Proposed Registration Decision PRD2015-14

Spiroxamine

(publié aussi en français)

8 May 2015

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2015-14E (print version)
H113-9/2015-14E-PDF (PDF version)

Table of Contents

Overview

Proposed Registration Decision for Spiroxamine

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Spiroxamine Technical Fungicide and Impulse 500 EC Fungicide, containing the technical grade active ingredient spiroxamine, to control powdery mildew (*Uncinula necator*, syn. *Erysiphe necator*) on grape.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Spiroxamine Technical Fungicide and Impulse 500 EC Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

---

[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on spiroxamine, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on spiroxamine, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Spiroxamine?

Spiroxamine is a sterol biosynthesis inhibitor fungicide with systemic activity. This active ingredient provides control of powdery mildew caused by the ascomycetous fungus, *Uncinula necator* (syn. *Erysiphe necator*) in grapes.

Health Considerations

Can Approved Uses of Spiroxamine Affect Human Health?

Spiroxamine is unlikely to affect human health when Impulse 500 EC Fungicide is used according to label directions.

Potential exposure to spiroxamine may occur through the diet (food and water) or when handling and applying the end-use product Impulse 500 EC Fungicide. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, the technical grade spiroxamine was moderately to highly acutely toxic by the oral route and slightly acutely toxic by the dermal and inhalation routes of exposure. Spiroxamine was non-irritating to the eyes but moderately irritating to the skin. Spiroxamine caused an allergic skin reaction. Based on the acute toxicity data, the signal words and hazard statements DANGER – POISON, SKIN IRRITANT and POTENTIAL SKIN SENSITIZER are required on the label.

---

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Impulse 500 EC Fungicide, containing spiroxamine, was moderately acutely toxic by the oral route, of low dermal toxicity, and slightly acutely toxic by the inhalation route. It was severely irritating to the eye and moderately irritating to the skin. It caused an allergic skin reaction. Based on the acute toxicity data, signal words and hazard statements DANGER – POISON, EYE and SKIN IRRITANT, POTENTIAL SKIN SENSITIZER and their associated symbols are required on the product label.

Health effects in animals given repeated doses of spiroxamine included effects on the liver, lining of the gastrointestinal and urogenital tracts, the eye and body weight. Spiroxamine did not cause cancer in animals and did not damage genetic material. There was no indication that spiroxamine caused damage to the nervous or immune systems.

When spiroxamine was given to pregnant or nursing animals, it delayed the development of the fetuses and offspring at doses that were toxic to the mother. The risk assessment protects against the effects of spiroxamine by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the total population and children 1-2 years old, the subpopulation which would ingest the most spiroxamine relative to body weight, are expected to be exposed to less than 31% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from spiroxamine is not of health concern for all population subgroups.

The risk assessment is protective of both the non-cancer effects and potential tumor formation.

Acute dietary (food plus drinking water) intake estimates for the total population and all population subgroups were less than 33% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was children 1-2 years old.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted in the United States and other countries using spiroxamine on grapes and bananas are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation Document.

Occupational Risks from Handling Impulse 500 EC Fungicide

Occupational risks are not of concern when Impulse 500 EC Fungicide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Impulse 500 EC Fungicide, as well as field workers re-entering freshly treated vineyards, can come in direct contact with spiroxamine residues on the skin or through inhalation of spray mists. Therefore, the label specifies that anyone mixing, loading and applying Impulse 500 EC Fungicide, or involved in equipment clean-up and repairs, must wear long pants, a long-sleeved shirt, chemical-resistant gloves made of waterproof material, socks, shoes and goggles. In addition, all applicators driving an open-cab tractor must wear a chemical-resistant headgear (includes Sou'Wester hats or large brimmed waterproof hats and hoods with sufficient neck protection). The label also requires that workers do not enter treated fields for 12 hours after application to conduct activities such as transplanting, scouting, hand pruning, hand weeding, propagating, bird control and trellis repairs; three days to conduct activities such as hand set irrigation; 17 days to conduct activities such as tying/training, hand harvesting and leaf pulling; and 24 days to conduct activities such as girdling and turning. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals are not expected to be of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are also not of concern.

Environmental Considerations

What Happens When Spiroxamine Is Introduced Into the Environment?

When used according to label directions, spiroxamine is not expected to pose an unacceptable risk to the environment. Labelled risk reduction measures mitigate potential risks posed by spiroxamine to freshwater/marine/estuarine organisms.

Spiroxamine will enter the environment when applied as Impulse 500 EC Fungicide on grapes for the control of powdery mildew. Spiroxamine breaks down in the environment mainly through soil microbial activities and is not expected to persist for long periods of time. Spiroxamine is considered to have low potential to move through the soil and enter groundwater. However, it does have the potential to enter aquatic environments through surface run-off and spray-drift. Spiroxamine dissolves readily in water but is expected to move into sediments in aquatic environments. Spiroxamine is not expected to enter the atmosphere in large amounts and is not expected to be transported long distances from where it was applied. Spiroxamine is unlikely to accumulate in the tissues of organisms.

Spiroxamine presents a negligible risk to most terrestrial organisms including earthworms, honeybees, birds, and vascular plants. If exposed to high enough levels, it could pose a reproductive risk to mammals, a chronic risk to certain aquatic organisms (for example, amphibians, freshwater fish, freshwater invertebrates,) and an acute risk to amphibians, as well as freshwater and marine algae. Statements to inform the user of the potential hazards to mammals and aquatic organisms as well as spray buffer zones to protect sensitive aquatic habitats are proposed for the label.

Value Considerations

What Is the Value of Impulse 500 EC Fungicide?

Impulse 500 EC Fungicide is a foliar applied conventional fungicide for use on grapes to control powdery mildew. It has a low to medium risk for resistance development. It will address a high priority disease as identified by Canadian growers.

Impulse 500 EC Fungicide has demonstrated good control of powdery mildew on grape, and its availability offers growers a new mode of action for resistance management. This product can be incorporated into integrated pest management programs with other chemical and cultural controls for disease and resistance management.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Impulse 500 EC Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with spiroxamine on the skin or through inhalation of spray mists, anyone mixing, loading and applying Impulse 500 EC Fungicide, or involved in equipment clean-up and repairs, must wear long pants, a long-sleeved shirt, chemical-resistant gloves made of waterproof material, socks, shoes and goggles. In addition, all applicators driving an open-cab tractor must wear chemical-resistant headgear. Chemical-resistant headgear includes Sou'Wester hats or large brimmed waterproof hats and hoods with sufficient neck protection. Furthermore, workers re-entering freshly treated vineyards to perform postapplication activities are required to respect the following restricted-entry intervals:

Re-Entry Activity	Restricted-entry interval
Transplanting, scouting, hand pruning, hand weeding, propagating, bird control, trellis repairs	12 hours[1]
Irrigation (hand set)	3 days
Tying/training, hand harvesting, leaf pulling	17 days
Girdling, turning	24 days

[1] A minimum of 12 hours is applicable for all agricultural workers to allow residues to dry and vapors to dissipate, hence limiting potential effects such as irritation or allergic reactions.

In addition, standard label statements to protect against drift during application are on the label.

Environment

Statements to inform the user of the potential hazards to mammals and aquatic organisms as well as spray buffer zones to protect sensitive aquatic habitats are proposed for the label. Spray buffer zones of 1 to 40 metres are required to protect sensitive freshwater habitats, and spray buffer zones of 2 to 35 metres are required to protect sensitive estuarine/marine habitats. These spray buffer zones are to be specified on the product label.

Next Steps

Before making a final registration decision on spiroxamine, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

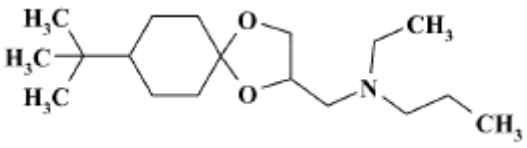
When the PMRA makes its registration decision, it will publish a Registration Decision on spiroxamine (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Spiroxamine

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	spiroxamine
Function	fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	8-*tert*-butyl-1,4-dioxaspiro[4.5]decan-2-ylmethyl(ethyl)(propyl)amine
2. Chemical Abstracts Service (CAS)	8-(1,1-dimethylethyl)-*N*-ethyl-*N*-propyl-1,4-dioxaspiro[4.5]decane-2-methanamine
CAS number	118134-30-8
Molecular formula	$C_{18}H_{35}NO_2$
Molecular weight	297.5
Structural formula	
Purity of the active ingredient	97.2%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product–Spiroxamine Technical Fungicide

Property	Result
Colour and physical state	Yellowish liquid
Odour	Weak amine-like odour reminiscent of pyridine
Melting range	Not available
Boiling point or range	Decomposes at 120°C before boiling
Density at 20°C	0.930 g/mL

Property	Result
Vapour pressure at 20°C	**Diastereomer** **Pa (20°C)** **Pa (25°C)** A 4.0×10^{-3} 7.1×10^{-3} B 5.7×10^{-3} 1.0×10^{-2}
Ultraviolet (UV)-visible spectrum	Absorption at $\lambda > 300$ nm was not observed.
Solubility in water at 20°C	**pH** **diastereomer A** **diastereomer B** 3 >200 g/L of mixture of A and B 7 470 mg/L 340 mg/L 9 14 mg/L 10 mg/L
Solubility in organic solvents at 20°C	>200 g/L in the following solvents: n-hexane, toluene, dichloromethane, 2-propanol, 1-octanol, polyethylene glycol, polyethylene glycol + ethanol, acetone, dimethylformamide, ethyl acetate and acetonitrile
n-Octanol-water partition coefficient (K_{ow})	**pH** **log K_{ow}** **isomer A** **isomer B** 5.5 1.28 1.41 7 2.79 2.98 9 4.88 5.08
Dissociation constant (pK_a)	$pK_a = 7.9$ of conjugate base in an aqueous system containing 40% of 2-propanol, so fully or partially ionized at environmental pH.
Stability (temperature, metal)	Decomposes at 370°C (measured in glass, heating rate: 5 K/min); decomposes >120°C (open cup, heating rate: 5 K/min) Stable for 2 weeks at 54°C

End-Use Product – Impulse 500 EC Fungicide

Property	Result
Colour	Yellow to brown
Odour	Aromatic
Physical state	Clear liquid
Formulation type	Emulsifiable concentrate
Guarantee	500 g/L
Container material and description	HDPE bottles
Density	0.998 g/mL at 20°C
pH of 1% dispersion in water	9.3
Oxidizing or reducing action	The product is not an oxidizing agent, and does not contain any reducing agent either.
Storage stability	Stable for 2 weeks stored in HDPE bottles at 54°C
Corrosion characteristics	No negative effects to HDPE bottles were observed.
Explodability	The product does not contain any explosive components.

1.3 Directions for Use

Impulse 500 EC Fungicide is applied preventatively to grapes at early growth stages or when conditions are conducive to the development of powdery mildew, caused by *Uncinula necator*. Application may be made by means of either a field or airblast sprayer at rates ranging between 400-600 mL per hectare with a spray interval of 14 days. The higher rate is recommended when conditions favour the development of heavy disease pressure or in vineyards with a history of heavy disease pressure. As the maximum seasonal rate is 1.2 L/ha, up to two or three applications may be made per growing season. The use of a surfactant is not required.

1.4 Mode of Action

Spiroxamine is a systemic fungicide that is absorbed by leaf tissue and is acropetally translocated. It is known to have protective and curative action against powdery mildew on grape. Spiroxamine is a sterol biosynthesis inhibitor (SBI) that inhibits the biosynthesis of ergosterol, which is a major component of the plasma membrane of certain fungi, including that of *Uncinula necator*.

Spiroxamine belongs to the SBI Class II active ingredients, which are classified by the Fungicide Resistance Action Committee (FRAC) as Group 5 fungicides, and pose a low to medium risk for resistance to develop.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

A gas chromatography method with mass spectrometry detection (GC-MS; Method 00407 in plant matrices) was developed and proposed for data generation and enforcement purposes in foodstuffs. The method fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement method was successfully validated by an independent laboratory. Adequate extraction efficiencies were demonstrated using samples of grape and banana with bioincurred residues and analyzed with the enforcement method.

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) and gas chromatography with mass spectrometry (GC-MS) were developed and proposed for data generation and enforcement purposes in environmental media. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for spiroxamine was conducted. The database consists of the full array of toxicity studies currently required for health hazard assessment purposes. There are also studies assessing acute oral and short-term dietary toxicity as well as genotoxicity of a plant metabolite and several impurities. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is acceptable. The database is considered adequate to define the majority of toxic effects that may result from exposure to spiroxamine.

Metabolism and toxicokinetics were investigated using radiolabelled spiroxamine (cyclohexyl-1-^{14}C-spiroxamine and 1,3-dioxolan-4-^{14}C-spiroxamine) in single low and high dose as well as repeated low dose oral gavage studies in the rat. Absorption was rapid for both radiolabels and dose regimens. The maximum levels of radioactivity in plasma were reached within 1.5-2 and 4-8 hours respectively after low and high-dose administration. Based on the amounts excreted in urine, at least 51 and 67% of the administered dose (AD) (single or repeat doses of cyclohexyl-1-^{14}C-spiroxamine) were absorbed in female and male rats respectively. Excretion of oral doses was similar and rapid for both radiolabels. Elimination via expired air was very low. Following single low- and high-dose administration, the main route of elimination was urinary, while faecal excretion played a secondary role. Total recovery of radioactivity in 48 hours ranged from 80 to 94%. Urinary excretion of radioactivity was lower in female when compared to males under the same dosing regimen. At the high dose of cyclohexyl-1-^{14}C-spiroxamine, absorption was lower, at 39 and 51% AD in female and male rats, respectively. For 1,3-dioxolan-4-^{14}C-KWG 4168, between 60 to 75% AD was absorbed. The rapid absorption of orally dose spiroxamine was confirmed in the whole-body radiography assay. Analyses of the plasma concentrations showed that the radioactivity was readily distributed from the plasma into peripheral compartments. Radioactivity levels in the tissues were low. After low dose administration, the highest concentrations were found in the liver, thymus and adrenals. Minor amounts of the AD were retained in tissues and carcass by 48 hours.

Metabolism of spiroxamine involved an initial oxidation, with subsequent sulfation, dealkylation, hydroxylation, conjugation with glucuronide, and the ring cleavage. The major metabolite was spiroxamine-acid, which resulted from oxidation of the tertiary alkyl moiety. The acid was further metabolized by dealkylation, hydroxylation, and conjugation with glucuronide and sulfate. Cleavage of the ring resulted in the formation of the metabolite aminodiol which was exclusively excreted in the urine. The acid forms of the metabolites were also mainly excreted in the urine while the sulfate conjugates were mainly excreted in the faeces.

In the rat, the acute toxicity of spiroxamine was moderate by the oral route, and slight by the dermal and inhalation routes of exposure. In the mouse, it was highly toxic by the oral route. Spiroxamine was non-irritating to the eyes but moderately irritating to the skin of the rabbit. Spiroxamine was a potential skin sensitizer in guinea pigs (Maximization assay) but tested negative in a human skin patch test. It was concluded that it had skin sensitizing potential.

Assessment of acute toxicity studies with Impulse 500 EC Fungicide end-use product showed that it was moderately toxic via the oral route of exposure in rats. The product was of low toxicity by the dermal route, but was slightly toxic by the inhalation route in rats. In the rabbit, it was severely irritating to the eyes and moderately irritating to the skin. Dermal sensitization studies in guinea pigs demonstrated that Impulse 500 EC Fungicide was not a dermal sensitizer based on the Buehler protocol, but was a potential dermal sensitizer based on the local lymph node assay in the mouse.

In repeated dose gavage/dietary toxicity studies in mice, rats, and dogs, the liver, and epithelial lining of the respiratory, digestive, and urogenital tract were the main target organs. At high doses, spiroxamine induced increased liver weights, hypertrophy of hepatocytes, degenerative alterations of the liver (centrilobular fatty deposition), and induction of liver enzymes. The liver effects were reversible following cessation of spiroxamine administration.

In rats and mice, histopathological alterations of the mucosal epithelium of the gastrointestinal and the urogenital tract were found after repeated oral administration of spiroxamine. Hyperkeratosis of the epithelium was seen on the tongue and in the fore-stomach; the oesophagus showed hyperkeratosis, hyperplasia and hypertrophy. These effects were related to the strong irritant effect of spiroxamine following surface contact. Histopathological alterations of the mucosal epithelium were reversible after termination of spiroxamine exposure.

In dogs, ophthalmological findings such as bilateral sub-capsular clouding and cataract changes of the lens were observed at high doses after prolonged dietary exposure. The liver exhibited signs of hepatocytomegaly.

No systemic toxicological effects occurred in rabbits following daily dermal application of a concentration of 0.25% over a period of three weeks. However, the concentration caused severe skin reaction. The skin of animals treated with a lower concentration also exhibited erythema. Swelling, hardening and cracking of the skin developed at higher concentrations. In this study, dosing was limited by skin irritation and no systemic effects occurred even at doses that caused severe skin reactions.

In a 4-week inhalation study in rats, irritation-related findings were prominent in the respiratory tract at high concentrations. These changes consisted of metaplasia, hyperplasia and hyperkeratosis of the epithelium of larynx and nasal cavity. In the lungs, the number of macrophages was increased and there was bronchiolo-alveolar proliferation.

Spiroxamine was tested for potential genotoxic activity in a battery of in vitro and in vivo assays. Based on the uniformly negative results of these studies, spiroxamine was not considered genotoxic.

In long-term dietary toxicity studies in rats and mice, histopathological alterations of the epithelium of the gastrointestinal tract were noted. These effects (hyperkeratosis and acanthosis of the epithelium of tongue, oesophagus and fore-stomach) were related to the continuous irritant property of spiroxamine. Skin alterations of the ears and tips of the tail were observed in mice. Clear systemic toxicity at higher dose levels was demonstrated by lower body weights.

There was no clear evidence of oncogenic potential of spiroxamine in rats and mice. However, in the mouse, incidences of adrenal cortical adenoma were observed in both male control and male test animals in one of two studies. Although the incidence was numerically increased in the treated males compared to the concurrent control males, the increase was not statistically significant and both incidences were higher than the historical control values from the testing laboratory. There was no clear relationship between occurrence of adrenal cortical adenoma and adrenal hyperplasia, and there was no progression from adenoma to carcinoma. No other treatment-related tumours were observed in the female or in the rat. No genotoxicity was demonstrated for spiroxamine. Based on the weight of evidence, the slight increase of adrenal cortical adenoma in male mice was considered equivocal.

