichokes, Asparagus and Fruiting Vegetables (Crop Group 8) (PP# 9E7564). Summary of Analytical Chemistry and Residue Data. D. Rate, DP371636, 3/31/10*

Crop Field Trials

Bayer CropScience submitted field trial data in support of their request to establish import tolerances on artichokes, asparagus and fruiting vegetables grown in Mexico and Peru. The results of the field trials are summarized in Table 4.1.5a. Although samples were analyzed for both spiroxamine and total spiroxamine, only total spiroxamine residues are included in Table

4.1.5a; refer to DERs 47724902 through 47724904 for complete presentation of residue data. The submitted data for each crop are discussed below.

Table 4.1.5a. Summary of Total Spiroxamine Data from Crop Field Trials.

Commodity	Total Applic. Rate (lb ai/A) [kg ai/ha]	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Fruiting Vegetables [Mexico use on tomato and pepper = 0.96 lb ai/A (1.1 kg ai/ha) total application rate, 3-day PHI] [Peru use on pepper only = 0.80 lb ai/A (0.90 kg ai/ha) total application rate, 7-day PHI]									
Tomato	0.946-0.980 [1.06-1.10]	3	24	<0.050	0.20	0.17	0.050	0.069	0.043
Bell Pepper	0.946-0.980 [1.06-1.10]	3	12	<0.050	0.22	0.19	0.10	0.12	0.072
	0.964[2] [1.08]	7	2	0.24	0.27	0.25	0.25	0.25	--
		10	2	0.20	0.29	0.24	0.24	0.24	--
		14	2	0.38	0.44	0.41	0.41	0.41	--
Non-bell Pepper[3]	0.484 [0.541]	3	2	0.17	0.37	0.27	0.27	0.27	--
	0.765 [0.858]	3	2	0.08	0.08	0.08	0.08	0.08	--
	0.967 [1.08]	3	2	0.12	0.12	0.12	0.12	0.12	--
Asparagus [Mexico and Peru use =1.34-1.67 lb ai/A (1.5-1.9 kg ai/ha) total application rate, 21-day PHI]									
Asparagus, fresh spears	1.64-1.71 [1.84-1.92]	21	20	<0.050	<0.050	0.050	0.050	0.050	--
Artichoke [Peru use = 0.80 lb ai/A (0.90 kg ai/ha) total application rate, 3-day PHI]									
Artichoke	0.796-0.826 [0.893-0.927]	3	6	0.06	0.36	0.32	0.09	0.16	0.13

[1] HAFT = Highest average field trial result.
[2] Data from the bell pepper decline trial were included because results at longer PHIs had higher residues.
[3] Although 2 of the trials were under-applied, these data are included because the results of the trial with the lowest application rate had the highest residues.

Vegetable, Fruiting (Crop Group 8)

47724092.der.doc, D. Rate, 03/02/2010

Bayer CropScience has submitted field trial data for spiroxamine on tomato and pepper (bell and non-bell), the representative crops of the fruiting vegetable, crop group 8. Twenty-one field trials were conducted during the 2007 and 2008 growing seasons.

Conclusions. The submitted tomato, bell pepper and non-bell pepper field trial data are adequate. The tomato and bell pepper trials were conducted according to the labeled use pattern for fruiting vegetables grown in Mexico and Peru, an adequate number of trials were conducted, and samples were analyzed for residues of concern using an adequate method. Two of the three submitted non-bell pepper field trials were under-applied (50-79% of target) and the results showed inconsistent results; the non-bell pepper samples treated at 50% of the target rate bore the highest residues. Several conditions may account for the inconsistent residues on the non-bell pepper field trials, including the size and morphology of the pepper varieties used in the trials.