Two dietary reproductive toxicity studies in rats were conducted for spiroxamine. A high dose level caused clinical signs, increased mortality, lower food intake, and reduced body weights of the parental animals as well as hyperkeratosis in the esophagus in both studies. At this dose in the first study, offspring effects included clinical signs (laboured breathing, cyanotic, cold, thin, increased urination, and/or bloody nose), decreased litter size and decreased survival in both generations during postnatal days 0-4. The concern of these offspring effects was low because these effects were not observed in a subsequent study at the same dose level. In the subsequent study, the observed offspring effects were slightly delayed balanopreputial separation and vaginal patency in F_1 pups at the same dose which was also maternally toxic. The reproductive toxicity data demonstrated that adverse effects occurred only at a maternally toxic dose.

Three developmental toxicity studies were conducted in the rat via oral gavage. In the first study, the highest dose tested had no effect on the fetuses or maternal animals. In the second study, conducted at a much higher dose, most of the rats died, limiting the utility of this study. In the third study conducted at doses that covered a range between the first two studies, maternal and developmental toxicity were observed at the high dose. The maternal animals demonstrated decreased food intake and lower body-weight gains. The fetuses showed slightly delayed development (decreased body weight and delayed ossification). Malformations were observed in four fetuses (palatoschisis (cleft palate), three fetuses from three litters; caudal malposition of the left hindleg, one fetus). Historically, palatoschisis was recorded occasionally in rat fetuses. However the occurrence was invariably seen in a single litter. Thus, the observation of palatoschisis in three fetuses from three litters was considered to be treatment-related.

A dermal developmental toxicity study in rats was also conducted. Maternal and fetotoxicity occurred at the high dose. At this dose level the maternal animals had decreased body weight and there was a slightly higher number of fetuses with wavy ribs. There was no evidence of sensitivity of the young.

A developmental toxicity study was conducted in the rabbit by oral gavage. Toxicity occurred at a high dose level. Maternal animals exhibited encrustation at the corner of the mouth, anal prolapse, decreased food intake, decreased body weight, and few/soft feces. Developmental toxicity was demonstrated by the slight decrease in fetal and placental weights at this dose. There was no evidence that the fetus was more sensitive than adults.

There were no gross or histopathological changes in either the central or peripheral nervous system following either acute gavage or subchronic dietary exposure to spiroxamine in the rat. Nevertheless, there were transient behavioural changes in the rat following acute gavage exposure to spiroxamine. The behavioural changes included incoordination, piloerection, and decreased forelimb grip strength and foot splay shortly after dosing. The effects were not observed subsequently. Additional clinical and behavioural signs were also observed at higher doses including gait incoordination, dragging forelimbs and hindlimbs, decreased movement when aroused, laboured breathing, lying flat, decreased rearing, decreased forelimb and hindlimb strength, and decreased foot splay. The effects were reversible within one day of dosing. The short-term study in the rat did not demonstrate neurotoxicity but showed systemic toxicity similar to that observed in other short-term studies of spiroxamine. The effects included hyperkeratosis in the esophagus, and at higher doses decreased food and water intake, decreased body weight and body-weight gains, alteration of some clinical chemistry parameters, increased liver weight, hyperkeratosis in stomach, esophagus and tongue, and slight focal urothelial hyperplasia in urinary bladder.

Inhalation sensory irritation studies were investigated in the rat and mouse. The animals were exposed to an aerosol of spiroxamine for one hour. After exposure, the animals showed laboured breathing, reduced motility, and/or sniffing noises. The effects were reversible within one day. Lung function tests showed slight pulmonary irritation potential.

Special in vitro assays were conducted to investigate aromatase and steroidogenesis inhibition. Although the rationales for conducting these assays were not stated, the assays demonstrated that spiroxamine did not inhibit aromatase or steroidogenesis.

Numerous studies were conducted on a plant metabolite (spiroxamine-N-oxide) and impurities of spiroxamine, assessing acute oral and short-term toxicity as well as genotoxicity. Studies with spiroxamine-N-oxide showed that this plant metabolite was moderately acutely toxic by the oral route in the rat. Repeat dietary dosing of spiroxamine-N-oxide in the rat demonstrated that the toxicity potential of this metabolite was similar to that of the parent compound. The main effects were liver enzyme induction, decreased body weights, and irritation of the mucosal epithelium of the gastrointestinal and the urogenital tract (hyperkeratosis in esophageal and forestomach epithelium and mild transitional cell hyperplasia in urinary bladder). Spiroxamine-N-oxide and several impurities of spiroxamine were assayed for bacterial gene mutation in vitro. All assays were negative. Spiroxamine-N-oxide also tested negative for gene mutation in mammalian cell systems in vitro.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Information on the reporting of incidents can be found in the Pesticides and Pest Management portion of Health Canada's website. Spiroxamine is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient spiroxamine have been reported to the PMRA and the applicant did not submit any additional data.

3.1.1 *Pest Control Products Act* Hazard Consideration

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contained the standard complement of required studies including developmental toxicity studies in rats (oral and dermal) and rabbits and two reproductive toxicity studies in the rat.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of the young animals compared to parental animals in the reproductive or prenatal developmental toxicity studies. In the rat reproductive toxicity studies, offspring toxicity was observed at maternally toxic doses. The effects on the offspring included clinical signs, decreased litter size and decreased survival (both generations in the first study), decreased body weights, as well as slightly delayed balanopreputial separation and vaginal patency (subsequent study). Although, decreased litter size and decreased survival are considered serious endpoints, the concern was low because these effects were slight and were not observed at the same dose

level in a subsequent study. The reproductive toxicity data demonstrated that adverse effects occurred only at a maternally toxic dose. In the rabbit developmental toxicity, a slight decrease in fetal and placental weights occurred at a dose level that induced maternal toxicity (anal prolapse, reduced food intake, reduced body weight, few/soft feces). In the rat oral developmental toxicity study, there was a serious effect, malformations, at the high dose which also caused maternal toxicity (decreased food intake and body-weight gain). The concern for malformations was tempered by the presence of maternal toxicity suggesting a 3-fold *Pest Control Products Act* factor would be required. When the endpoints selected for risk assessment provide an intrinsic margin to the endpoint of malformation, the *Pest Control Products Act* factor was reduced to 1-fold. In other cases when the selected end-points did not provide an intrinsic safety margin, the 3-fold *Pest Control Products Act* factor was retained.

3.2 Acute Reference Dose (ARfD)

To estimate acute dietary risk (one day), the acute neurotoxicity study in the rat with a NOAEL of 10 mg/kg bw was selected for risk assessment. At the LOAEL of 30 mg/kg bw, transient behavioural changes occurred. The effects included incoordination, piloerection, decreased forelimb grip strength, and decreased foot splay. The effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Consideration section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10\,\text{mg/kg bw}}{100} = 0.1\,\text{mg/kg bw}$$

This provides a margin of 300 to the NOAEL for malformations in the rat developmental toxicity study.

3.3 Acceptable Daily Intake (ADI) for all populations

To estimate risk from repeat dietary exposure, the 1-year dietary toxicity study in the dog with a NOAEL of 2.47 mg/kg bw/day was selected. At the LOAEL of 26 mg/kg bw/day, bilateral subcapsular clouding and cataractic change, decreased serum albumin, and minimal diffuse hepatocytomegaly were observed. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Consideration section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.47\,\text{mg/kg bw/d}}{100} = 0.02\,\text{mg/kg bw/d}$$

This provides a margin of 1200 to the NOAEL for malformations in the rat developmental toxicity study.

Cancer Risk Assessment

As previously discussed in Section 3.1, the slight increased incidence of adrenal adenoma in male mice in the second study was considered equivocal based on the weight of evidence. Overall, the endpoints selected for the non-cancer risk assessment are protective of this equivocal finding.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to Impulse 500 EC Fungicide is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation routes.

Short- and Intermediate-term Dermal Exposure

For short- and intermediate-term dermal risk assessment, the 18-day dermal toxicity study in rabbits was selected. A NOAEL of 5 mg/kg bw/day (HDT) did not induce systemic toxicity. The target margin of exposure (MOE) selected for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. The selection of the endpoint provides an adequate margin to the serious end-point of concern (malformations) when considering dermal versus oral absorption. The selection of this study and MOE is considered protective of all populations including nursing infants and the unborn children of exposed female workers.

Short-term Inhalation Exposure

For short-term exposure via the inhalation route, the rat oral development toxicity study was selected for risk assessment. A NOAEL of 30 mg/kg bw/day was established based on developmental toxicity, malformations, at the LOAEL of 100 mg/kg bw/day where maternal toxicity was also observed. The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding developmental toxicity as outlined in the *Pest Control Products Act* Hazard Consideration section, an additional 3-fold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females of child-bearing age. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

Although in vitro and in vivo dermal absorption studies were submitted, spiroxamine did not meet the requirements and minimal standards of the triple-pack approach. The experimental designs and dose levels of each study were very different and a comparison of the study results was impossible. As such, the representativeness of the human in vitro absorption results as an indicator of in vivo absorption could not be validated and the rat in vivo study was chosen to determine a dermal absorption value.

The rat in vivo dermal absorption of spiroxamine was determined using an emulsifiable concentrate containing ^{14}C-labelled active ingredient which was applied to shaved dorsal areas on rats at three target dose levels reflecting the undiluted commercial product, and the typical concentration recommended for use on grapes. For each dose level, six groups of four rats were exposed to one of the following exposure durations: 0.5, 1, 2, 4, 8 and 24 hours. Following each exposure period, the rats were sacrificed and the application sites were washed. The washing solution, cotton swabs, treated skin, surrounding skin, blood, gastrointestinal tract plus content, residual carcass, urine, feces and cage washes were all collected and analyzed by a liquid scintillation counter (LSC). The protective dressing and all material that was in contact with the animals were also washed and the rinsing solutions were analyzed to determine the recovery of the applied dose compared to the actual administered dose.

There is evidence to suggest that residue continues to be absorbed beyond the exposure period, therefore, as a conservative measure, all skin-bound residues were considered potentially absorbed. The lower dose level resulted in more absorption of the radiolabelled active ingredient. Therefore, the dermal absorption estimate was taken from this dose. Furthermore, the 8-hour exposure duration, which is the closest to a regular field work day (usually 10 hours), also resulted in a higher dermal absorption value than the other exposure durations, and was selected. Hence, the dermal absorption value of 63% from the in vivo rat study was considered to be the most appropriate for use in risk assessments to refine the dermal exposure of workers handling and/or re-entering an area treated with spiroxamine.

However, given that the toxicological endpoint selected for short- and intermediate-term dermal exposure was derived from a dermal study (Section 3.4.1), this dermal absorption estimate was not required for the current risk assessment.

3.4.2 Occupational Exposure and Risk

In order to determine the acceptability for registration of the proposed end-use product, Impulse 500 EC Fungicide, quantitative exposure and risk assessments for occupational handlers and postapplication workers were conducted as described below.

Endpoints selected for the risk assessments are protective of both non-cancer and equivocal oncogenic effects.

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to spiroxamine during mixing, loading and application. Exposure to workers mixing, loading and applying Impulse 500 EC Fungicide is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. According to typical agricultural practices, exposure estimates were derived for workers applying Impulse 500 EC Fungicide to grapes using an airblast sprayer. Although not commonly used on grapes, field sprayer equipment is also mentioned on the proposed label to cover off any type of modified small groundboom sprayer that could potentially be used by growers. However, a separate mixer/loader/applicator risk assessment using groundboom was not conducted as the exposure from an airblast application is expected to be equivalent to or higher than that of field sprayer equipment. The exposure estimates are based on the proposed personal protective equipment - in other words, mixers/loaders/applicators wearing a single layer of clothing and chemical-resistant gloves.

As chemical-specific data for assessing human exposures during pesticide handling activities were not submitted, dermal and inhalation exposures for workers involved in mixing and loading the liquid formulation were estimated using the Pesticide Handlers Exposure Database (PHED), version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. Dermal and inhalation exposures for open-cab airblast applicators were estimated using revised unit exposure values that are based on data provided by the Agricultural Handler Exposure Task Force (AHETF, 2010). Selected unit exposure values are summarized in Table 3.4.2.1.1 below.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day. A dermal absorption value was not required since the short-term dermal endpoint is based on a dermal study. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAEL; no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 100 for dermal risk and 300 for inhalation risk. Dermal and inhalation MOEs were not combined, since the dermal and inhalation endpoints are not based on the same toxicological effects. Table 3.4.2.1.2 below presents the estimates of exposure and risk for Impulse 500 EC Fungicide.

Table 3.4.2.1.1 Unit Exposure Estimates for Mixers, Loaders and Applicators Handling Impulse 500 EC Fungicide

Exposure Scenarios and PPE[1]		Unit Exposure (µg/kg a.i. handled)[2]	
		Dermal	Inhalation[3]
Open Mixing/Loading a Liquid			
A_1	Single layer, CR gloves	51.14	1.60
Open-Cab Airblast Application			
B_1	Single layer, CR gloves	3 769.30*	9.08*
B_2	Single layer, CR gloves, CR headgear	414.93*	9.08*
Closed-Cab Airblast Application			
B_3	Single layer, CR gloves	41.75	0.58

1 PPE: personal protective equipment; CR: chemical-resistant; CR headgear includes Sou'Wester hats or large brimmed waterproof hats, and hoods with sufficient neck protections.
2 Values identified with an asterisk (*) are from the memorandum "Revised Unit Exposure Values for Open Cab Airblast Applicators" (January 2014). Other values are from the PHED Tables (Version 1.1, February 2002).
3 Light inhalation rate

Table 3.4.2.1.2 Mixer/Loader/Applicator Risk Assessment for Workers Handling Impulse 500 EC Fungicide

Exposure Scenario and PPE[1]		Total Unit Exposure (µg/kg a.i. handled)[2]		ATPD (ha/day)[3]	Max. App. Rate (kg a.i./ha)	Daily Exposure (mg/kg bw/day)[4]		Calculated MOE[5]	
		Dermal	Inhalation			Dermal	Inhalation	Dermal[6]	Inhalation[7]
Open M/L a liquid & open-cab airblast application									
$A_1 + B_1$	Single layer, CR gloves *(proposed on label)*	3 820.44	10.68	20	0.300	2.87×10^{-1}	8.01×10^{-4}	17	37 453
$A_1 + B_2$	Single layer, CR gloves and CR headgear for applying	466.07	10.68	20	0.300	3.50×10^{-2}	8.01×10^{-4}	143	37 453
Open M/L a liquid & closed-cab airblast application									
$A_1 + B_3$	Single layer, CR gloves	92.89	2.18	20	0.300	6.97×10^{-3}	1.64×10^{-4}	718	183 486

1 PPE: personal protective equipment; M/L: mixing/loading; CR: chemical-resistant; CR headgear includes Sou'Wester hats or large brimmed waterproof hats, and hoods with sufficient neck protections.
2 Calculated using the total unit exposure values from Table 3.4.2.1.1.
3 ATPD: Area Treated per Day; default value for airblast application (ATPD Table Revised Version 2.1, July 2010).
4 Daily exposure = (Total unit exposure × ATPD × rate) / (80 kg bw × 1000 µg/mg).
5 MOE = NOAEL / Daily exposure; shaded numbers are below the target MOE.
6 Based on a short- to intermediate-term dermal NOAEL of 5 mg/kg bw/day and a target MOE of 100.
7 Based on a short-term inhalation NOAEL of 30 mg/kg bw/day and a target MOE of 300.

The exposure scenario proposed on the label ($A_1 + B_1$; open mixing/ loading a liquid and open-cab airblast application for a worker wearing single layer with gloves) resulted in a calculated dermal MOE of 17 which is significantly below the target MOE of 100 (shaded number). As such, even though the calculated inhalation MOE of 37 453 is well above the target MOE of 300, this scenario is inadequate to protect for dermal exposure to mixers, loaders and/or applicators handling Impulse 500 EC Fungicide.

As a mitigation measure, the addition of chemical-resistant headgear for workers applying the product with an open-cab tractor (scenario $A_1 + B_2$) was assessed. Consequently, the dermal exposure was decreased and the calculated dermal MOE was increased to 143, which is above the target of 100 and not of concern. The calculated inhalation MOE remained unchanged at 37 453. Hence, this scenario with increased PPE is sufficient to protect the workers handling and/or applying Impulse 500 EC Fungicide.

Furthermore, should a grower use a closed-cab tractor and wear the proposed PPE consisting of a single layer and gloves (scenario $A_1 + B_3$), both the dermal and inhalation exposures would be decreased, with the calculated dermal and inhalation MOEs of 718 and 183 486, respectively, which are not of concern.

Additional PPE Based on Acute Toxicity of Impulse 500 EC Fungicide

Although the quantitative risk assessment presented above for the mixer/loader/applicator exposure scenario shows that only a single layer of clothing with chemical-resistant gloves for mixers/loaders/applicators, as well as the addition of a chemical-resistant headgear (includes Sou'Wester hats or large brimmed waterproof hats and hoods with sufficient neck protection) for applicators are required, results of the acute toxicity studies also need to be taken into consideration. As such, results of the acute eye irritation study indicate that goggles or protective eyewear are required for all mixers, loaders, applicators, and any other workers involved in clean-up and repair activities.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Impulse 500 EC Fungicide to conduct postapplication activities such as: scouting, hand weeding, thinning, staking, canopy management, irrigation, hand harvesting, tying, pinching, pruning, girdling and training. Given the nature of activities performed, the duration of exposure is expected to be short-term and the primary route of exposure would be through the dermal route. Inhalation exposure is not considered to be a significant route of exposure for people entering treated areas compared to the dermal route since the active ingredient spiroxamine is relatively non-volatile according to NAFTA criteria for outdoor use, and as such, a risk assessment was not required.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients (TCs). Activity transfer coefficients are based on Agricultural Re-entry Task Force (ARTF) data.