Based on the residue data from the representative crops (tomato, bell pepper, and non-bell pepper), HED recommends for the proposed tolerance of 1.2 ppm in/on vegetables, fruiting, crop group 8. For non-bell pepper, residues were adjusted using proportionality to a 1X use rate for the MRL calculator. The MRL calculated tolerances were 0.3 ppm for tomato at a 1X use rate (3 day PHI), 0.6 ppm for bell peppers at a 1X use rate (3 day PHI), 1.0 ppm for bell peppers at a 1X use rate (3-14 day PHI), 0.6 ppm for non-bell peppers unadjusted for use rate (3 day PHI) and 1.1 ppm for non-bell peppers with residues adjusted to a 1X use rate (3 day PHI). The maximum reported residue for each individual commodity is approximately 5X or less than the recommended group tolerance, allowing for a group tolerance to be set.

Asparagus
47724903.der.doc, D. Rate, 03/02/2010

Bayer CropScience has submitted field trial data for spiroxamine on asparagus. Ten asparagus field trials were conducted during the 2008 growing season.

Conclusions. The submitted asparagus field trial data are adequate and approximate the use patterns listed in the GAP Summary from Section B of the petition. Total spiroxamine residues were nondetectable in/on all asparagus samples; therefore, the tolerance spreadsheet was not used to determine the appropriate tolerance level. The residue data support a tolerance for total spiroxamine residues in/on asparagus at the method LOQ (0.05 ppm).

Artichoke
47724904.der.doc, D. Rate, 03/03/2010

Bayer CropScience has submitted field trial data for spiroxamine on globe artichokes. Three field trials were conducted in Peru during the 2008 growing season.

Conclusions. The submitted globe artichoke field trial data are adequate and approximate the use patterns listed in the GAP Summary from Section B of the petition. The residue data for total spiroxamine residues in/on artichokes were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Tolerances Based on Field Trial Data* SOP (August 2009 version) to determine the appropriate tolerance level. Based on the spreadsheet, HED recommends for a tolerance of 0.7 ppm for artichoke. However, a revised Section F must be submitted to correct the commodity definition from artichoke to artichoke, globe.

Processed Food and Feed
Tomato
47724905.der.doc, D. Rate, 03/03/2010

Bayer CropScience has submitted a processing study on tomatoes. At a trial conducted in 2007 in CA, an 800 g/L EC formulation of spiroxamine was applied to tomatoes as three broadcast foliar applications at ~1.606 lb ai/A/application (1.80 kg ai/ha/application), with 7-day

retreatment intervals, for a total rate of 4.797 lb ai/A (~5X the maximum seasonal rate for tomato in Mexico).

Conclusions. The tomato processing study is acceptable. Residues of total spiroxamine concentrated in paste (1.8X) but residues did not concentrate in puree (0.8X). The maximum expected residue of total spiroxamine in tomato paste, resulting from the proposed use, is ~0.3 ppm. This value was calculated by multiplying the processing factor of 1.8 by the HAFT of 0.17 ppm (see Table 4.1.5a). Based on these data, tolerances are not needed for the processed commodities of tomato since any expected residues in tomato paste resulting from the proposed use pattern will be covered by the recommended tolerance of 1.2 ppm for the fruiting vegetable group.

The additional samples generated for risk assessment indicate that residues of spiroxamine and total spiroxamine did not concentrate in washed fruit, cooked tomato, canned tomato and tomato juice, but did concentrate in dried tomato fruit (11X).

Table 4.1.5b. Summary of Processing Factors for Spiroxamine.

RAC	Processed Commodity	Total Spiroxamine Processing Factor
Tomato, fruit	Paste	1.8X
	Puree	0.8X
	Washed fruit	0.7X
	Cooked tomato	0.6X
	Canned tomato	0.3X
	Juice	0.4X
	Dried fruit	11X

4.1.6 International Residue Limits

There are no Codex, Canadian or Mexican maximum residue limits (MRLs) established for residues of spiroxamine in crop or livestock commodities. An International Residue Limit (IRL) form is appended to this document as Appendix C.

4.2 Dietary Exposure and Risk

Reference: *Spiroxamine: Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Proposed Tolerances on Imported Artichoke, Asparagus and Fruiting Vegetables (Crop Group 8)* D371637.drs, C. Walls, 5/5/10.