Chemical-specific dislodgeable foliar residue (DFR) data were submitted. The DFR study was designed to estimate dislodgeable foliar residues and their dissipation on foliage of grape plants after treatment with spiroxamine at one test site in California. Four sequential foliar spray applications of BAY KWG 4168 300 CS fungicide (28% w/v of spiroxamine) were made to grape vines at a nominal rate of 400 g a.i./ha per application, a retreatment interval of 10 days and a total seasonal rate of 1600 g a.i./ha. Applications were made with an airblast sprayer. There were three replicates per sampling interval and 37 intervals monitored up to 35 days after the last application. Field sample residues, expressed as $\mu g/cm^2$, were corrected to 100%

recovery based on the results of corresponding field fortification samples. Corrections were made using the midpoint method for all field samples residues with recoveries below 95%. The arithmetic mean of the triplicates was calculated and the natural logarithm of the mean residue levels was plotted against the number of days following the last application to create a dissipation curve for spiroxamine. First-order kinetics were used to estimate the linear regression. The equation of the line was $y = -0.1174x - 0.6938$ with a R-squared value of 0.8859. Using the slope of -0.1174, a half-life ($t_{1/2}$) of approximately six days and a daily dissipation rate of 11% were calculated. Using the four applications, the percentage of DFR on Day 0 was also estimated at 11%.

Given that the study protocol was more conservative than the proposed use pattern of Impulse 500 EC Fungicide (four instead of three applications; 10-day instead of 14-day RTI; application rate of 400 g a.i./ha/application instead of 300 g a.i./ha/application) and that the climatic conditions of the Californian test site were dryer than the Canadian grape-growing regions, thus favoring less residue dissipation, the overall study results were more conservative that what would be expected from the proposed use of Impulse 500 EC Fungicide in Canada. As such, the study was considered acceptable for use in the current risk assessment.

Hence, the default DFR values (25% dislodgeable on Day 0 and 10% dissipation per day) were replaced with chemical-specific values obtained from the submitted DFR study: 11% dislodgeable on Day 0 and 11% dissipation per day. The peak DFR was calculated at 0.3946 $\mu g/cm^2$ as illustrated in Table 3.4.2.2.1.

The postapplication dermal exposure was calculated for the day of the last application, immediately after the spray has dried (Day 0), with the default exposure duration of eight hours per day, the default adult body weight of 80 kg, and the maximum transfer coefficient for all activities listed for grapes (wine/juice or table/raisin) in the ARTF Transfer Coefficients Table (May 2013). Postapplication exposure estimates were compared to the short- and intermediate-term dermal toxicological endpoint presented in section 3.4.1 to obtain the margin of exposure (MOE) as presented in Table 3.4.2.2.1.

Table 3.4.2.2.1 Postapplication Exposure and Risk Estimate for the Proposed Use of Impulse 500 EC Fungicide on the Day of Last Application (Day 0)

Crop	Max. App. Rate (kg a.i./ha)	No. of App./Year (RTI)	Peak DFR ($\mu g/cm^2$)[1]	Re-Entry Activity	Transfer Coefficient (cm^2/hour)[2]	Dermal Exposure (mg/kg bw/day)[3]	Calculated MOE[4]
Grapes (wine or table)	0.300	2 (14 days)	0.3946	Transplanting	230	0.0091	**551**
				Scouting Hand pruning Hand weeding Propagating Bird control Trellis repairs	640	0.0253	**198**
				Irrigation (hand set)	1 750	0.0690	**72**
				Tying/Training Hand harvesting Leaf pulling	8 500	0.3354	**15**
Grapes (table)	0.300	2 (14 days)	0.3946	Girdling Turning	19 300	0.7615	**7**

[1] Dislodgeable foliar residues (DFR) were calculated using 11% dislodgeable on Day 0 and 11% dissipation per day; peak DFR is the DFR on Day 0.
[2] Transfer coefficients (TCs) obtained from ARTF Transfer Coefficients Table (May 2013).
[3] Dermal exposure = (Peak DFR [$\mu g/cm^2$] × TC [cm^2/hour] × 8 hours) / (80 kg bw × 1000 µg/mg).
[4] MOE = NOAEL / Dermal Exposure; based on a dermal NOAEL of 5 mg/kg bw/day and a dermal target MOE of 100.

The postapplication risk assessment resulted in a calculated MOE of 551 on Day 0 for transplanting and 198 for scouting, hand pruning, hand weeding, propagating, bird control and trellis repairs. Therefore, no restricted-entry interval (REI) is required to perform these activities apart from the default 12 hours to allow the spray to dry. However, the calculated MOEs on Day 0 for all other activities are below the target MOE of 100, and ranged from 72 to 7 (shaded numbers). As such, longer REIs are required to obtain calculated MOEs equal to or above the target of 100 as presented in Table 3.4.2.2.2.

Table 3.4.2.2.2 Required Number of Days to Reach the Target MOE for the Proposed Use of Impulse 500 EC Fungicide

Crop	Re-Entry Activity	Transfer Coefficient (cm^2/hour)[1]	Calculated REI (days)[2]	DFR ($\mu g/cm^2$)[3]	Dermal Exposure (mg/kg bw/day)[4]	Calculated MOE[5]
Grapes (wine or table)	Irrigation (hand set)	1 750	**3**	0.2782	0.0487	103
	Tying/Training Hand harvesting Leaf pulling	8 500	**17**	0.0544	0.0463	108
Grapes (table)	Girdling Turning	19 300	**24**	0.0241	0.0465	108

[1] Transfer coefficients (TCs) obtained from ARTF Transfer Coefficients Table (May 2013).
[2] REI = Restricted-entry interval to reach a dermal exposure ≤ 0.05 mg/kg bw/day, and hence a calculated MOE ≥ 100.
[3] Dislodgeable foliar residues (DFR) calculated using 11% dislodgeable on Day 0 and 10% dissipation per day.
[4] Dermal exposure = (DFR [$\mu g/cm^2$] × TC [cm^2/hour] × 8 hours) / (80 kg bw × 1000 µg/mg).

[5] Based on a dermal NOAEL of 5 mg/kg bw/day and a dermal target MOE of 100.

The calculated REIs (in other words, the number of days required to reach the target MOE of 100, for the three activity groups described in Table 3.4.2.2.2) are considered agronomically feasible and acceptable to protect postapplication re-entry workers. The required REIs of 3 days for hand set irrigation, 17 days for tying, training, hand harvesting and leaf pulling, as well as 24 days for girdling and turning, will sufficiently reduce the workers' exposure levels to spiroxamine residues, while allowing them to perform these necessary tasks at an appropriate time.

3.4.3 Residential Exposure and Risk Assessment

There are no residential uses for Impulse 500 EC Fungicide, and as such, a residential risk assessment was not required.

3.4.4 Bystander Exposure and Risk Assessment

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversion, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in grape and banana commodities is spiroxamine and the metabolites containing the aminodiol common moiety, expressed as parent equivalents. The data gathering/enforcement analytical method is valid for the quantitation of the total spiroxamine residues in crop matrices. The total spiroxamine residues are stable in grape matrices for up to 585 days/18 months and in banana matrices for up to 719 days/24 months, when stored in a freezer at < -20°C. The total spiroxamine residues concentrated in raisins (4.0×). Crop field trials conducted throughout Europe, the United States, Central and South America using end-use products containing spiroxamine at approved and/or exaggerated rates in or on grape and banana are sufficient to support the proposed maximum residue limits.

3.5.2 Exposure from Drinking Water

3.5.2.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of spiroxamine combined with the transformation product spiroxamine oxide (M03) in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of

spiroxamine and M03 in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile. The PRZM-GW model was used to estimate concentrations in groundwater over a 50-year period for eight of eleven geographic scenarios, and for 100 years for three scenarios. The concentrations calculated using PRZM-GW are average concentrations in the top 1 m of the water table. EECs of spiroxamine and M03 in surface water were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EECs are expected to allow for future use expansion into other crops at this application rate. Table 3.5.2.1.1 lists the application information and main environmental fate characteristics used in the simulations. A range of initial application dates spanning May-September were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 3.5.2.1.2 below.

Table 3.5.2.1.1 Major groundwater and surface water model inputs for Level 1 assessment of spiroxamine combined with the transformation product M03

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Grapes
	Use pattern	2 applications of 300 g a.i./ha, applied at a 14 day interval
	Method of application	Airblast spray equipment
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (days)	236 days
	Adsorption K_d (mL/g)	6.88 (20^{th} percentile of 10 K_d values for spiroxamine and M03)
	Aerobic soil biotransformation half-life (days at 25ºC)	156 (90 percent confidence bound on the mean of 6 combined half-life values adjusted to 25ºC)
	Aerobic aquatic biotransformation half-life (days at 25ºC)	150 (80^{th} percentile of 3 combined half-life values adjusted to 25ºC)
	Anaerobic aquatic biotransformation half-life (days at 25ºC)	799 (single combined half-life value adjusted to 25ºC)

Table 3.5.2.1.2 Level 1 estimated environmental concentrations of spiroxamine combined with M03 in potential drinking water sources

Crop and use pattern	Groundwater EEC (µg a.i./L)			Surface Water EEC (µg a.i./L)	
				Reservoir	
	Daily[1]	Yearly[2]	Simulation End[3]	Daily[4]	Yearly[5]
Grapes – 2 × 300 g a.i./ha at a 14-day interval	7.2	7.2	7.4	24	6.8

Notes:
1 90th percentile of daily average concentrations
2 90th percentile of 365-day moving average concentrations
3 The concentration simulated at the end of the 100-year model run. Because groundwater concentrations were increasing at the end of the run, a longer run would have produced EECs slightly higher than this value
4 90th percentile of yearly peak concentrations
5 90th percentile of yearly average concentrations

3.5.3 Dietary Risk Assessment

Acute and chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 4.2, 05-10-c), which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) dietary survey for the years 2003-2008 available through CDC's National Center for Health Statistics (NCHS).

3.5.3.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic analysis for spiroxamine: 100% crop treated, default and experimental processing factors (where available), residues of grapes and bananas based on supervised trial median residue (STMdR) values. The refined chronic dietary exposure from all supported spiroxamine food uses (alone) for the total population is 11% of the acceptable daily intake (ADI), and for all other representative population subgroups, including infants and children, is less than 30% of the ADI. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to spiroxamine from food and drinking water is 12% (0.002351 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 31% (0.006164 mg/kg bw/day) of the ADI.

3.5.3.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the refined acute analysis for spiroxamine: 100% crop treated, experimental processing factors where applicable, and maximum residues in/on crops. The refined acute dietary exposure (food alone) for all supported spiroxamine registered commodities is estimated to be 11% (0.010753 mg/kg bw/day) of the ARfD for the total population (95^{th} percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: 12% of the ARfD for the total population. The highest exposure and risk estimate is for children 1-2 years old at 33% (0.032918 mg/kg bw/day) of the ARfD (95^{th} percentile, deterministic).

3.5.4 Aggregate Exposure and Risk

The aggregate risk for spiroxamine consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.5 Maximum Residue Limits

Table 3.5.5 Proposed Maximum Residue Limits

Commodity	Recommended Maximum Residue Limit (ppm)
Raisins	4
Bananas	3
Grapes	2

For additional information on maximum residue limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 6 and 7.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The persistence of spiroxamine ranges from non-persistent to moderately persistent under aerobic conditions in both aquatic and terrestrial systems. Under anaerobic aquatic conditions spiroxamine is persistent. Biotransformation is the major route of dissipation for spiroxamine in the environment. Spiroxamine transforms into several major transformation products: spiroxamine desethyl (M01), spiroxamine despropyl (M02), spiroxamine oxide (M03) and spiroxamine acid (M06) which all have similar chemical structures as well as fate and toxicity properties to the parent. M03 is particularly important as it can transform back to the parent and the two are, therefore, thought to be in equilibrium. Experimental findings on the volatilisation behaviour of spiroxamine show that spiroxamine may have a tendency to volatilize under

practical use conditions. However, an estimate of a short chemical life-time of spiroxamine in the troposphere indicates that an accumulation of spiroxamine in the air and subsequent transport to areas far away from where it was applied are not expected. Based on field dissipation studies, spiroxamine and its transformation products are not expected to carry over in important amounts to the next growing season.

In water, spiroxamine is soluble and does not break down suggesting that it may have a potential to leach. Leaching is, however, expected to be mitigated by its tendency to bind tightly to soil particles and low to moderate persistence. Based on various leaching criteria, a low potential for leaching is expected. This is supported by conservative concentrations in groundwater predicted by modelling, the results from leaching studies in aged soils, and terrestrial field dissipation studies which indicated little movement of spiroxamine down the soil profile. In all 19 field studies, spiroxamine was detected at measurable levels below 20 cm only once and at a very low concentration. The potential for leaching and levels of spiroxamine in groundwater are, therefore, expected to be low. Field and laboratory data indicate that transformation products of spiroxamine are generally expected to have similar mobility to the parent and, thus, are not likely to leach. A bioconcentration study carried out with bluegill sunfish indicated that spiroxamine is unlikely to bioaccumulate in the environment.

The physical and chemical characteristics of spiroxamine are summarized in Appendix 1, Table 8. The chemical structures and formation levels of transformation products can be found in Appendix 1, Table 9. The environmental fate data for spiroxamine are summarized in Appendix 1, Table 10.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is

below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A risk assessment for spiroxamine was conducted for terrestrial organisms. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 are typically used to modify the toxicity values (EC_{50} and LC_{50}) for terrestrial invertebrates, birds and mammals when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints. A summary of terrestrial toxicity data for spiroxamine is presented in Appendix I, Table 9; and the accompanying risk assessment is presented in Appendix I, Table 12 for beneficial arthropods, Appendix I, Table 13 for terrestrial organisms other than beneficial arthropods, birds and mammals, and Appendix I, Tables 15 - 17 for birds and mammals.

Invertebrates

Earthworms and Collembola
Screening level risk quotients for spiroxamine and its transformation products (M01, M02 and M03) did not exceed the LOC, on an acute or chronic basis, for earthworms or collembola (where toxicity data was available). The use of spiroxamine is not expected to pose a risk to earthworms or collembola.

Bees
Acute oral and contact exposure to spiroxamine did not result in treatment-related mortality in honey bees. The resulting risk quotients for both acute contact and oral exposure routes were all below the LOC, indicating spiroxamine is expected to pose a negligible risk to pollinators. Two semi-field and one field study done using single applications at rates greater than the proposed maximum cumulative seasonal application rate in Canada given no dissipation between applications (600 g a.i./ha) found no significant effects on bee mortalities or effects on bee colonies or brood. The use of spiroxamine is not expected to pose a risk to larval bees.

Arthropods
Spiroxamine affected the survival of predatory mites, *Typhlodromus pyri*, and parasitoid wasps, *Aphidius rhopalosiphi*, on an acute exposure basis when exposed to the chemical on glass plates. The screening level risk assessment indicated, however, that the risk quotient for predatory mites resulting from this exposure to spiroxamine did not exceed the LOC. The risk quotient for the parasitoid wasp, *Aphidius rhopalosiphi*, from off-field exposure to spiroxamine from a ground boom sprayer also did not exceed the LOC.

A potential risk to the parasitic wasp was, however, identified when exposed to high enough concentrations both in-field and off-field from early and late season airblast application and, therefore, a more refined assessment was conducted by examining extended lab studies conducted with barley plants. The application rates used in both studies exceeded the proposed maximum cumulative seasonal application rate in Canada given no dissipation between applications (600 g a.i./ha) and found no clear treatment-related effects on mortality or fecundity of wasps (LR_{50} of >750 and >900 g a.i./ha). Using these refined endpoints, the risk quotients from in-field and off-field exposure to spiroxamine did not exceed the LOC.

Risk assessments were also carried out on the following soil-dwelling arthropods: ladybird beetles, green lacewings, wolf spiders and carabid beetles. Extended lab, semi-field or field studies with these species showed no adverse effects following applications at rates higher than the maximum proposed cumulative seasonal rate in Canada given no dissipation between applications (600 g a.i./ha).

The use of spiroxamine is, therefore, not expected to pose a risk to either foliage- or soil-dwelling arthropods.

Birds and mammals

The EECs on food items (vegetation and insects) can be found in Appendix I, Table 14.

Some mortality was observed when birds were dosed with spiroxamine through oral gavage. Less mortality was observed when birds were exposed to spiroxamine through the diet, and mortality occurred only at the highest test concentrations. A decrease in food consumption was observed in the dietary studies as the concentration in the diet increased suggesting that spiroxamine may be unpalatable to birds. Spiroxamine slightly affected avian reproduction. In tests with the bobwhite quail, a reduction in the body weights of 14-day old survivors was observed at the highest test concentration. In tests with the mallard duck, slight (but not statistically significant) effects on egg production, number of hatchlings, and number of 14-day survivors, as well as a statistically significant decrease of hatchling body weights, were observed at the highest test concentration.

Spiroxamine caused mortality in mice and rats when administered through oral gavage. When spiroxamine was administered through the diet in longer-term reproduction studies, significant effects were noted at high enough doses, such as a reduction in litter size at birth, reduced pup survival, reduced body weight at birth and reduced pup body weight.

For the bird and mammal risk assessment, the ingestion of food items contaminated by spray droplets is considered to be the main route of exposure. The risk assessment is, thus, based on the estimated daily exposure which takes into account the expected concentration of spiroxamine on various food items immediately after the last application and the amount of food consumed by different sizes of birds and mammals. At the screening level, the most conservative exposure estimates are used for each category of animal weights.

The screening level risk assessment shows no concern for birds or mammals on an acute basis, but highlights a potential for concern on a reproductive basis (Appendix I, Table 15). The reproductive risk was, therefore, further characterized (Appendix I, Tables 16 and 17).

For birds, risk quotients calculated with the NOEL exceed the LOC for small and medium insectivores when considering both maximum and mean residue values, and for large herbivorous birds when considering maximum residues. The overall reproductive risk to birds is, nonetheless, believed to be low. Risk quotients are below the LOC for most feeding guilds, and when exceeded, the margin is relatively small. In addition, the LOC is not systematically exceeded when using mean residues and is not exceeded for birds feeding off the treatment area. When using the LOEL, risk quotients are generally below the LOC, except for small insectivorous birds where the LOC is only very slightly exceeded using the maximum residues. In such cases, between 71% and close to 100% of the bird's diet would need to be comprised of insects contaminated with maximum residue levels to reach the LOC. This is not likely to occur under most field situations, as birds are expected to feed on a variety of different food items which are not all contaminated. Therefore, the likelihood of birds consuming spiroxamine at levels that are high enough to elicit reproductive effects is low. If the LOC was to be reached, effects would not be severe (only a possible reduction in offspring body weight, as indicated by laboratory data).