4.2.1 Acute Dietary Exposure/Risk

Acute dietary risk analyses were conducted with the DEEM-FCID™ model to form a conservative evaluation of exposure for spiroxamine. The modeled exposure estimates for the acute assessment are based on tolerance level residues assuming 100% of the crops were treated and include the highest EWDC relevant to the scenario (surface water). At the 95th percentile of

exposure, all acute analyses yielded risk estimates well below 100% of the aPAD threshold level of concern for each population subgroup. For the U.S. Population subgroup, acute aggregate dietary risk was calculated at 11% of the aPAD with an exposure level of 0.011 mg/kg/day. For the subgroup with the highest calculated exposure, Children 1-2 years old, acute aggregate dietary risk occupied 36% of the aPAD with an exposure of 0.036 mg/kg/day. Comparison of the food only results to the food + water results demonstrates that the additional risk added by water consumption is very small. An overview summarizing the results of the acute dietary assessments with the population subgroup having the highest exposure noted in bold is presented in Table 4.2

4.2.2 Chronic Dietary Exposure/Risk

A chronic dietary assessment was conducted with the DEEM-FCID™ model to form a conservative evaluation of exposure for spiroxamine. The assessment was conducted assuming that 100%of crops with the requested uses and currently registered uses of spiroxamine are treated and that all treated crops contain residues at tolerance level. All chronic analyses yielded risk estimates well below the 100% of the cPAD threshold level of concern for each population subgroup. For the U.S. Population subgroup, chronic aggregate dietary risk was calculated at 13% of the cPAD with an exposure level of 0.0032 mg/kg/day. For the subgroup with the highest calculated exposure, Children 1-2 years old, chronic aggregate dietary risk occupied 40% of the cPAD with an exposure of 0.010 mg/kg/day. Comparison of the food only results to the food + drinking water results demonstrates that the additional risk added by water consumption is small. An overview summarizing the results of the chronic dietary assessment with the population subgroup having the highest exposure noted in bold is presented in Table 4.2.

Table 4.2 Result of Acute and Chronic Dietary Exposure and Risk Estimates for Spiroxamine.

Population Subgroup	PAD, (mg/kg/day)	DEEM-FCID (food only)		DEEM-FCID (food and water)	
		Exposure, (mg/kg/day)	% PAD	Exposure, (mg/kg/day)	%PAD
Acute Dietary Estimates (95th Percentile of Exposure)					
U.S. Population	0.1	0.011036	11	0.011423	11
All infants (< 1 yr)		0.031673	32	0.033505	34
Children 1-2 yrs		**0.035368**[1]	**35**	**0.036363**	**36**
Children 3-5 yrs		0.024648	25	0.025317	25
Children 6-12 yrs		0.013940	14	0.014150	14
Youth 13-19 yrs		0.007044	7.0	0.007329	7.3
Adults 20-49 yrs		0.009166	9.2	0.009667	10
Adults 50+ yrs		0.008577	8.6	0.009020	9.0
Females 13-49 yrs		0.007966	8.0	0.008423	8.4
Chronic Dietary Estimates					
U.S. Population		0.002860	11	0.003176	13

Table 4.2 Result of Acute and Chronic Dietary Exposure and Risk Estimates for Spiroxamine.

Population Subgroup	PAD, (mg/kg/day)	DEEM-FCID (food only)		DEEM-FCID (food and water)	
		Exposure, (mg/kg/day)	% PAD	Exposure, (mg/kg/day)	%PAD
All infants (< 1 yr)	0.025	0.005377	22	0.006414	26
Children 1-2 yrs		**0.009525**	**38**	**0.009995**	**40**
Children 3-5 yrs		0.005890	24	0.006330	25
Children 6-12 yrs		0.002952	12	0.003255	13
Youth 13-19 yrs		0.001640	6.6	0.001869	7.5
Adults 20-49 yrs		0.002465	9.9	0.002760	11
Adults 50+ yrs		0.002468	9.9	0.002779	11
Females 13-49 yrs		0.002026	8.1	0.002320	9.3

[1]The population subgroup with the highest estimated chronic dietary (food + drinking water) exposure and risk is indicated by bold text

5.0 Residential (Non-Occupational) Exposure/Risk Characterization

This document addresses the proposed tolerances on imported artichokes, asparagus and fruiting vegetables of spiroxamine. No residential uses are being requested at this time, and no residential uses currently exist; therefore, no residential exposure is expected. Consequently, no risk assessment has been conducted.