For mammals, risk quotients calculated with the NOEL exceed the LOC for most insectivorous and herbivorous mammals when considering both mean and maximum residues. The reproductive risk to mammals is believed to be more of a concern than for birds given that risk quotients exceed the LOC for most feeding guilds using a range of residues, and the margin at which the LOC is exceeded is higher. The LOC is, however, not exceeded for mammals feeding off the treated area. When using the LOEL, risk quotients exceed the LOC for herbivores feeding on the treated field, when using maximum residues. However, risk quotients are not exceeded for mammals feeding adjacent to the treated field. Because of the potential reproductive effects on mammals, a statement to inform the user of the potential hazard to mammals must be included on the label.

Terrestrial plants

Exposure of terrestrial vascular plants to spiroxamine resulted in no treatment related effects on seedling emergence and only limited effects on vegetative vigour. The risk quotients resulting from both studies did not, however, exceed the LOC for seedling emergence and vegetative vigour. The use of spiroxamine is not expected to pose a risk to terrestrial vascular plants.

4.2.2 Risks to Aquatic Organisms

A risk assessment for spiroxamine was conducted for freshwater and marine aquatic organisms based on available toxicity data. A summary of aquatic toxicity data is presented in Appendix I, Table 18.

For acute toxicity studies, uncertainty factors of 1/2 and 1/10 are typically used to modify the toxicity values (EC_{50} or LC_{50}) for aquatic plants and invertebrates, and fish species, respectively, when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints. For groups where the LOC is exceeded (in other words, RQ $\geq$1), a refined Tier 1 assessment is conducted to determine risk resulting from spray drift and runoff separately. Risk quotients for spiroxamine and its transformation products were calculated based on the highest maximum seasonal application rate. The calculated risk quotients for spiroxamine and its transformation products are summarized in Appendix I, Table 19 (screening level), Table 20 (Tier 1 – spray drift only) and Table 21 (Tier 1 – runoff only).

Freshwater Invertebrates

The risk quotients for freshwater invertebrates, based on toxicity studies exposing *Daphnia magna* to either spiroxamine or M03 on an acute basis, did not exceed the LOC at the screening level. The risk quotient for daphnids resulting from chronic exposure to spiroxamine did exceed the LOC at the screening level.

The refined risk quotients for daphnids used estimated environmental concentrations of spiroxamine from spray drift, and exceeded the LOC for airblast application but not for ground boom application. Therefore, Spiroxamine may pose a chronic risk to freshwater invertebrates through spray drift and risk mitigation measures, such as buffer zones, will be required.

Risk quotients for daphnids from exposure to spiroxamine through runoff did not exceed the LOC.

Fish and amphibians

Spiroxamine affected the survival of rainbow trout, bluegill sunfish, and zebra fish on an acute exposure basis in laboratory studies. Effects on the length of rainbow trout, hatching rate of zebra fish and decreased vitellogenin levels in fathead minnows and zebra fish were observed following screening assays, early life-stage and full life-cycle exposures to spiroxamine. When compared to EECs, risk quotients for freshwater fish resulting from acute exposure to spiroxamine did not exceed the LOC at the screening level. The risk quotients resulting from chronic exposure did, however, exceed the LOC, and a more refined assessment was conducted.

The acute and chronic risk for amphibians was characterized at the screening level by comparing EECs in a 15 cm water depth using fish toxicity endpoints as surrogates for aquatic life-stages of amphibians. The risk quotients for amphibians resulting from exposure to spiroxamine exceeded the LOC at the screening level.

A refined risk assessment was conducted using endpoints from chronic exposure to fish and amphibians and risk quotients for potential exposure to spray drift exceeded the LOC for all application methods. The refined risk quotients for amphibians acutely exposed to spiroxamine from spray drift also exceeded the LOC from airblast application but not for ground boom application. Mitigative measures will be required, such as spray buffer zone label statements on spiroxamine product labels.

Risk quotients for fish and amphibians chronically exposed to spiroxamine through runoff exceeded the level of concern. Risk quotients for amphibians acutely exposed to spiroxamine through runoff did not exceed the level of concern. Standard label statements to mitigate excessive runoff into aquatic habitats will be required on the label for the spiroxamine end-use product.

Algae

Spiroxamine was toxic to freshwater green algae and freshwater and marine diatoms, but was relatively non-toxic to freshwater blue-green algae. Recovery studies indicated that green algae cells exposed to up to 0.032 mg a.i./L of spiroxamine were able to recover completely and grow at pre-exposure rates after elimination of the chemical.

As multiple EC_{50} values were available for freshwater algae, the program ETX 2.0 was used to generate a species sensitivity distribution (SSD) based on normally distributed toxicity data. The hazardous concentration to 5% of the species (HC_5) was then calculated from the SSD. The HC_5 is the concentration which is theoretically protective for 95% of species. At the HC_5 exposure level, 5% of all species will be exposed to a concentration which exceeds their LC_{50} toxicity value. The HC_5 values were used to calculate the risk quotients for freshwater algae instead of the most sensitive species tested. This provides a more scientifically robust endpoint, which uses all of the data. No uncertainty factors are applied to the HC_5 when calculating risk quotients. Using the HC_5 value from the SSD for freshwater algae, the calculated risk quotients exceeded the LOC at the screening level. The risk quotient for marine diatoms also exceeded the LOC at the screening level.

The risk quotients for freshwater green algae, based on toxicity studies with *Desmodesmus subspicatus* exposed to spiroxamine transformation products, M01, M03 and M06, did not exceed the LOC at the screening level.

To further investigate the effects of spiroxamine on various trophic levels, including algal species, an outdoor mesocosm was treated with a formulation of Spiroxamine EC 500.

The taxa-based results for the mesocosm study were generally in agreement with the available laboratory-based data for phytoplankton and zooplankton at the concentrations of spiroxamine tested. Based on significant treatment-related effects on the abundance of *Rotatoria*, and the percent coverage, biomass, similarity indices, and chlorophyll a of two species of algae (*Achnantes spec. (Diatomeae*), *Cryptomonas spec.* (*Cryptophyceae*)) observed at a treatment concentration of 4.4 µg a.i./L, a $NOEC_{mesocosm}$ of 2.1 µg a.i./L was determined, and was used to further characterize the risk to freshwater algae. Using the $NOEC_{mesocosm}$ of 2.1 µg a.i./L, the calculated risk quotients for freshwater algae exceeded the LOC.

The refined risk quotients for freshwater and marine algae exposed to spiroxamine from spray drift exceeded the LOC for all application methods. Spray buffer zones will be required on spiroxamine product labels to protect aquatic organisms from the potential effects of spray drift. The spray buffer zones for spiroxamine will range from 1 to 40 metres for freshwater habitats and 2 to 35 metres for estuarine/marine habitats.

Risk quotients for freshwater and marine algae exposed to spiroxamine through runoff exceeded the LOC. Standard label statements to mitigate excessive runoff into aquatic habitats will be required on the label for the spiroxamine end-use product.

Freshwater vascular plants
The risk quotient for freshwater vascular plants, based on a toxicity study with *Lemna gibba*, did not exceed the LOC at the screening level and spiroxamine is not expected to pose a risk to freshwater vascular plants.

4.2.3 Incident Reports

There were no incident reports for spiroxamine or its major transformation products.

5.0 Value

5.1 Consideration of Benefits

Impulse 500 EC Fungicide and Spiroxamine Technical Fungicide were submitted as User Requested Minor Use Registration applications. Impulse 500 EC Fungicide has been identified as a user priority by the British Columbia Grape Growers' Association; the Grape Growers' Association of Nova Scotia, the Grape Growers of Ontario, and Vignobles Saint-Rémi in Québec. The need for additional options to control powdery mildew on grape is evidenced by the nine currently identified priorities in the Grower Priority Database, each rated intermediate or high, for this particular crop-disease combination.

Impulse 500 EC Fungicide when applied as labelled is expected to provide control of powdery mildew caused by *Uncinula necator*, a common disease of grape, thereby protecting fruit yield and quality. The availability of Impulse 500 EC Fungicide will provide grape growers with an additional option for controlling powdery mildew. As a fungicide with a different mode of action from other fungicides registered for control of powdery mildew on grape, the use of Impulse 500 EC Fungicide will help to mitigate the development of resistance of powdery mildew to currently registered fungicides, thereby extending the life of these other fungicides as effective tools against powdery mildew.

Spiroxamine is classified as a FRAC group 5 fungicide. According to FRAC, the amines present a low to medium risk for the development of resistance and the pathogen risk for resistance development for *Uncinula necator* is also considered to be medium, and represents a lower level of resistance development risk than alternative products that contain active ingredients known to have a medium to high risk of resistance development.

Impulse 500 EC Fungicide may be applied as an integral component of an overall powdery mildew management spray program on grape. The availability of Impulse 500 EC Fungicide will not only offer growers an alternative product for control of this disease but will also be a tool in managing the risk of resistance development by *Uncinula necator* to this product and those containing active ingredients belonging to other modes of action.

5.2 Effectiveness Against the Pest

The Canadian use pattern for Impulse 500 EC Fungicide is broadly consistent with use patterns registered in several European jurisdictions for the same formulation of spiroxamine on grapes for control of powdery mildew. Data from 17 replicated field trials conducted in Germany, Italy and France from 1994 to 2005 in which the efficacy of Impulse 500 EC Fungicide applied at 100-400 g a.i./ha was evaluated for control of powdery mildew were summarized in a European Union summary document of efficacy data and information. While the application rates evaluated in three of these trials were less (100-150 g a.i./ha) than labelled rates of 200 to 300 g a.i./ha, the data were useful in justifying this rate range. Impulse 500 EC Fungicide applied within the labelled rate range was demonstrated to consistently control powdery mildew on leaves and fruit of grapevines. This was corroborated with additional studies that were summarized in recent national biological dossiers for France and Italy.

5.3 Non-Safety Adverse Effects

The summarized efficacy studies and the long history of use in several European nations, including Italy, France and Germany indicate that Impulse 500 EC Fungicide applied at up to 400 g a.i./ha from shoot emergence until 35 days prior to harvest can be expected to be safe to the crop and have no discernible effect on grape quality, including yield. Results from eight European vinification studies in addition to the long history of use indicate that Impulse 500 EC Fungicide is unlikely to have any discernible effect on wine quality. Furthermore, by preventing grapes from being damaged by powdery mildew, Impulse 500 EC Fungicide can be expected to protect the quality of harvested produce and products derived from it.

5.4 Supported Uses

The value of Impulse 500 EC Fungicide, when applied as labelled for the control of powdery mildew, caused by *Uncinula necator* (syn. *Erysiphe necator*) on grape has been adequately demonstrated.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, spiroxamine was assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

Spiroxamine does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 22 for comparison with Track 1 criteria.

Spiroxamine does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade spiroxamine and the end-use product Impulse 500 EC Fungicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

---

[5] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern*.

[7] NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

[8] DIR2006-02, Regulatory Directive: Formulants Policy and Implementation Guidance Document.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for spiroxamine is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Low incidences of malformations were observed in fetuses of rats at a dose that also caused maternal toxicity. Spiroxamine was not neurotoxic with repeated dosing, but did cause acute transient behavioral effects in the rat. In short-term and chronic studies in laboratory animals, the primary target of toxicity was the liver. Because of its irritating properties, spiroxamine also consistently caused hyperkeratosis (tongue, esophagus, forestomach mucosa, and urinary tract), hyperkeratosis and acanthosis in the epidermis (pinnas and tail), desiccation of auricular epidermis, and bilateral subcapsular clouding and cataractic change in the eye. There was no clear evidence of oncogenic potential of spiroxamine in rats and mice. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residues in grape and banana is adequately understood. The residue definition for enforcement for grape and banana matrices is spiroxamine and the metabolites containing aminodiol common moiety, expressed as parent equivalents. The proposed use of spiroxamine on grapes and the importation of spiroxamine treated grapes and bananas do not constitute a risk of concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for the total residues of spiroxamine.

Commodity	Recommended MRL (ppm)
Raisins	4
Bananas	3
Grapes	2

Provided that label amendments are made, that the appropriate PPE is worn and that all label restrictions are followed, mixers, loaders and applicators handling Impulse 500 EC Fungicide, as well as workers re-entering treated vineyards, are not expected to be exposed to levels of spiroxamine that will result in health risks of concern. Bystander exposures are expected to be negligible.

7.2 Environmental Risk

The use of Impulse 500 EC Fungicide, containing the active ingredient, spiroxamine, may pose a potential risk to mammals, freshwater and marine algae, freshwater invertebrates, freshwater fish, and amphibians at the proposed rate of application. With appropriate mitigation in place such as spray buffer zones to protect sensitive aquatic habitats from spray drift and hazard label statements, to inform users of potential risks to the environment, these risks are deemed to be acceptable.

7.3 Value

The information submitted to register Impulse 500 EC Fungicide is adequate to demonstrate value and supports use of this product on grape for control of powdery mildew caused by *Uncinula necator*.

Impulse 500 EC Fungicide has been demonstrated to be effective in controlling powdery mildew on grape. This product can be incorporated into integrated pest management programs with other chemical and cultural controls for disease and resistance management. Impulse 500 EC Fungicide has been identified as a user priority by the British Columbia Grape Growers' Association; the Grape Growers' Association of Nova Scotia, the Grape Growers of Ontario, and Vignobles Saint-Rémi in Québec. The nine currently listed priorities in the Canadian Grower Priority Database for control of powdery mildew on grape are indicative of the need for additional control options for this particular crop-disease combination. Impulse 500 EC Fungicide was concluded to have value as there is a clear need by grape growers for additional tools to control powdery mildew, and in consideration of the product's expected contribution to resistance management and its demonstrated performance in controlling this economically important disease.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Spiroxamine Technical Fungicide and Impulse 500 EC Fungicide containing the technical grade active ingredient spiroxamine, to control powdery mildew (*Uncinula necator*, syn. *Erysiphe necator*) on grape.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♂	male
♀	female
↑	increase
↓	decrease
>	greater than
≥	equal to or greater than
<	less than
≤	equal to or less than
~	approximately
λ	wavelength
℃	degrees Celsius
µg	microgram(s)
µM	micromole(s)
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ALT	alanine transaminase
AP	alkaline phosphatase
App.	application
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate transaminase
ATPD	area treated per day
BAF	Bioaccumulation Factor
BBA	German Federal Biological Research Centre for Agriculture and Forestry
BCF	Bioconcentration Factor
BW or bw	body weight
bwg	body-weight gain
^{14}C	radiolabelled carbon atom
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC	Centres for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
cm	centimetre(s)
cm^2	centimetre(s) squared
cm^3	centimetre(s) cubed
CO^2	carbon dioxide
CR	chemical-resistant
CS	capsule suspension
d	day
DACO	data code
DAT	days after treatment

DEEM-FCID	Dietary Exposure Evaluation Model – Food Commodity Intake Database
DFOP	double first-order in parallel
DFR	dislodgeable foliar residue
DIR	Directive
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
E_bC_{50}	EC_{50} in terms of algal biomass
EC	emulsifiable concentrate
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ELS	early life stage
EP	end-use product
ER_{25}	effective rate for 25% of the population
ER_{50}	effective rate for 50% of the population
ErC_{50}	EC_{50} in terms of reduction of growth rate
ET	expiration time
EU	European Union
F_0	parent generation
F_1	first generation
F_2	second generation
FAH	foci of altered hepatocytes
FDA	*Food and Drugs Act*
FIR	food ingestion rate
FOB	functional observational battery
FOMC	First Order Multi-Compartment
FRAC	Fungicide Resistance Action Committee
FSA	Fish Screening Assay
fw	fresh weight
g	gram(s)
GAP	Good Agricultural Practice
GC	Gas Chromatography
GUS	groundwater ubiquity score
ha	hectare(s)
HAFT	highest average field trial
Hb	haemoglobin
HC_5	hazardous concentration to 5% of the species
Hct	hematocrit
HDPE	High Density Polyethylene
HDT	highest dose tested
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HPLC	high performance liquid chromatography
ID	identification
IORE	indeterminate order rate equation
IT	inspiration time

IUPAC	International Union of Pure and Applied Chemistry
K	Kelvin degree(s)
kg	kilogram(s)
K_d	soil-water partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
KWG 4168	code name for spiroxamine
KWG 4557	8-(1,1-dimethylethyl)-N-propyl-1,4-dioxaspiro[4.5]decane-2-methanamine
KWG 4669	8-(1,1-dimethylethyl)-N-ethyl-1,4-dioxaspiro[4.5]decane-2-methanamine
L	litre(s)
LAFT	lowest average field trial
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LLNA	local lymph node assay
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	low observed effect concentration
LOEL	low observed effect level
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LSC	liquid scintillation counter
m	metre(s)
M01	Spiroxamine desethyl (also known as KWG 4557)
M02	Spiroxamine despropyl (also known as KWG 4669)
M03	Spiroxamine oxide (also known as WAK 6301)
M05	Spiroxamine hydroxy (also known as WAK 5868)
M06	Spiroxamine acid (also known as WAK 5708)
M11	Spiroxamine desethyl acid (also known as 5756)
M12	Spiroxamine despropyl acid (also known as BNF 5534)
M15	Spiroxamine ketone (also known as WAK 5428)
M17	Spiroxamine ketone acid (also known as WAK 6131)
m^2	squared metre(s)
m^3	cubic metre(s)
Max.	maximum
mg	milligram(s)
min	minute(s)
Min.	minimum
M/L	mixer/loader
mL	millilitre(s)
MOE	margin of exposure
mol	mole
mPCE	micronucleated polychromatic erythrocyte
MRL	maximum residue limit
MS	mass spectrometry
n	number of field trials
N/A	not applicable

NAFTA	North American Free Trade Agreement
NCE	normochromatic erythrocyte
NCHS	National Center for Health Statistics
n.d.	not detected
NHANES/ WWEIA	National Health and Nutritional Examination Survey, What We Eat in America
nm	nanometre(s)
NMRI	Naval Medical Research Institute
No.	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOI	Notice of Intent
NZW	New Zealand white
OC	organic carbon content
OECD	Organization for Economic Cooperation and Development
OH/cm^3	hydroxyl radicals per cubic centimetre
P	parental generation
Pa	Pascal
PCE	polychromatic erythrocyte
PCPA	*Pest Control Products Act*
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PLNA	popliteal lymph node assay
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRZM-EXAMS	Pesticide Root Zone Model – Exposure Analysis Modeling System
PRZM-GW	Pesticide Root Zone Model – Ground Water
RD_{50}	exposure concentration producing a 50% respiratory rate decrease
REI	restricted-entry interval
RQ	risk quotient
RTI	retreatment interval
SBI	Sterol Biosynthesis Inhibitor
SC	soluble concentrate
SD	standard deviation
SFO	single first-order
SPF	specific pathogen free
SPN	Science Policy Notice
SSD	species sensitivity distribution
STMdR	supervised trial median residue
syn	synonym
$t_{1/2}$	half-life
TC	transfer coefficient
trep	representative half life
TRR	total radioactive residue

TSMP	Toxic Substances Management Policy
UK	unknown
US	United States
USA	United States of America
UV	ultraviolet
WAK 6301	8-(1,1-dimethylethyl)-N-ethyl-N-propyl-1,4-dioxaspiro[4.5]decane-2-methanamine-N-oxide
wt(s)	weight(s)
w/v	weight per volume dilution
w/w	weight per weight dilution

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Plant (grape and banana)	00407	The total residues of spiroxamine and the metabolites containing aminodiol common moiety, expressed as parent equivalents	GC-MS	0.05 ppm	2331318, 2331311, 2331337, 2331353, 2331335, 2331339
	01089		LC-MS/MS		2331347
Soil/sediment	01088	Active	HPLC/MS/MS	1.0 µg/kg	2331366
	00433	Active	HPLC/MS/MS	5 µg/kg	2331368
	00433	KWG 4557	HPLC/MS/MS	5 µg/kg	2331368
	00433	KWG 4669	HPLC/MS/MS	5 µg/kg	2331368
	00433	WAK 6301	HPLC/MS/MS	5 µg/kg	2331368
Drinking water	00574	Active	GC/MS	0.1 µg/L	2331371
Surface water	00574	Active	GC/MS	0.1 µg/L	2331371

Table 2 Toxicity Profile of Impulse 500 EC Fungicide

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study	Study findings
Acute, oral Rat, Wistar PMRA# 2332344	LD_{50} ♂ = 1000; ♀ >200-<1000 mg/kg bw clinical signs (apathy, piloerection, labored breathing, increased salivation, red colored salivation, red secretion around eyes, protruding eyes, narrowed palpebral fissure, reduced motility, staggering gait, spastic gait, extended legs, temporary rolling over, temporary lying on the side, temporary spasmodic state, and/or temporary chewing movements) **Moderate toxicity**
Acute, oral Rat, Wistar PMRA# 2332344	LD_{50} ♂♀ >500 mg/kg bw clinical signs (decreased motility and reactivity, staggering and uncoordinated gait, spasmodic state, labored breathing, temporary rolling over (♂) and increased salivation (♀)) **Moderate toxicity**
Acute, dermal Rat, Wistar PMRA# 2332344	LD_{50} ♂♀ >2000 mg/kg bw clinical signs (red secretion around the snout and eyes, and a red incrustation around the snout in ♂ and in ♀ apathy, piloerection, pallor, labored breathing, increased salivation, narrowed palpebral fissure, red secretion around the snout, incrustation at the labial commissure, red secretion around the left eye, staggering gait, spastic gait, extended hind legs, spasmodic state, uncoordinated motions, decreased motility, lateral position, and lateral position of the head) **Low toxicity**

Study	Study findings
Acute, inhalation Rat, Wistar PMRA# 2332344	LD_{50} ♂♀ >1.03 mg/L Clinical signs: piloerection, ungroomed hair-coat, bradypnea, labored breathing, reduced motility, nasal discharge (serous), nostrils with red encrustations, pallor, tremor and breathing sounds (stridor and wheezing) **Slight toxicity**
Primary eye irritation Rabbit, NZW PMRA# 2332348	Mean irritation score (24, 48, 72 hours) = 44.7/110 **Highly irritating**
Primary skin irritation Rabbit, NZW PMRA# 2332348	Mean irritation score (24, 48, 72 hours) = 3.8/8 **Moderately irritating**
Skin sensitization (Buehler) Guinea pig PMRA# 2332349	**Not a dermal sensitizer**
Skin sensitization (Local lymph node assay) Mouse PMRA# 2388647	**POTENTIAL SKIN SENSITIZER**

Table 3 Toxicity Profile of Spiroxamine Technical (KWG 4168)
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.)

Study Type /Animal/PMRA #	Study Results
Metabolism/Toxicokinetic, oral (gavage, single dose and repeat dosing) Rat, Wistar cyclohexyl-1-^{14}C-KWG 4168 and 1,3-dioxolan-4-^{14}C-KWG 4168 (1 and 100 mg/kg bw, single dose; 1 mg/kg bw/day, repeated dosing for 15 days) cyclohexyl-1-^{14}C-KWG 4168 (5 mg/kg bw, single dose) PMRA# 2331378,	**Absorption:** Absorption was rapid for both labels and dose regimens. The maximum levels of radioactivity in plasma were reached within 1.5-2 and 4-8 hours respectively after the low and high-dose administration. Based on the amounts excreted in urine, at least 51 and 67% of the administered dose (AD) of 1 mg/kg bw (single or repeat doses of cyclohexyl-1-^{14}C-spiroxamine) were absorbed in ♀ and ♂ rats respectively. At the high dose of 100 mg/kg bw of cyclohexyl-1-^{14}C-spiroxamine, absorption was lower, at 39 and 51% AD in ♀ and ♂ rats. For 1,3-dioxolan-4-^{14}C-spiroxamine, between 60 to 75% AD were absorbed. The rapid absorption of spiroxamine was confirmed in the whole-body radiography assay. **Tissue distribution:** Analyses of the plasma concentrations showed that the radioactivity was readily distributed from the plasma into peripheral compartments. Radioactivity levels in the tissues were low, After low dose administration (1 mg/kg bw), the highest concentrations were found in the liver, thymus and adrenals. Less than 2% of the AD was retained in tissues and carcass by 48 hours. **Metabolism:** Metabolism of spiroxamine involved an initial oxidation, then sulfation, dealkylation, hydroxylation, conjugation with glucuronide, and the cleavage of the rings. The major metabolite was spiroxamine-acid resulted from oxidation of the tertiary alkyl

Study Type /Animal/PMRA #	Study Results
2331381, 2331379	moiety. From the acid, desalkylation formed spiroxamine-despropyl-acid and spiroxamine-desethyl-acid; hydroxylation formed spiroxamine-hydroxyl-acid, conjugation with glucuronide formed spiroxamine-acid flucuronide, sulfation formed spiroxamine-sulfate, which in turn formed spiroxamine-despropyl-sulfate and spiroxamine-desethyl-sulfate by dealkylation. Cleavage of the ring resulted in the formation of the metabolite aminodiol. Aminodiol was exclusively excreted in the urine. The acid forms of the metabolites were also mainly excreted in the urine while the sulfate conjugates were mainly excreted in the faeces. **Excretion:** Excretion of cyclohexyl-1-^{14}C-spiroxamine and 1,3-dioxolan-4-^{14}C-spiroxamine was similar and rapid. Elimination via expired air was low, ≤0.37% AD. Following single low- and high-dose administration, the main route of elimination was urinary (45-78% AD), while faecal excretion (21-52% AD) played a secondary role. Total recovery of radioactivity in 48 hours ranged from 80 to 94%. Urinary excretion of radioactivity was lower in ♀ when compared to males under the same dosing regimen. There were no substantial differences in pharmacokinetics of spiroxamine that was labelled at the cyclohexyl-1-^{14}C- or the 1,3-dioxolan-4-^{14}C- positions.
Acute oral Mouse, NMRI PMRA# 2331384	LD_{50} : ♂ = 460, ♀ = 561 mg/kg bw ≥355 mg/kg bw: clinical signs (apathy, piloerection, laboured breathing, reduced motility, staggering or creeping, vocalisation, spasms, periodic twitching, periodic rolling over, outstretched extremities, and lying on side) **High toxicity**
Acute oral Rat, Wistar PMRA# 2331383	LD_{50} : ♂ = 595, ♀ ~500 mg/kg bw ≥100 mg/kg bw: clinical signs (apathy, increased salivation, piloerection, laboured or faster breathing, reduced motility, staggering gait, lying on side, spasms and outstretched extremities) **Moderate toxicity**
Acute dermal Rat, Wistar PMRA# 2331385	LD_{50}: ♂ = 1600, ♀ = 1068 mg/kg bw ≥1000: ↓ bw; clinical signs (apathy, reduced motility, piloerection, staggering gait and laboured breathing) Slight toxicity
Acute inhalation Rat, Wistar PMRA# 2331386	LC_{50}: ♂ = 2.77, ♀ = 1.98 mg/L ≥1.140 mg/L: clinical signs (piloerection, un-groomed fur, reduced motility, tremors, laboured breathing, stridor, prostration, tonical spasms with rolling over movements, staggering gait) ≥1.982 mg/L: ↓ bw (♂) Slight toxicity
Primary eye irritation Rabbit, NZW PMRA# 2331387	Mean irritation score (24, 48, 72 hours) = 0.2/110 Non-irritating
Primary skin irritation Rabbit, NZW PMRA# 2331387	Mean irritation score (24, 48, 72 hours) = 4.1/8 Moderately irritating

Study Type /Animal/PMRA #	Study Results
Skin sensitization (maximization method) Guinea pigs PMRA# 2331389	POTENTIAL SKIN SENSITIZER
Skin irritation/sensitization (Human patch test) Human volunteer PMRA# 2331391	Spiroxamine not irritating at low concentrations, ≤0.2%, but was irritating at concentrations ≥ 0.2% Spiroxamine was not a dermal sensitizer
28-Day dietary Rat, Wistar PMRA# 2331392	NOAEL = 30 ppm (♂ = 3.4, ♀ = 3.8 mg/kg bw/day) LOAEL = 100 ppm (♂ = 10.8, ♀ = 12.2 mg/kg bw/day) Based on hyperkeratosis of the esophageal mucosa, ↑ liver fatty deposits
28-Day oral gavage Rat, Wistar PMRA# 2331393	NOAEL = not established LOAEL = 10 mg/kg bw/day Based on ↑ water intake, clinical signs (salivation and tremor, digging and preening activities)
90-Day dietary Mouse, B6C3F1 PMRA# 2331396	NOAEL = 80 ppm (♂ = 24.9, ♀ = 28.5 mg/kg bw/day) LOAEL = 320 ppm (♂ = 88.4, ♀ = 126.3 mg/kg bw/day) Based on minimal epidermal hyperplasia in the auricle (♂) and ↑ centrilobular fatty change of the hepatic lobules (♀)
90-Day oral gavage Mouse, B6C3F1 PMRA# 2331397	NOAEL = 60 mg/kg bw/day LOAEL = 180 mg/kg bw/day Based on urinary tract epithelial hyperplasia, liver enzyme induction
90-Day dietary Rat, Wistar PMRA# 2331395	NOAEL = 25 ppm (♂= 1.9, ♀ = 2.7 mg/kg bw/day) LOAEL = 125 ppm (♂= 9.3, ♀ = 13.2 mg/kg bw/day) Based on hyperkeratosis in esophageal and forestomach epithelium
90-Day dietary Dog, Beagle PMRA# 2331399, 2331400	NOAEL = 500 ppm (♂= 16.2, ♀ = 15.1 mg/kg bw/day) LOAEL = 750 ppm (♂= 20.0, ♀ = 21.3 mg/kg bw/day) Based on ↑ relative liver wt, minimal diffuse hepatocytomegaly (♂);↓ albumin (♀)
1-Year dietary Dog, Beagle PMRA# 2331402	NOAEL = 75 ppm (♂= 2.47, ♀ = 2.48 mg/kg bw/day) LOAEL = 1000 ppm (♂= 28.0, ♀ = 25.8 mg/kg bw/day) Based on bilateral subcapsular clouding and cataractic change, , serum albumin, minimal diffuse hepatocytomegaly; ↓ triglyceride (♀)
18-Day dermal Rabbit, NZW PMRA# 2331407	NOAEL systemic >5 mg/kg bw/day (HDT); local effects = 0.2 mg/kg bw/day LOAEL local = 0.5 mg/kg bw/day
28-Day inhalation Rat, Wistar PMRA# 2331404, 2331405	NOAEC = 600 ppm (0.09 mg/L) LOAEC = 3000 ppm (0.52 mg/L) Based on ↑ polymorphonuclear granulocyte, ↓ lymphocyte, ↓ Hb, Hct (♀), ↓ cholesterol, ↑ triple phosphate (♀),↑blood coagulation time, leucocyte, ALT, AST, globulin, urinary proteins, bilirubin, urobilinogen, ketone bodies, ammonium-magnesium (triple) phosphate & corpuscular components, organ wts (liver, kidneys), liver O-demethylase, ↓ thrombocyte, cholinesterase (♀), total protein & albumin, organ wts (thymus, heart, spleen), N-demethylase/cytochrome P-450 activities (♂), squamous epithelial metaplasia in the nasal cavity, epithedial hyperplasia and hyperkeratosis in larynx zone, bronchiolo-alveolar proliferation with ↑ alveolar macrophages lungs, hyperkeratosis in esophagus, corneal hyperplasia, hyperplasia/hyper-keratosis of eyelids, hyperplastic

Study Type /Animal/PMRA #	Study Results
	lesions in urothelium of urinary bladder, and atrophic thymus changes (♂), local dermal lesions - hyperkeratosis, epithelial hyperplasia, and extended inflammatory infiltration and scab in muzzle zone, hyperkeratoses and epithelial hyperplasia in mamma zone and tail.
2-Year dietary oncogenicity Mouse, B6C3F1 PMRA# 2331429	NOAEL = 20 ppm; ♂= 4.5; ♀ = 7.8 mg/kg bw/day LOAEL = 160 ppm; ♂ = 36.7; ♀ = 59.5 mg/kg bw/day Based on tail acanthosis; ↓ bw, hyperkeratosis in esophagus (♂) No evidence of carcinogenicity
2-Year dietary oncogenicity Mouse, B6C3F1 PMRA# 2331430	NOAEL = 160 ppm; ♂= 41.0; ♀ = 64.6 mg/kg bw/day LOAEL = 600 ppm; ♂ = 149.8; ♀ = 248.1 mg/kg bw/day Based on ↓ bw, bwg, hyperkeratosis (tongue, esophagus, and forestomach mucosa ♀), hyperkeratosis and acanthosis in the epidermis (pinnas and tail ♀) Neoplasm: adrenal cortical adenoma, ♂ (5, 7, 10 at 0, 160, 600 ppm, respectively), not statistically significant Evidence of oncogenicity equivocal
2-Year dietary / oncogenicity Rat, Wistar PMRA# 2331425, 2331426	NOAEL = 70 ppm; ♂= 4.22; ♀ = 5.67 mg/kg bw/day LOAEL = 490 ppm; ♂ = 32.8; ♀ = 43.0 mg/kg bw/day based on hyperkeratosis and acanthosis (esophagus), desiccation of auricular epidermis, acanthosis (esophagus & tail) No evidence of carcinogenicity
2-Generation dietary reproductive Rat, Wistar PMRA# 2331433, 2331427	Parental systemic toxicity: NOAEL = 20 ppm (♂ = 2.1, ♀ = 2.4 mg/kg bw/day) LOAEL = 80 ppm (♂ = 9.2, ♀ = 10.5 mg/kg bw/day) based on ↓ food, bw, during lactation, hyperkeratoses in esophagus, P F1♀, ↓ liver wt, P♂ Reproductive toxicity: NOAEL = 80 ppm (♂ = 9.2, ♀ = 10.5 mg/kg bw/day) LOAEL = 300 ppm (♂ = 35.9, ♀ = 41.9 mg/kg bw/day), based on ↓ litter size at birth Offspring toxicity: NOAEL = 80 ppm (♂ = 9.2, ♀ = 10.5 mg/kg bw/day) LOAEL = 300 ppm (♂ = 35.9, ♀ = 41.9 mg/kg bw/day) based on F1 - laboured breathing, cyanotic, cold, thin, increased urination, bloody nose; F2 – laboured breathing, cyanotic, ↓ pup survival, F1 and F2 pups days 0-4 lactation
2-Generation dietary reproductive Rat, Wistar PMRA# 2331434	Parental systemic toxicity: NOAEL = 80 ppm (♂ = 5.5, ♀ = 6.7 mg/kg bw/day) LOAEL = 300 ppm (♂ = 21.0, ♀ = 24.5 mg/kg bw/day) based on ↓ bw, P♀ during premating, gestation, lactation, F1♂♀ during premating, F1♀ during gestation and lactation, ↓ food intake, F1♀ during pre-mating, ↑ activated partial prothrombin time, P♂♀, F1♀, hyperkeratosis of the esophagus, PF1♂♀ Reproductive toxicity: NOAEL = 80 ppm (♂ = 5.5, ♀ = 6.7 mg/kg bw/day), ↓ bw at birth in F1F2 pups Offspring toxicity: NOAEL = 80 ppm (♂ = 5.5, ♀ = 6.7 mg/kg bw/day) LOAEL = 300 ppm (♂ = 21.0, ♀ = 24.5 mg/kg bw/day) based on ↓ bw, F1F2, delays in vaginal patency and preputial separation, F1
Developmental, oral gavage Rat, Wistar	Maternal toxicity: NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day based on ↓ food intake, bwg Developmental toxicity:

Study Type /Animal/PMRA #	Study Results
PMRA# 2331437, 2331439, 2331440, 2331438, 2331441	NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day based on palatoschisis (3 fetuses from 3 litters), caudal malposition of the left hind leg (1 fetus), and slight delay in development (↓ bw, delayed ossification) Low incidence of malformations at maternally toxic dose
Developmental, dermal Rat, Wistar PMRA# 2331442, 2331444	Maternal toxicity: NOAEL = 20 mg/kg bw/day LOAEL = 80 mg/kg bw/day based on ↓ bw Developmental toxicity: NOAEL = 20 mg/kg bw/day LOAEL = 80 mg/kg bw/day based on slight ↑ fetuses with wavy ribs No evidence of sensitivity of the young.
Developmental, oral gavage Rabbt, Himalayan PMRA# 2331448, 2331449, 2331450	Maternal toxicity: NOAEL = 20 mg/kg bw/day LOAEL = 80 mg/kg bw/day based on encrustation at the corner of the mouth, anal prolapse, ↓ food intake, bw, few/soft feces Developmental toxicity: NOAEL = 20 mg/kg bw/day LOAEL = 80 mg/kg bw/day based on slight ↓ fetal bw, placental wt No evidence of sensitivity of the young.
Bacterial reverse mutation assay (Ames test) PMRA# 2331409	Cytotoxicity ≥400 µg/plate Negative
In vitro mammalian cell gene mutation (CHO HGPRT) PMRA# 2331419	Cytotoxicity 100 µg/mL Precipitation ≥ 100 µg/mL: Negative
In vitro chromosome aberration in CHO cells PMRA# 2331417	Negative
In vitro unscheduled DNA synthesis assay in primary rat hepatocytes PMRA# 2331420	Cytotoxicity ≥62.5 µg/mL Negative
In vivo mouse micronucleus assay NMRI mice (bone marrow) PMRA# 2331423	Mortality: 4/40 test mice died PCE/NCE ratio, mPCEs similar among groups Negative
Acute neurotoxicity, oral gavage Rat, Wistar PMRA# 2331452	NOAEL: ♂ = 10, ♀ = 30 mg/kg bw LOAEL: ♂ = 30, ♀ = 100 mg/kg bw Based on: ♂ incoordination, piloerection, ↓ forelimb grip strength, foot splay at 1hour; ♀ ↓ motility, ↓ reactivity, staggering gait, piloerection, laboured breathing, lateral position, and ↑ salivation, most reversible within 1 day, FOB (gait incoordination, dragging forelimbs and hindlimbs, ↓ movement when aroused, laboured breathing, lying flat, ↓ rearing, ↓ forelimb and hindlimb strength, and ↓ foot splay)