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 methods. 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. On a chemical by chemical basis, 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 database 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 with specific products with significant risks associated with drift.

6.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (*e.g.*, a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

6.1 Acute Aggregate Risk

Refer to Section 4.2.1, which discusses acute dietary exposure (food and drinking water) in detail. The dietary route alone is relevant for acute exposure and risk assessment; and the acute dietary exposure and risk assessment conducted for spiroxamine is screening-level (the assessment assigns tolerance level residue values to all food commodities proposed to be treated with spiroxamine and modeled residue values to all drinking water).

6.2 Short- and Intermediate-Term Aggregate Risk

Because there are no residential uses proposed for spiroxamine, there is no potential for short- and intermediate-term exposure to spiroxamine.

6.3 Long-Term Aggregate Risk

Refer to Section 4.2.2, which discusses chronic dietary exposure (food and drinking water) in detail. The dietary route alone is relevant for long-term/chronic exposure and risk assessment; and the chronic dietary exposure and risk assessment conducted for spiroxamine is health protective (the assessment assigns average field trial residue values to all food commodities proposed to be treated with spiroxamine and modeled residue values to all drinking water).

7.0 Cumulative Risk Characterization/Assessment

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 mammalian 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 mammalian 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/.

8.0 Occupational Exposure/Risk Pathway

This document only presents the assessment of the proposed new agricultural uses of spiroxamine. No domestic crop uses are being requested at this time; therefore, no occupational risk assessment has been conducted for the present action. Refer to the memo, *SPIROXAMINE: Occupational and Residential Risk on Assessment to support Request for Section 3 registration of Spiroxamine on Hops and Grapes.. DP287042, J. Arthur, 11/18/03*, for occupational risk associated with domestic crops.

9.0 Data Needs and Label Requirements

9.1 Toxicology

870.7800 Immunotoxicity

- As part of the new 40 CFR §158 Guidelines, an immunotoxicity study in rats and/or mice is required (see Appendix A3).

9.2 Residue Chemistry

860.1200 Directions for Use

- The label submitted for Prosper® EC 500 from Peru does not include all pertinent use pattern information. The following information should be included: the maximum number of applications specific to the crop, the maximum annual application rate, application type and timing (as it relates to plant growth stage), re-treatment interval, application tank-mix preparation, volume of spray mix per unit area, application equipment, and the preharvest interval.. Since the data were generated without the use of adjuvants, adjuvants should be prohibited on both labels.

860.1380 Storage Stability

- Deficiency No. 5 from Agency memo (DP#310311, N. Dodd, 03/01/2006) must still be satisfied. For hops, the dates of sample analysis for samples reported in MRIDs 46052804 and 46052805 must be submitted.

860.1500 Crop Field Trials

- A revised Section F must be submitted correcting the commodity definitions for artichoke, globe and vegetable, fruiting, crop group 8. See the summary tolerance table (Table 1).

860.1650 Submittal of Analytical Reference Standards

- The analytical standard for *N*-ethyl-*N*-propyl-1,2-dihydroxy-3-aminopropane (a.k.a. aminodiol) must be submitted to the National Pesticide Standards Repository.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food uses for spiroxamine are in Table A.1.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1. Toxicology Data Requirements – Spiroxamine

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (non rodent)	yes	yes
870.3200	21-Day Dermal (28/29-day)	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation*	yes	yes*
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (non rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (non rodent)	-	-
870.4200a	Oncogenicity (rat)	-	-
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	yes	no
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	no	-
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes
870.7800	Immunotoxicity	yes	no