Study Type /Animal/PMRA #	Study Results
90-Day dietary neurotoxicity Rat, Wistar PMRA# 2367660	Systemic toxicity: NOAEL 35 ppm (♂ = 2.4, ♀ = 2.5 mg/kg bw/day) LOAEL 155 ppm (♂ = 10.6, ♀ = 11.1 mg/kg bw/day) Based on hyperkeratosis in the esophagus, 1/sex No evidence of neurotoxicity
Inhalation sensory irritation Rat, Wistar (SPF) PMRA 2331468	Lung function tests: no effects in specific breathing parameters, or in breathing rate; mild decrease in tidal volume ≥858 mg/m^3 air; influence on the IT/ET ratio at 1584 mg/m^3 Conclusion: slight pulmonary irritation potential
Inhalation sensory irritation Mouse PMRA 2331469	Lung function tests: ≥3000 mg/m^3: ↓ peak expiratory flow, tidal volume, respiratory rate, and minute volume; ↑ inspiration time ≥10000 mg/m^3: ↑ maximum expiration time Pulmonary irritant threshold concentration (RD_{50}) and non-irritating concentration (RD_0) = 713 (594-886) and 16 mg/m^3, respectively
10-Week oral Rat, Wistar PMRA# 2331473	assessment of foci of altered hepatocytes (FAH) following 4 week daily oral dosing of spiroxamine followed by 6 week daily dose of phenobarbital (carcinogenic promotor) similarity of findings in control and test groups; provided insufficient evidence of increased FAH
In vitro aromatase inhibition PMRA# 2331470	Human recombinant CYP19 aromatase as enzyme source; radiolabeled androst-4-ene-3,17-dione [1β-3H (n)] as substrate Spiroxamine at concentrations up to 100 µM did not inhibit aromatase
In vitro steroidogenesis inhibition rat testicular fragment culture PMRA# 2331471	Measured testosterone secreted into medium and testosterone contained in testicular fragments Spiroxamine at concentrations up to 100 µM did not inhibit steroidogenesis; testosterone in medium and in tissues similar to those of vehicle control
Immunostimulation popliteal lymph node assay (PLNA) local lymph node assay (LLNA) Rat, Wistar, ♀ Mouse, NMRI, ♀ PMRA# 2331472	PLNA: stimulation indices similar between test & control animals Conclusion: unacceptable study due to deficiency in methodology and reporting LLNA: stimulation indices exceeded value of 2 when dosed with 10% spiroxamine in mice and 2% in rats Conclusion: spiroxamine is a potential dermal sensitizer

Table 4 Toxicity data of metabolite (KWG 4168 N-oxide) and impurities (KWG4168-bisadduct, Spiroketal, EP-Amin) of Spiroxamine

Study	Study findings
Acute, oral KWG 4168 N-oxide Rat, Wistar PMRA# 2331457	LD_{50} ♀ = 707 mg/kg bw ≥1000 mg/kg bw: ↓ bw; clinical signs (apathy, reduced motility, piloerection, staggering gait and laboured breathing) **Moderate toxicity**
28-Day dietary KWG 4168 N-oxide Rat, Wistar PMRA# 2331462	NOAEL = 150 ppm (♂=12.9, ♀ = 13.2 mg/kg bw/day) LOAEL = 1000 ppm (♂=114.6, ♀ = 94.3 mg/kg bw/day) Based on piloerection 1♀, ↑ food intake ♂, ↓ body weights ♂, ↓ cholesterol, liver enzyme induction, mild transitional cell hyperplasia in urinary bladder, hyperkeratosis of epithelium of esophagus and fore-stomach
90-Day dietary KWG 4168 N-oxide Rat, Wistar PMRA# 2331460	NOAEL = 125 ppm (♂= 8.8, ♀ = 9.7 mg/kg bw/day) LOAEL = 625 ppm (♂= 45.0, ♀ = 53.6 mg/kg bw/day) Based on ↑ food intake ♀, ↓ bw ♂, ↑ clotting time, ↑ AP, ALT, ↓ cholesterol, protein, albumin, ↑ aminopyrine-N-demethylase & cytochrome P450, hyperkeratosis in esophageal and forestomach epithelium
Bacterial reverse mutation assay (Ames test) KWG 4168 N-oxide PMRA# 2331458	Cytotoxicity ≥ 500 µg/plate **Negative**
Bacterial reverse mutation assay (Ames test) KWG4168-bisadduct PMRA# 2331411	Cytotoxicity all doses **Negative**
Bacterial reverse mutation assay (Ames test) Spiroketal PMRA# 2331413	Cytotoxicity ≥50 µg/plate **Negative**
Bacterial reverse mutation assay (Ames test) EP-Amin PMRA# 2331415	Cytotoxicity ≥500 µg/plate **Negative**
In vitro mammalian cell gene mutation (V79 HGPRT) KWG 4168 N-oxide PMRA# 2331461	Cytotoxicity ≥500 µg/plate **Negative**
In vitro chromosome aberration (CHL cells) KWG 4168 N-oxide PMRA# 2331459	Cytotoxicity ≥300 µg/plate **Negative**

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Spiroxamine

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary	acute neurotoxicity, rat	NOAEL = 10 mg/kg bw Incoordination, piloerection, ↓ forelimb grip strength & foot splay	100
	ARfD = 0.1 mg/kg bw		
Repeated dietary	1-year dog dietary	NOAEL = 2.47 mg/kg bw/day bilateral sub-capsular clouding and cataract changes of the lens	100
	ADI = 0.025 mg/kg bw/day		
Short- and intermediate term dermal	18-day rabbit dermal	NOAEL = 5 mg/kg bw/day (HDT)	100
Short-term inhalation[2]	rat oral developmental	NOAEL = 30 mg/kg bw/day incidence of malformations	300
Intermediate-term inhalation	28-day rat inhalation	NOAEC = 600 ppm (24.4 mg/kg bw/day) induction of liver enzymes, alteration of blood parameters, alteration of the epithelial lining of the respiratory tract, hyperkaeratosis of the esophagus and eyelids, and corneal hyperplasia	300
Long-term dermal[3] and inhalation[2]	1-year dog dietary	NOAEL = 2.47 mg/kg bw/day bilateral sub-capsular clouding and cataract changes of the lens	100
Cancer	Equivocal increase in the incidence of adrenal cortical adenoma in male mice. Endpoints selected for the non-cancer risk assessment are protective of these equivocal findings		

1 CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

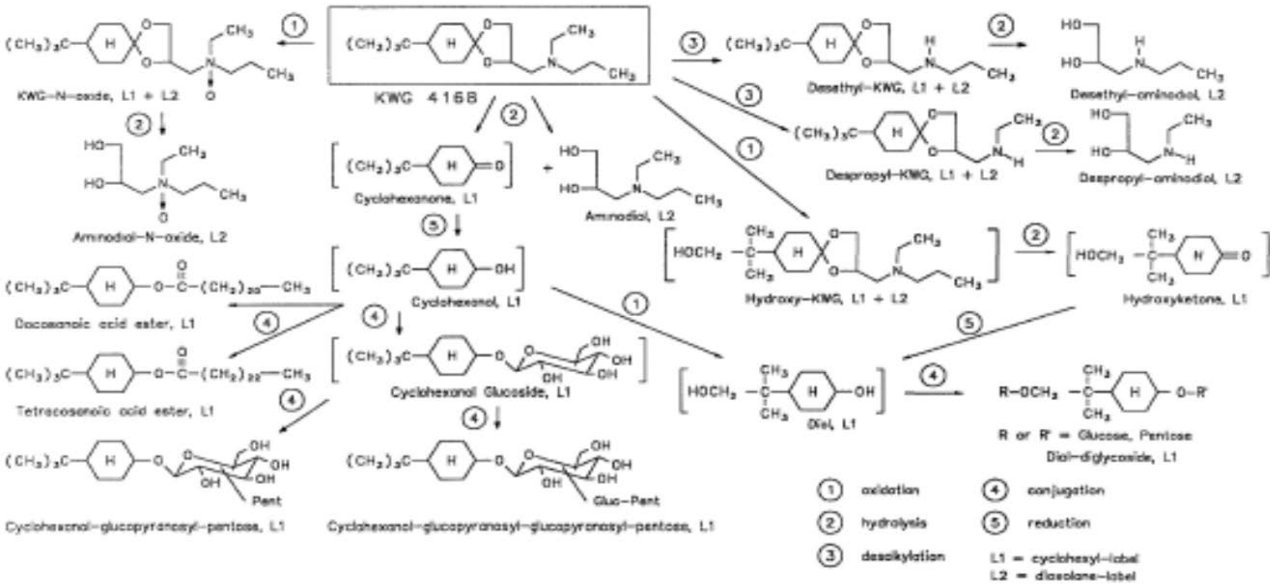
2 Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

3 An oral NOAEL was selected and a dermal absorption factor of 63% was used in route-to-route extrapolation.

Table 6 Integrated Food Residue Chemistry Summary

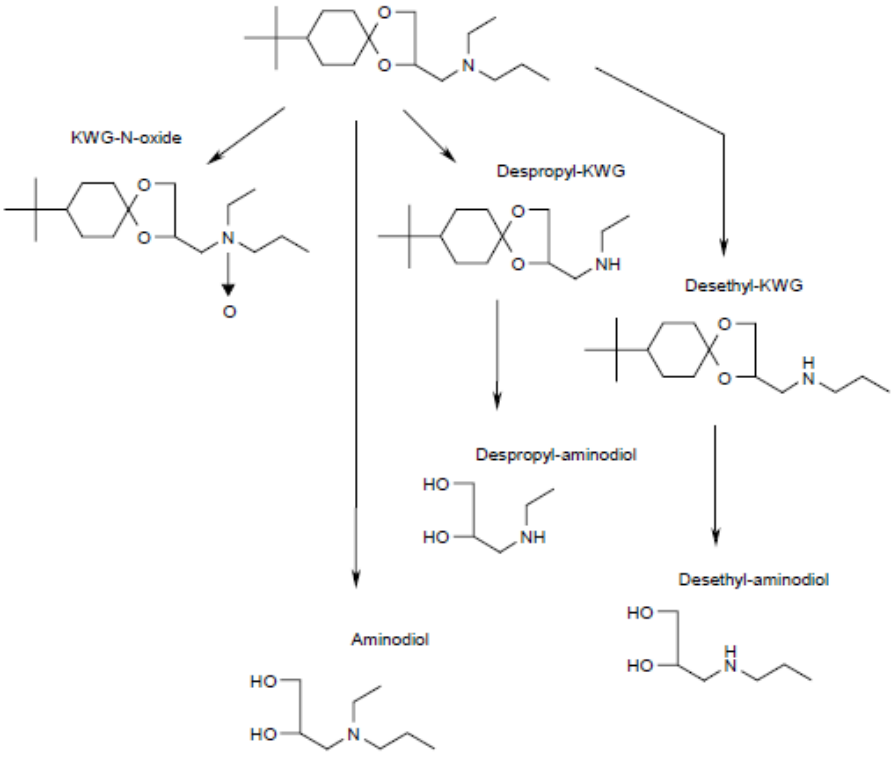
NATURE OF THE RESIDUE IN GRAPES			**PMRA #s 2331492 and 2331493**	
Radiolabel Position	[cyclohexyl-1-^{14}C]-spiroxamine and [dioxolane-4-^{14}C]-spiroxamine			
Test Site	In container in greenhouse			
Treatment	Foliar treatment			
Total Rate	2 × 1.2-1.3 mg a.i./grape bunch; total rate of 1600 g a.i./ha/season			
Formulation	Emulsifiable concentrate (EC) formulation			
Preharvest interval	35 days			
Matrices	**[cyclohexyl-1-^{14}C]**		**[dioxolane-4-^{14}C]**	
	TRRs (ppm)		**TRRs (ppm)**	
Mature grape	3.41		13.08	
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[cyclohexyl-1-^{14}C]**	**[dioxolane-4-^{14}C]**	**[cyclohexyl-1-^{14}C]**	**[dioxolane-4-^{14}C]**
Mature grape	Spiroxamine, M35, M33/34 and M24	Spiroxamine, M28	M01, M02, M03, M15, M16, M36 and M37	M01, M02, M03, M05, M29, M30 and M31

Proposed Metabolic Scheme in grapes



NATURE OF THE RESIDUE IN BANANAS			**PMRA #s 2331495, 2331496 and 2331497**	
Radiolabel Position	[cyclohexyl-1-^{14}C]-spiroxamine and [dioxolane-4-^{14}C]-spiroxamine			
Test Site	In container in greenhouse			
Treatment	Foliar treatment			
Total Rate	3 applications to banana bunches; total rate of 3200 g a.i./ha/season			
Formulation	Emulsifiable concentrate (EC) formulation			
Preharvest interval	0 day			
Matrices	**[cyclohexyl-1-^{14}C]**		**[dioxolane-4-^{14}C]**	
	TRRs (ppm)		**TRRs (ppm)**	
Banana pulp	0.444		0.553	
Banana peel	4.77		6.60	
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[cyclohexyl-1-^{14}C]**	**[dioxolane-4-^{14}C]**	**[cyclohexyl-1-^{14}C]**	**[dioxolane-4-^{14}C]**
Banana pulp	Spiroxamine, M33a	Spiroxamine, M28	M01, M02, M03 M24 and M33	M01, M02, M03, M30 and M31
Banana peel	Spiroxamine	Spiroxamine, M28	M01, M02, M03 M24, M33a and M33	M01, M02, M03, M30 and M31

Proposed Metabolic Scheme in bananas



FREEZER STORAGE STABILITY	PMRA #s 2331489 and 2331490

Plant matrices: grape, grape juice, raisins and banana

The freezer storage stability data indicate that residues of spiroxamine and aminodiol are stable at -20°C in grape, grape juice and raisins for up to 18 months, in banana for up to 24 months.

CROP FIELD TRIALS & RESIDUE DECLINE ON GRAPE	PMRA # 2331517

Field trials were conducted in 1996-1998 in NAFTA Growing Region 10 (12 trials). A concentrate solution formulation of spiroxamine was applied twice as foliar broadcast sprays at a rate of 383-452 g a.i./ha/application at growth stages of 50% and 80% maturity for a seasonal application rate of 781-849 g a.i./ha. The applications were made at 26-29 days of intervals. The pre-harvest interval was in the range of 26-29 days.

Residue decline data show that the total residues of spiroxamine remained unchanged in grape with increasing preharvest intervals (PHIs) from 21-42 days.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Total Spiroxamine Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Grape	781-849	26-29	12	<0.05	0.634	<0.05	0.61	0.125	0.177	0.16

Values based on total number of samples.
* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON GRAPE	PMRA #s 2331502 to 2331512

A total of 58 field trials for spiroxamine on grapes were conducted in European countries during the 1994-2007 growing seasons.

In Northern Europe (Germany and France), a total of 33 trials on grapes were conducted from 1994-2007. Three to four post-blossom applications of spiroxamine in EC formulations were performed at rates between 280 to 640 g a.i./ha/application. The intervals between the applications were 10-31 days.

In Southern Europe (France, Portugal, Spain, Italy and Greece), a total of 25 trials on grapes were conducted from 1994-2007. Three post-blossom applications of spiroxamine in EC formulations were performed at rates of 170-450 g a.i./ha/application. The applications intervals were 9-16 days.

The total seasonal application rates were 630-2240 g a.i./ha for all grape field trials. Table grapes (berries) were harvested at a PHI of 14 days, while wine grapes (grape bunch with stems and stalks) were harvested at PHIs of 35-36 days. Residue decline data show that the total residues of spiroxamine decreased in grape with increasing PHIs from 0-42 days.

Commodity	Total Application Rate (g a.i./ha/season)[1]	PHI (days)	Total Spiroxamine Residue Levels (ppm)					
			n *	Min. #	Max. #	Median	Mean	SD *
Table grape	1520-2240	14	3	0.46	0.93	0.52	0.64	0.15
Wine grape	1500-2240	35	10	0.27	1.4	0.485	0.574	0.11

Values based on total number of samples.
* SD = Standard Deviation; n = number of field trials.
[1] Only data representing ±25% German GAP are reported herein.

CROP FIELD TRIALS & RESIDUE DECLINE ON BANANA — **PMRA #s 2331518 and 2331520**

Field trials on banana were conducted in 2000-2001 in South and Central America (4 trials each in Costa Rica and Ecuador, 1 trial each in Guatemala and Mexico, 2 trials in Honduras). EC Formulation of spiroxamine was applied 12-14 times as foliar broadcast sprays at a rate of 3647- 4403 g a.i./ha/season. Samples of banana whole fruit were harvested from all trials on the day of the last application (0-day PHI), after the product had dried. Samples from two trials were processed into banana pulp by washing and peeling.

Residue decline data show that the total residues of spiroxamine remained unchanged with increasing PHIs from 7-22 days.

Commodity	Total Application Rate (g a.i./ha/season)	PHI (days)	Total Spiroxamine Residue Levels (ppm)					
			n *	Min. #	Max. #	Median	Mean	SD *
Bagged banana	3647-4403	0	12	<0.05	0.46	0.06	0.13	0.04
Unbagged banana	3664-4403	0	12	0.14	2.44	1.17	1.13	0.18

Values based on total number of samples.
* SD = Standard Deviation; n = number of field trials.