*28-day inhalation toxicity study in rats

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Spiroxamine

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat	45090125	LD50 >500 mg/kg	III
870.1200	Acute dermal- rat	45090128	LD50 >1068 mg/kg	II
870.1300	Acute inhalation – rat	45090130	LC50 >2.029 mg/L[a]	IV
870.2400	Acute eye irritation –rabbit	45090132	Non-irritant	IV
870.2500	Acute dermal irritation – rabbit	45090132	Severely irritating	I
870.2600	Skin sensitization – guinea pig	45090205	Sensitizer	N/A

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Spiroxamine

Guideline No	Study Type	MRID No. (year)/ Classification /Dose	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.
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/Non-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)	**Maternal NOAEL = 30 mg/kg/day** **LOAEL = 100 mg/kg/day based on decreased**

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Spiroxamine

Guideline No	Study Type	MRID No. (year)/ Classification /Dose	Results
		Acceptable/Guideline Doses:0, 10, 30, or 100 mg/kg/day	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).
870.3700a (rats)	Prenatal (dermal) developmental in rodents	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 > HDT**
870.3800	Reproduction and fertility effects (rat)	47526301 (2008) Acceptable /Guideline Doses: 0, 20, 80 or 300 ppm M: 0, 1.4, 5.6 and 22.2 mg/kg/day F: 0, 1.8, 6.8 and 25.6 mg/kg/day	**Parental NOAEL = 5.6 mg/kg/day** **LOAEL = 22.2 mg/kg/day** based on decreased body weight gains in the P males and females, decreased body weights and body weight gains in the F1 males and females, and decreased relative food **consumption in the** F1 males during premating, decreased body weights and body weight gains during gestation in the P females, and diffuse hyperkeratosis of the esophagus in both sexes of both generations **Offspring NOAEL = 5.6 mg/kg/day** **LOAEL = 22.2 mg/kg/day** based on decreased body weights and body

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Spiroxamine

Guideline No	Study Type	MRID No. (year)/ Classification /Dose	Results
			weight gains, and increased balanopreputial separation and vaginal patency in the F1 and F2 pups
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.
870.4300	Combined Chronic Toxicity/Carcinogenicity (rat)	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.
870.4200	Carcinogenicity (mouse)	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.**
870.4200	Carcinogenicity (mouse)	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.**
870.5100	Gene Mutation (*in vitro* bacteria)	45090223 (1990) Acceptable/Guideline (a.i.)	Negative, ± S9 up to cytotoxic 1000 µg/plate.
870.5395	Mammalian Cytogenetics (mouse micronucleus)	45090225 (1991) Acceptable/Guideline (a.i.)	Negative, at clinically toxic i.p. dose.
870.5300	Gene Mutation (*in vitro* mammalian V79)	45090224 (1991) Acceptable/Guideline (a.i.)	Negative, ± S9 up to cytotoxic /precipitation 200 µg/mL.
870.5375	Mammalian Cytogenetics *(in vitro*	45090226 (1995)	Negative, ± S9 up to cytotoxic doses.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Spiroxamine

Guideline No	Study Type	MRID No. (year)/ Classification /Dose	Results
	CHL)	Acceptable/Guideline (a.i.)	
870.5550	Unscheduled DNA Synthesis	45090227 (1991) 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 (rat)	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 (rat)	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.

A.3 Executive Summaries

A.3.1 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction toxicity study (MRID 47526301), Spiroxamine (95.1% a.i.; Batch No. EDTH004650) was administered in the diet to 30 Wistar (Crl:WI[HAN]) rats/sex/dose group at dietary levels of 0, 20, 80, or 300 ppm (equivalent to 0/0, 1.4/1.8, 5.6/6.8, and 22.2/25.6 mg/kg in males/females during pre-mating) for two successive generations with one litter per generation. The P generation animals were fed the test diets for at least ten weeks prior to mating to produce the F1 litters. The F1 litters were culled on post-natal day 4 (PND 4) to eight pups/litter (four/sex where possible). On PND 21, a sufficient number of pups/sex/litter were selected and fed the same test diet concentration as their dam. These animals were fed the test diets for approximately ten weeks prior to mating to produce the F2 litters.