PROCESSED FOOD AND FEED - CROP — **PMRA # 2331523**

Test Site	Ten trials in European countries
Treatment	Broadcast foliar applications
Rate	3-4 foliar applications for a total rate of ~1.2 kg a.i./ha/season.
End-use product/formulation	EC formulation
Preharvest interval	35 days for wine grape and 14 days for table grape
Processed Commodity	**Median Processing Factor**
Must	0.6-fold
Bottle wine	0.6-fold
Young wine	0.5-fold
Juice	0.7-fold
Raisins	4.0-fold

Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT Primary crops (list crops; grape and banana)	Spiroxamine and the metabolites containing aminodiol common moiety, expressed as parent equivalents
RESIDUE DEFINITION FOR RISK ASSESSMENT Primary crops	Spiroxamine and the metabolites containing aminodiol common moiety, expressed as parent equivalents
METABOLIC PROFILE IN DIVERSE CROPS	Similar in grape and banana.
ANIMAL STUDIES	
ANIMALS	**Ruminant and Poultry**
RESIDUE DEFINITION FOR ENFORCEMENT	Not required
RESIDUE DEFINITION FOR RISK ASSESSMENT	Not required
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	Not required
FAT SOLUBLE RESIDUE	Not applicable

DIETARY RISK FROM FOOD AND WATER

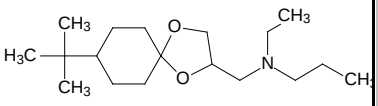
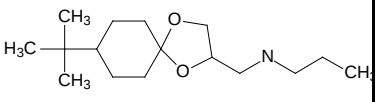
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
Refined chronic non-cancer dietary exposure analysis **ADI = 0.02 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.0074 µg/L**	**Total Population**	11.0	11.8
	All Infants (<1 year old)	14.1	16.9
	Children 1-2 years old	29.8	30.8
	Children 3-5 years old	20.6	21.4
	Children 6-12 years old	10.3	10.9
	Youth 13-19 years old	6.7	7.3
	Adults 20-49 years old	11.1	11.8
	Adults 50+ years old	9.4	10.1
	Females 13-49 years old	8.2	8.9

	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Water**
Refined acute dietary exposure analysis, 95th percentile **ARfD =0.1 mg/kg bw** **Estimated acute drinking water concentration = 0.024 µg/L**	**Total Population**	10.8	11.4
	All Infants (<1 year old)	28.3	29.4
	Children 1-2 years old	32.3	32.9
	Children 3-5 years old	23.0	23.5
	Children 6-12 years old	10.9	11.7
	Youth 13-19 years old	6.3	6.8
	Adults 20-49 years old	9.5	10.2
	Adults 50+ years old	8.5	9.1
	Females 13-49 years old	7.9	8.5

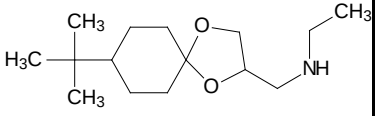
Table 8 Physical and chemical properties of spiroxamine

Property	Result	Comment
Vapour pressure	Diastereoisomer Pa (20°C) Pa (25°C) A 4.0×10^{-3} 7.1×10^{-3} B 5.7×10^{-3} 1.0×10^{-2} Mixture of A & B Pa (20°C) 9.7×10^{-3}	High to very high volatility
Henry's law constant (Calculated by reviewer)	Diastereoisomer Pa m^3 mol^{-1} (20°C) A 2.53×10^{-3} B 4.99×10^{-3}	Non-volatile from moist soil or water
Ultraviolet (UV) / visible spectrum	Absorption at $\lambda > 300$ nm was not observed.	Phototransformation is unlikely in the UV range.
Solubility in water at 20°C	pH diastereoisomer A diastereoisomer B 3 >200 g/L of mixture of A and B 7 470 mg/L 340 mg/L 9 14 mg/L 10 mg/L	Very soluble at acidic and neutral pHs; soluble at alkaline pHs
n-Octanol/water partition coefficient (log K_{ow})	pH log K_{ow} isomer A isomer B 5.5 1.28 1.41 7 2.79 2.98 9 4.88 5.08	Potential for bioaccumulation at neutral or alkaline pHs
Dissociation constant (p*K*a)	p*K*a = 7.9 of conjugate base in an aqueous system containing 40% of 2-propanol, so fully or partially ionized at environmental pH	Spiroxamine is a weak acid and is expected to be fully or partially ionized at environmentally-relevant pHs This is one indicator of the potential mobility of spiroxamine in soil

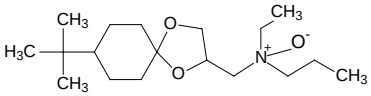
Table 9 Table of maximum formation of transformation products

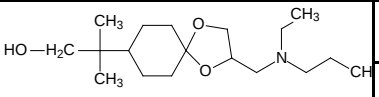
Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
PARENT						
Spiroxamine N-[(8-tert-butyl-1,4-dioxaspiro[4.5]dec-2-yl)methyl]-N-ethylpropan-1-amine CAS No. 118134-30-8						
TRANSFORMATION PRODUCTS						
Spiroxamine desethyl **M01** **KWG 4557**		Aerobic soil	Silt loam (Exp. A)	7.3 (60)	7.2 (100)	2331535
			Silt loam (Exp. B)	7.0 (100)	7.0 (100)	2331535
			Sandy loam	8.8 (60)	7.7 (100)	2331535
			Sandy loam	3.9 (60)	3.4 (100)	2331535
			Loamy sand	8.1 (100)	8.1 (100)	2331536

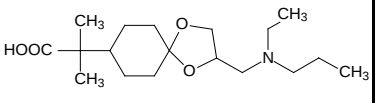
Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
			(Exp. A)			
			Loamy sand (Exp. B)	8.0 (100)	8.0 (100)	2331536
			Loam	6.1 (90)	3.8 (360)	2331537
			Silt loam	7.9 (58)	4.4 (120)	2331538
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Light: 9.1(17)	Light: 9.1 (17) Dark: 2.4 (17)	2331541
		Aqueous photolysis		Light: 4.53 (12)	Light 4.39 (15) Dark: n.d.	2331270
		Hydrolysis (at 25°C, max of two replicates)	pH 5 pH 7 pH 9	Not identified Not identified 1.90 (30)	Not identified Not identified 1.90 (30)	2331268
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	3.1 (33)	1.7 (100)	2331564
			Silty clay loam (max of two replicates)	1.3 (7)	0.7 (100)	2331564
			Sand (mean of two replicates)	Not identified	Not identified	2331567
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		2.2 (61)	1.9 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	7.3 (62)	7.3 (62)	2331561
			Sand	8.5 (60)	8.5 (60)	2331561
			Silty loam	8.1 (62)	8.1 (62)	2331561
			Loam (max of two replicates)	1.3 (30)	1.3 (30)	2331562
		Field studies[2]	Loam (max of three replicates)	**10.7** (10, 30)	< 3.4 (580)	2331554
			Loam (max of two	**11.8** (7)	n.d. (240)	2331549

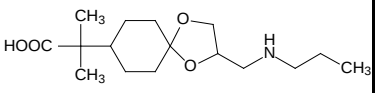
Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
			replicates)			
			Silty clay loam (max of two replicates)	7.9 (31)	n.d. (240)	2331549
			Loam (max of two replicates)	**11.3** (7)	n.d. (358)	2331550
			Sandy loam (max of two replicates)	9.0 (7)	n.d. (360)	2331550
		Other studies (controlled rotational crop study in greenhouse)	Sandy loam	5.5 (161)	5.5 (161)	2331526
Spiroxamine despropyl **M02** **KWG 4669**		Aerobic soil	Silt loam (Exp. A)	5.6 (100)	5.6 (100)	2331535
			Silt loam (Exp. B)	5.7 (100)	5.7 (100)	2331535
			Sandy loam	5.8 (60)	5.4 (100)	2331535
			Sandy loam	3.9 (60)	2.6 (100)	2331535
			Loamy sand (Exp. A)	5.4 (100)	5.4 (100)	2331536
			Loamy sand (Exp. B)	5.6 (100)	5.6 (100)	2331536
			Loam	4.2 (90)	2.8 (360)	2331537
			Silt loam	9.2 (31)	4.8 (120)	2331538
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Light: 6.1 (17)	Light: 6.1 (17) Dark: 1.6 (17)	2331541
		Aqueous photolysis		Light: 4.47 (15)	Light: 4.47 (15) Dark: n.d.	2331270
		Hydrolysis (at 25°C, max of two replicates)	pH 5	Not identified	Not identified	2331268
			pH 7	Not identified	Not identified	
			pH 9	2.42 (30)	2.42 (30)	
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	2.6 (33)	1.9 (100)	2331564

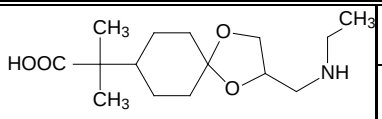
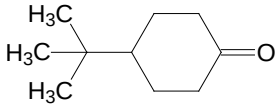
Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
			Silty clay loam (max of two replicates)	1.4 (100)	1.4 (100)	2331564
			Sand (mean of two replicates)	Not identified	Not identified	2331567
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		4.1 (61)	2.1 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	4.7 (62)	4.7 (62)	2331561
			Sand	5.5 (60)	5.5 (60)	2331561
			Silty loam	5.8 (62)	5.8 (62)	2331561
			Loam (max of two replicates)	2.5 (0)	0.8 (30)	2331562
		Field studies[2]	Loam (max of three replicates) Sandy loam	**10.1** (10, 30) 0 – 15 cm 4.0 (51) 15 – 30 cm	< 3.4 (580)	2331554
			Loam (max of two replicates)	**13.1** (7)	n.d. (240)	2331549
			Silty clay loam (max of two replicates)	8.3 (31)	n.d. (240)	2331549
			Loam (max of two replicates)	**11.6** (7)	n.d. (358)	2331550
			Sandy loam (max of two replicates)	9.0 (7)	n.d. (360)	2331550
		Other studies (controlled rotational crop study in greenhouse)	Sandy loam	3.7 (161)	3.7 (161)	2331526
		Aerobic soil	Silt loam (Exp. A)	2.4 (14)	1.8 (100)	2331535

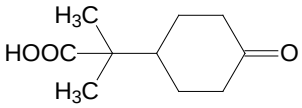
Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
Spiroxamine oxide **M03** **WAK 6301**			Silt loam (Exp. B)	2.5 (14)	1.9 (100)	2331535
			Loamy sand (Exp. A)	4.6 (30)	1.6 (100)	2331536
			Loamy sand (Exp. B)	2.0 (30)	1.8 (100)	2331536
			Loam	7.9 (181)	6.6 (360)	2331537
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Light: 6.2 (11)	Light: 4.7 (17) Dark: 2.1 (17)	2331541
		Aqueous photolysis		Light: 4.01 (5)	Light: 3.22 (15) Dark: 1.60 (15)	2331270
		Hydrolysis (at 25°C, max of two replicates)	pH 5 pH 7 pH 9	Not identified Not identified 5.7 (22)	Not identified Not identified 4.32 (30)	2331268
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	2.1 (0)	1.4 (100)	2331564
			Silty clay loam (max of two replicates)	**11.8** (0)	1.1 (100)	2331564
			Sand (mean of two replicates)	Not identified	Not identified	2331567
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		2.5 (250)	0.5 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	1.9 (0)	1.7 (62)	2331561
			Sand	2.0 (32, 60)	2.0 (60)	2331561
			Silty loam	2.3 (30)	1.9 (62)	2331561
			Loam (max of two replicates)	**48.4** (0)	1.1 (30)	2331562
		Field studies[2]	Loam (max of three replicates)	**49.0** (37) 0 – 15 cm **34.9** (51)	< 3.4 (580)	2331554

Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
			Sandy loam	15 – 30 cm		
Spiroxamine hydroxy **M05** **WAK 5868**		Aerobic soil		Not identified	Not identified	---
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Light: 0.4 (7)	Light: 0.1 (17) Dark: 0.1 (17)	2331541
		Aqueous photolysis		Light: 3.13 (12)	Light: 2.50 (15) Dark: n.d.	2331270
		Hydrolysis (at 25°C) pH 5 pH 7 pH 9		Not identified Not identified Not identified	Not identified Not identified Not identified	2331268
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	1.7 (14)	0.7 (100)	2331564
			Silty clay loam (max of two replicates)	2.4 (14)	1.3 (100)	2331564
			Sand (mean of two replicates)	Not identified	Not identified	2331567
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		1.2 (61)	0.7 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	Not identified	Not identified	2331561
			Sand	Not identified	Not identified	2331561
			Silty loam	Not identified	Not identified	2331561
			Loam (max of two replicates)	Not identified	Not identified	2331562
		Field studies		Not identified	Not identified	---

Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
Spiroxamine acid M06 WAK 5708		Aerobic soil	Silt loam (Exp. A)	1.6 (7)	0.7 (100)	2331535
			Silt loam (Exp. B)	1.6 (7, 14)	0.7 (100)	2331535
			Loamy sand (Exp. A)	3.5 (59)	3.1 (100)	2331536
			Loamy sand (Exp. B)	3.5 (59)	3.1 (100)	2331536
			Loam	0.4 (120, 269)	0.2 (360)	2331537
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Not identified	Not identified	2331541
		Aqueous photolysis		Not identified	Not identified	2331270
		Hydrolysis pH 5 (at 25°C) pH 7 pH 9		Not identified Not identified Not identified	Not identified Not identified Not identified	2331268
		Aerobic aged soil leaching studies (%AR in soil)	Silt loam (max of two replicates)	7.0 (56)	2.2 (100)	2331564
			Silty clay loam (max of two replicates)	**10.8** (14)	7.1 (100)	2331564
			Sand (mean of two replicates)	**31.3** (30)	**7.3** (118)	2331567
			Sandy loam (mean of two replicates)	**14.3** (14)	**13.6** (118)	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		7.4 (122)	5.1 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	0.9 (62)	0.9 (62)	2331561
			Sand	4.1 (32)	3.3 (60)	2331561
			Silty loam	1.7 (30)	1.0 (62)	2331561
			Loam (max of two replicates)	Not identified	Not identified	2331562
		Field studies		Not identified	Not identified	---

Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
Spiroxamine desethyl acid **M11** **WAK 5756**		Aerobic soil	Silt loam (Exp. A)	0.1 (7, 30, 60)	< 0.1 (100)	2331535
			Silt loam (Exp. B)	0.2 (30)	< 0.1 (100)	2331535
			Loam	0.2 (120, 181)	0.1 (360)	2331537
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Not identified	Not identified	2331541
		Aqueous photolysis		Not identified	Not identified	2331270
		Hydrolysis pH 5 (at 25°C) pH 7 pH 9		Not identified Not identified Not identified	Not identified Not identified Not identified	2331268
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	Not identified	Not identified	2331564
			Silty clay loam (max of two replicates)	0.7 (14)	0.4 (100)	2331564
			Sand (mean of two replicates)	Not identified	Not identified	2331567
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		1.7 (250)	0.8 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	0.2 (62)	0.2 (62)	2331561
			Sand	0.6 (60)	0.6 (60)	2331561
			Silty loam	0.3 (30)	0.2 (62)	2331561
			Loam (max of two replicates)	Not identified	Not identified	2331562
		Field studies		Not identified	Not identified	---
Spiroxamine despropyl acid **M12**		Aerobic soil	Loam	0.1 (181, 269, 360)	0.1 (360)	2331537
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Not identified	Not identified	2331541

Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
BNF 5534		Aqueous photolysis		Not identified	Not identified	2331270
		Hydrolysis (at 25°C) pH 5		Not identified	Not identified	2331268
		pH 7		Not identified	Not identified	
		pH 9		Not identified	Not identified	
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	Not identified	Not identified	2331564
			Silty clay loam (max of two replicates)	Not identified	Not identified	2331564
			Sand (mean of two replicates)	Not identified	Not identified	2331567
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		1.9 (250)	0.4 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	0.2 (30, 62)	0.2 (62)	2331561
			Sand	0.4 (60)	0.4 (60)	2331561
			Silty loam	0.2 (30, 62)	0.2 (62)	2331561
			Loam (max of two replicates)	Not identified	Not identified	2331562
		Field studies		Not identified	Not identified	---
Spiroxamine Ketone **(4 tert-Butylcyclohexanone)** **M15** **WAK 5428**		Aerobic soil	Loam	1.6 (269)	0.2 (360)	2331537
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Light: 2.7 (3)	Light: 1.4 (17) Dark: n.d.	2331541
		Aqueous photolysis		Not identified	Not identified	2331270
		Hydrolysis (at 25°C) pH 5		Not identified	Not identified	2331268
		pH 7		Not identified	Not identified	
		pH 9		Not identified	Not identified	
		Aerobic aquatic	Silt loam	Not	Not	2331564

Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
		(water & sediment total)	(max of two replicates)	identified	identified	
			Silty clay loam (max of two replicates)	Not identified	Not identified	2331564
			Sand (mean of two replicates)	Not identified	Not identified	2331567
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		3.2 (7)	2.1 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	0.4 (62)	0.4 (62)	2331561
			Sand	0.4 (0)	n.d. (60)	2331561
			Silty loam	0.7 (62)	0.7 (62)	2331561
			Loam (max of two replicates)	Not identified	Not identified	2331562
		Field studies		Not identified	Not identified	---
Spiroxamine Ketone acid **M17** **WAK 6131**		Aerobic soil		Not identified	Not identified	---
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Not identified	Not identified	2331541
		Aqueous photolysis		Not identified	Not identified	2331270
		Hydrolysis pH 5 (at 25°C) pH 7 pH 9		Not identified Not identified Not identified	Not identified Not identified Not identified	2331268
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	Not identified	Not identified	2331564
			Silty clay loam (max of two replicates)	Not identified	Not identified	2331564
			Sand (mean of two	Not identified	Not identified	2331567

Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
			replicates)			
			Sandy loam (mean of two replicates)	Not identified	Not identified	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		Not identified	Not identified	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	Not identified	Not identified	2331561
			Sand	Not identified	Not identified	2331561
			Silty loam	Not identified	Not identified	2331561
			Loam (max of two replicates)	Not identified	Not identified	2331562
		Field studies		Not identified	Not identified	---
Carbon dioxide	O=C=O	Aerobic soil	Silt loam (Exp. A)	**44.7** (100)	**44.7** (100)	2331535
			Silt loam (Exp. B)	**44.5** (100)	**44.5** (100)	2331535
			Sandy loam	**30.5** (100)	**30.5** (100)	2331535
			Sandy loam	**35.2** (100)	**35.2** (100)	2331535
			Loamy sand (Exp. A)	**22.0** (100)	**22.0** (100)	2331536
			Loamy sand (Exp. B)	**21.8** (100)	**21.8** (100)	2331536
			Loam	**53.5** (360)	**53.5** (360)	**2331537**
			Silt loam	**40.5** (120)	**40.5** (120)	**2331538**
		Anaerobic soil		Not required		---
		Soil photolysis	Loam	Not identified	Not identified	2331541
		Aqueous photolysis		Not identified	Not identified	2331270
		Hydrolysis pH 5 (at 25°C) pH 7 pH 9		Not identified Not identified Not identified	Not identified Not identified Not identified	2331268
		Aerobic aquatic (water & sediment total)	Silt loam (max of two replicates)	9.3 (57)	7.0 (100)	2331564