No treatment-related effects were observed on mortality, clinical signs, hematology, clinical chemistry, organ weights, or macroscopic findings.

Systemic toxicity was observed in the parental animals at 300 ppm. During pre-mating, body weight gains were decreased by 9% during Days 0-70, and by 7% during Days 0-105 in the P males. In the P females, body weight gains were decreased by 14% during Days 0-70. In the F1 males, body weights were decreased by 8-10% during Days 0-98; body weight gains were decreased by 12% during Days 0-70 and by 7% during Days 0-98; and relative food consumption was increased by 4-10% during Days 0-70. In the F1 females, body weights were decreased by 7-9% during Days 0-70, and body weight gains were decreased by 11% during this period. During gestation, body weights were decreased by 4-5% during gestation day (GD) 6-20 in the P dams, resulting in decreased gestational body weight gains of 10%.

Diffuse hyperkeratosis of the esophagus was noted in all 300 ppm groups (vs. 0 controls) as follows: minimal to slight in the P males (17); minimal to moderate in the P females (25); minimal to marked in the F1 males (22); and minimal to moderate in the F1 females (27).

The LOAEL for parental toxicity is 300 ppm (equivalent to 22.2/25.6 mg/kg in males/females), based on decreased body weight gains in the P males and females, decreased body weights and body weight gains in the F1 males and females, and decreased relative food consumption in the F1 males during premating, decreased body weights and body weight gains during gestation in the P females, and diffuse hyperkeratosis of the esophagus in both sexes of both generations. The NOAEL is 80 ppm (equivalent to 5.6/6.8 mg/kg in males/females).

There were no effects of treatment on the survival indices, mean number of live pups, mean litter size, or sex ratio, clinical observations, organ weights, or macroscopic or microscopic findings in either the F1 or F2 offspring.

Offspring toxicity was observed at 300 ppm. In the F1 pups, body weight gains were decreased

as follows: 10% in the males, 12% in the females, and 11% in both sexes during PND 14-21; 8% in the males and females during PND 4-21; and 7% in both sexes during PND 0-21. This resulted in a 7% decrease in body weights (both sexes) on PND 21. In the F2 pups, body weight gains were decreased as follows: 13% in the males, 11% in the females, and 12% in both sexes during PND 14-21; 9% in the males, 8% in the females, and 9% in both sexes during PND 4-21; and 9% in both sexes during PND 0-21. This resulted in an 8-9% decrease in body weights on PND 21. Body weights were also decreased by 7% in the females and by 6% in both sexes on PND 0. Additionally in the F1 pups, preputial separation was slightly delayed (44.6 days treated vs. 42.0 days controls; $p \leq 0.01$) in the males, and vaginal patency was delayed (38.4 days treated vs. 34.3 days controls) in the females. These values were above the range of historical controls (40.7-44.0 days for preputial separation; 33.4-35.5 days for vaginal patency), and were considered to be a reflection of the decreased body weights, which contributed to a delay in development.

The LOAEL for offspring toxicity is 300 ppm (equivalent to 22.2/25.6 mg/kg in males/females), based on decreased body weights and body weight gains, and delays in balanopreputial separation and vaginal patency in the F1 and F2 pups. The NOAEL is 80 ppm (equivalent to 5.6/6.8 mg/kg in males/females).

No treatment-related differences were observed in estrus cycle length or cyclicity, sperm parameters, numbers of primordial and pre-antral follicles and corpora lutea, mating, fertility, or gestation indices, pre-coital interval length, gestation length, or number of implantation sites.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 300 ppm (equivalent to 22.2/25.6 mg/kg in males/females).
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

A.4 Rationale for Toxicity Data Requirement

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic

effects.

Practical Utility of the Data

How will the data be used?

These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).

How could the data impact the Agency's future decision-making?

If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

APPENDIX B: Structure, Nomenclature and Physical and Chemical Properties

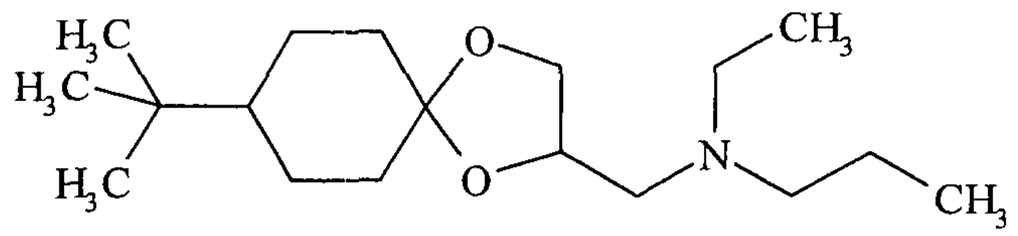
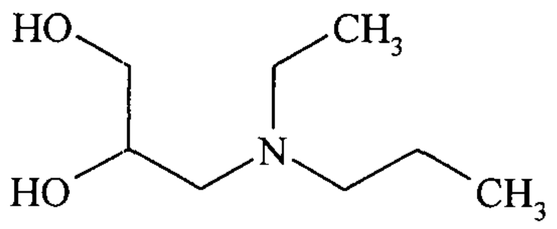
TABLE B.1. Test Compound Nomenclature.	
Compound	
Common name	Spiroxamine
Company experimental name	KWG 4168
IUPAC name	8-*tert*-butyl-1,4-dioxaspiro[4,5]decan-2-ylmethyl(ethyl)(propyl)amine
CAS name	8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine
CAS registry number	118134-30-8
End-use products (EP)	Impulse® 800 EC (Mexico) and Prosper® 500 EC (Peru)
Aminodiol	 3-[ethyl(propyl)amino]propane-1,2-diol

TABLE B.2. Physicochemical Properties of the Technical Grade Test Compound: Spiroxamine.		
Parameter	Value	Reference[1]
Boiling point	329°C at 1013.25 hPa	45090102
pH	9.9 (suspension of 1 g in 50 mL water)	45090102
Density	0.93 g/mL at 20°C	45090102
Water solubility	>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.	45090102
Solvent solubility	>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.	45090102
Vapor pressure	Diastereomer A: 4.0×10^{-5} hPa. Diastereomer B: 5.7×10^{-5} hPa.	45090102
Dissociation constant, pK_a	pK = 7.9 at 20°C in aqueous system containing 40% 2-propanol.	45090102
Octanol/water partition coefficient, Log(K_{OW})	Diastereomer A: 610 (log P_{ow} = 2.79) at pH 7 at 20°C. Diastereomer B: 960 (log P_{ow} = 2.98) at pH 7 at 20°C.	45090102
UV/visible absorption spectrum	Does not show a maximum absorbance in the range of 200 to 400 nm.	45090102

[1] As reported in DP# 284836, S. Malak, 2/6/2003

Appendix C: International Residue Limit Status

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: 8-(1,1-dimethylethy)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine	Common Name: Spiroxamine	X Proposed tolerance □ Reevaluated tolerance □ Other	Date: 1/25/10

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number: PP#9E7564 DP#: 371636 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: D. Rate, J.. Redden/RIMUERB
	Residue definition: 8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4,5]decane-2-methanamine] and its metabolites containing the aminodiol moiety

Crop (s)	MRL (mg/kg)	Crop(s)	Proposed Tolerance (ppm)
		Artichoke, globe	0.7
		Asparagus	0.05
		Vegetable, fruiting, group 8	1.2

Limits for Canada	Limits for Mexico
X No Limits □ No Limits for the crops requested	X No Limits □ No Limits for the crops requested
Residue definition: N/A	Residue definition: N/A

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions: S. Funk, 02/01/2010.

13544

R183591

Chemical Name: 1,4-Dioxaspiro?4,5Udecane-2-methanamine, 8-(1,1-dimethylethyl)-N-ethyl-N-propyl-

PC Code: 120759
HED File Code: 14000 Risk Reviews
Memo Date: 6/18/2010
File ID: 00000000
Accession #: 000-00-0135

HED Records Reference Center
6/30/2010