Code Chemical name	Chemical structure	Study		Max % AR (day reached)	% AR at study end (study length)[1]	Reference
			Silty clay loam (max of two replicates)	**22.2** (100)	**22.2** (100)	2331564
			Sand (mean of two replicates)	**27.1** (118)	**27.1** (118)	2331567
			Sandy loam (mean of two replicates)	7.6 (118)	7.6 (118)	2331567
		Anaerobic aquatic (water and sediment total, mean of two replicates)		2.8 (250)	1.9 (360)	2331539
		Aerobic aged soil leaching studies (%AR in soil)	Loamy sand	**11.9** (62)	**11.9** (62)	2331561
			Sand	**17.8** (60)	**17.8** (60)	2331561
			Silty loam	**29.5** (62)	**29.5** (62)	2331561
			Loam (max of two replicates)	1.4 (30)	1.4 (30)	2331562
		Field studies		Not identified	Not identified	---

[1] In DAT (days after treatment)
[2] All transformation products were observed at <10% AR in the top 15 cm of soil, and <5 µg/kg below the 15 cm soil depth throughout all 19 terrestrial field dissipation studies unless identified in this table
n.d. – Not Detected

Table 10 Fate and Behaviour in the Environment of Spiroxamine Technical Grade Active Ingredient and its Major Transformation Products (M01, M02, M03, M06)

Property	Test substance	Value	Transformation products	Comments	Reference
Terrestrial systems					
Abiotic transformation					
Hydrolysis	[cyclohexyl-1-^{14}C]- Spiroxamine	t½ at 25°C at pH 5, 7 and 9: Stable (30 days)	Minor: M01, M02, M03	Not expected to be a major route of dissipation for spiroxamine.	2331268
	Spiroxamine (non-radiolabelled)	t½ at 25 °C at pH 7 and 9: Stable t½ at pH 4: Stable (8 days; incubations for pH 4 were at 30 °C and extrapolated to 20 and 25 °C) Isomer A: 370 days at 25°C / 790 days at 20°C, pH 4 Isomer B: 68 days at 25°C /120 days at		Not expected to be a major route of dissipation for spiroxamine.	2331269

Property	Test substance	Value	Transformation products	Comments	Reference
		20°C, pH 4			
Photo-transformation on soil	[cyclohexyl-1-^{14}C]- Spiroxamine	**1 USA soil** Wolf Ranch (California) loam soil, 0.97% OC, pH 7.8-8.7, 25±1 °C); 17-days, continuous irradiation DT_{50}: 28.6 days (PMRA calculated - SFO) DT_{90}: 94.9 days (PMRA calculated - SFO) Conversion to a predicted environmental half-life using conservative solar conditions at Phoenix, USA: **119 days** DT_{50}s from dark samples could not be calculated by the PMRA as there were not enough data points measured to fit the model. The study author estimated the DT_{50} value for the dark samples by extrapolation of the data from day 17 by means of linear regression analysis. The **dark DT_{50} value** was calculated to be approximately **66 days** in this soil.	Minor: M03, M02, M01, M15, M05, UK1, UK2, UK3	Under the influence of light showed that photolysis contributed to the overall degradation, but that no new transformation products were formed. Not expected to be a major route of dissipation for spiroxamine.	2331541
Photo-transformation in the air	spiroxamine	DT_{50air} < 3 hours (24-hour day; 0.5×10^{-6} OH/cm^3) (estimated)	N/A	The chemical lifetime of Spiroxamine in the troposphere was in the range of **one to three hours**, with respect to the OH-radical reaction only. On account of the relatively short chemical lifetime of Spiroxamine in the air, it is not to be expected that the active ingredient can be transported in gaseous phase over large distances or can accumulate in the air.	2331276
Biotransformation					
Biotransformation in aerobic soil	[cyclohexyl-1-^{14}C]- Spiroxamine	**2 EU and 1 USA soil (20 °C)** Laacherhof (Germany) silt loam (0.9% OC, pH 8.1) DT_{50}: 39.3 days (PMRA calculated DFOP with M03 combined) DT_{90}: 166 days (PMRA calculated DFOP with M03 combined) t_{rep}: 54.6 days (PMRA calculated DFOP with M03 combined)	Major: CO_2 Minor: M01, M02, M03, M06, M11	Spiroxamine is slightly persistent to moderately persistent.	2331535

Property	Test substance	Value	Transformation products	Comments	Reference
		Monheim (Germany), sandy loam (1.98% OC, pH 6.5) DT_{50}: 50.2 days (PMRA calculated IORE) DT_{90}: 752 days (PMRA calculated IORE) t_{rep}: 226 days (PMRA calculated IORE) Howe (Indiana, USA), sandy loam (1.09% OC, pH 7.1) DT_{50}: 47.6 days (PMRA calculated DFOP) DT_{90}: 309 days (PMRA calculated DFOP) t_{rep}: 120 days (PMRA calculated DFOP)			
	[cyclohexyl-1-^{14}C]- Spiroxamine	**1 EU soil** BBA 2.2 (Germany), loamy sand (2.15% OC, pH 6.3) DT_{50}: 83.7 days (PMRA calculated DFOP with M03 combined) DT_{90}: 750 days (PMRA calculated DFOP with M03 combined) t_{rep}: 302 days (PMRA calculated DFOP with M03)		Spiroxamine is moderately persistent.	2331536
	[cyclohexyl-1-^{14}C]- Spiroxamine	**1 USA soil** Wolf Ranch (California) loam, 0.97% OC, pH 7.8-8.7) DT_{50}: 134 days (PMRA calculated IORE with M03 combined) DT_{90}: 603 days (PMRA calculated IORE with M03 combined) t_{rep}: 181 days (PMRA calcultaed IORE with M03 combined)	Major: CO_2 Minor: M01, M02, M03, M06, M11, M12, M15	Spiroxamine is moderately persistent.	2331537
	[1,3-dioxolane-4-^{14}C]-Spiroxamine	**1 EU soil** Hoefchen am Hohenseh (Germany) silt loam (2.25% OC, pH 6.4) **Technical Grade Active Ingredient** DT_{50}: 47.6 days (PMRA calculated DFOP) DT_{90}: 317 days (PMRA calculated DFOP) t_{rep}: 116 days (PMRA calculated DFOP) **M01** DT_{50}: 69.8 days (SFO) **M02** DT_{50}: 68.1 days (SFO)	Major: CO_2 Minor: M01, M02, and six unknowns	Spiroxamine is non-persistent. M01 and M02 are moderately persistent.	2331538
Biotransformation in anaerobic soil	Spiroxamine	In view of the proposed use pattern for spiroxamine in Europe, as a post-emergence spray applied fungicide for application to cereal crops, a specific anaerobic soil degradation study was not required by the EU. Information on the anaerobic aquatic metabolism degradation of spiroxamine in aquatic systems was found to be sufficient to address this data requirement (EU and PMRA).			

Property	Test substance	Value	Transformation products	Comments	Reference
Mobility					
Adsorption / desorption in soil	[cyclohexyl-1-^{14}C]- Spiroxamine	**5 EU (Germany) soils (20 °C)** Laacherhof 0-30 cm horizon, loamy sand (pH 6.4, 1.8% OC) K_d: 12.8 K_{oc} (mL/g): 710 Laacherhof 30-60 cm horizon, loamy sand (pH 6.3, 0.3% OC) K_d: 7.3 K_{oc} (mL/g): 2415 Höfchen, silt loam (pH 5.8, 2.4% OC) K_d: 45.0 K_{oc} (mL/g): 1874 Tonboden, silty clay (pH 7.4, 0.64% OC) K_d: 41.1 K_{oc} (mL/g): 6417 BBA 2.1, sand (pH 5.3, 0.7% OC) K_d: 4.6 K_{oc} (mL/g): 659		Low mobility to immobile in soils	2331556
	[1,3-dioxolane-4-^{14}C]-Spiroxamine	**5 USA soils** Vero Beach, Florida, sand (pH 6.7, 0.2% OC) K_d: 8.6 K_{oc} (mL/g): 4276 Grape Vinyard, sandy loam (pH 5.8, 0.45% OC) K_d: 14.5 K_{oc} (mL/g): 3216 Howe, Indiana, sandy loam (pH 6.7, 1.12% OC) K_d: 15.1 K_{oc} (mL/g): 1347 Wolf Ranch, California, loam (pH 7.8, 0.97% OC) K_d: 381.7 K_{oc} (mL/g): 39346 Stanley, Kansas, silty clay (pH 5.1, 1.05% OC) K_d: 892.6 K_{oc} (mL/g): 85008		Low mobility to immobile in soils	2331557
	[cyclohexyl-1-^{14}C]- Desethyl-spiroxamine **(M01)**	**4 USA soils** Vero Beach, Florida, sand (pH 6.3, 0.32% OC) K_d: 4.0 K_{oc} (mL/g): 1237 Howe, Indiana, sandy loam (pH 6.7, 1.12% OC) K_d: 16.3 K_{oc} (mL/g): 1453 Wolf Ranch, California, loam (pH 7.8, 0.97% OC) K_d: 58.8 K_{oc} (mL/g): 6063 Stanley, Kansas, silty clay loam (pH 5.5, 1.49% OC) K_d: 157 K_{oc} (mL/g): 10511		M01: Low mobility to immobile in soils	2331558

Property	Test substance	Value	Transformation products	Comments	Reference
	[cyclohexyl-1-^{14}C]- Despropyl-spiroxamine **(M02)**	**4 USA soils** Vero Beach, Florida, sand (pH 6.3, 0.32% OC) K_d: 2.9 K_{oc} (mL/g): 917 Howe, Indiana, sandy loam (pH 6.7, 0.97% OC) K_d: 12.8 K_{oc} (mL/g): 1142 Wolf Ranch, California, loam (pH 7.8, 0.97% OC) K_d: 54.4 K_{oc} (mL/g): 5607 Stanley, Kansas, silty clay loam pH 5.5, 1.49% OC) K_d: 134 K_{oc} (mL/g): 8994		M02: Low mobility to immobile in soils	2331559
	[cyclohexyl-1-^{14}C]- Spiroxamine-N-oxide **(M03)**	**4 USA soils** Vero Beach, Florida, sand (pH 6.3, 0.32% OC) K_d: 1.8 K_{oc} (mL/g): 552 Howe, Indiana, sandy loam (pH 6.7, 0.97% OC) K_d: 3.9 K_{oc} (mL/g): 351 Wolf Ranch, California, loam (pH 7.8, 0.97% OC) K_d: 15.9 K_{oc} (mL/g): 1641 Stanley, Kansas, silty clay loam pH 5.5, 1.49% OC) K_d: 370.9 K_{oc} (mL/g): 24893		M03: Moderately mobile to immobile in soils	2331560
Soil leaching	[cyclohexyl-1-^{14}C]- Spiroxamine	**3 EU soils** Immobile in soil The different application rates and soil types did not influence the percentage of radioactivity in the leachate, and on the basis of these findings, spiroxamine can be classified as immobile in soil after prior aging.	Minor : M01, M02, M03, M06, M11, M12, M15		2331561
	[cyclohexyl-1-^{14}C]- Spiroxamine	**1 USA soil** 53-69% radioactivity remained in soil at Day 30	Major: M03 Minor: M01, M02		2331562
Volatilization	[cyclohexyl-1-^{14}C]- Spiroxamine EC 500	The volatilization of parent compound and potential transformation products from bare soil, under field conditions, was low (2% AR after 24 hours) based on an analysis of soil samples and recovery of radioactivity (98% AR at 24 hours).			2331570
	[cyclohexyl-1-^{14}C]- Spiroxamine EC 500	The volatilization rate from a simulated winter wheat field, including soil, with different weather scenarios was on average 26% within the measuring period of 24 hours. This was determined by calculating the difference between radioactivity that had landed on plants directly after and 24 hours after application.			2331569
Field studies					
Field dissipation	Spiroxamine 300 CS	**1 USA soil** 550-day sampling duration; 4 applications of 400 g a.i./hectare, 10 day interval Fresno (California, USA), (0-15cm soil depth: loam soil, pH 7.6, 0.55% OC, bare soil) DT_{50}: 4 days (1st order)	Major: M01, M02, M03		2331554

Property	Test substance	Value	Transformation products	Comments	Reference
	Spiroxamine 500 EC	**2 German and 2 United Kingdom soils** 260-day study Höfchen (Germany), silt loam (pH 6.5, 0.97% OC), bare soil DT_{50}: 18 days (1st order) DT_{90}: 196 days Laacherhof (Germany), loam (pH 6.8, 1.08% OC), cropped soil DT_{50}: 23 days (2nd order) DT_{90}: 207 days Elm Farm (United Kingdom), sandy loam (pH 7.5, 1.14% OC), cropped soil DT_{50}: 7.2 days (1.5th order) DT_{90}: 197 days Old Hall Farm (United Kingdom), loamy sand (pH 7.3, 0.88% OC), cropped soil DT_{50}: 3.4 days (1.5th order) DT_{90}: 93 days	Minor: M01, M02		2331542
	Spiroxamine 500 EC	**5 German soils (all bare soils)** 260-day study Höfchen, silt loam (pH 6.4, 0.87% OC), bare soil DT_{50}: 48 days (2nd order) DT_{90}: 430 days Laacherhof, sandy loam (pH 6.6, 1.21% OC), bare soil DT_{50}: 13 days (1st order) DT_{90}: 145 days Maasen, sandy loam (pH 5.9, 1.27% OC), bare soil DT_{50}: 13 days (2nd order) DT_{90}: --- Swisstal-Hohn, silt loam (pH 6.7, 1.00% OC), bare soil DT_{50}: 8.2 days (1st order) DT_{90}: 91 days Albig, silty clay loam (pH 7.8, 1.40% OC), bare soil DT_{50}: 6.2 days (1st order) DT_{90}: 69 days	Minor: M01, M02		2331543

Property	Test substance	Value	Transformation products	Comments	Reference
	Spiroxamine 500 EC	**4 United Kingdom and 1 France soils (all cropped soils)** 260-day study Elm Farm (United Kingdom), sandy loam (pH 7.4, 1.08% OC), cropped soil DT_{50}: 1.0 days (2nd order) DT_{90}: 80 days Old Hall Farm (United Kingdom), sandy loam (pH 7.0, 1.88% OC), cropped soil DT_{50}: 20 days (1st order) DT_{90}: 221 days Elm Farm (United Kingdom), sandy loam (pH 7.4, 1.08% OC), cropped soil DT_{50}: 21 days (2nd order) DT_{90}: --- Old Hall Farm (United Kingdom), sandy loam (pH 7.0, 1.88% OC), cropped soil DT_{50}: 27 days (1st order) DT_{90}: 298 days La Ferme du Plessis , Touffreville (France), silt loam (pH 7.2, 1.29% OC), cropped soil DT_{50}: 4.5 days (1st order) DT_{90}: 49 days	Minor: M01, M02		PMRA# 2331544
	Spiroxamine 500 EC	**2 Italian and 2 France soils** 240-360-day study Laudun (France), silty loamy sand (pH 7.7, 0.78% OC), cropped soil DT_{50}: 14 days (1st order) DT_{90}: 157 days Laudun (France), sandy silty loam (pH 7.7, 1.16% OC), bare soil DT_{50}: 8.5 days (1st order) DT_{90}: 93.5 days Filetto (Italy), silty clay loam (pH 7.6, 1.29% OC), cropped soil DT_{50}: 40 days (1st order) DT_{90}: 441 days Pradelle di Nogarole Rocca (Italy), weak loamy sand (pH 7.7, 0.38% OC), bare soil DT_{50}: 2.9 days (1st order) DT_{90}: 31.6 days	Major in French soils: M01, M02 Minor in Italian soils: M01, M02		2331549 2331550

Property	Test substance	Value	Transformation products	Comments	Reference
	[cyclohexyl-1-^{14}C]- Spiroxamine	A plant container with a total area of 1 m^2 and a depth of 60 cm was used. The total residues in the 0-15 cm soil layer amounted to 1.21 mg/kg on day 0, 0.53 mg/kg on Day 30 and 0.67 mg/kg on Day 161. The residues consisted mainly of unchanged parent compound although some transformation products were also present in low concentrations (at any one time less than 6 % of the radioactivity in the soil).			2331526
Storage stability	Spiroxamine Spiroxamine desethyl (M01) Spiroxamine despropyl (M02) Spiroxamine oxide (M03)	Spiroxamine, M01, M02 and M03 in fortified soil samples were stored at -20°C. The concentrations of all analytes at increasing time intervals of up to two years were constant within the margin of accuracy of the analytical method. The initial loss cannot be associated with degradation during storage as there is no influence of time on the measured recoveries. For the duration of the field dissipation trials the proportion of spiroxamine and its transformation products remained constant.			2331365 2331546 2331548
Aquatic systems					
Abiotic transformation					
Hydrolysis	[cyclohexyl-1-^{14}C]- Spiroxamine	$t_{½\ at}$ pH 5, 7 and 9: Stable	Minor: M01, M02, M03	Not expected to be a major route of dissipation for spiroxamine.	2331268
	Spiroxamine	$t_{½\ at}$ 25 °C at pH 7 and 9: Stable $t_{½}$ at pH 4: Stable (8 days; incubations for pH 4 were at 30 °C and extrapolated to 20 and 25 °C) Isomer A: 370 days at 25°C / 790 days at 20°C, pH 4 Isomer B: 68 days at 25°C /120 days at 20°C, pH 4		Not a route of dissipation for spiroxamine.	2331269
Photo-transformation in water	[cyclohexyl-1-^{14}C]- Spiroxamine	DT_{50} : 48.1 days (PMRA calculated SFO) DT_{90}: 160 days (PMRA calculated SFO) (15 days; pH 7; 25 °C; no degradation was noted in dark controls) Conversion to a predicted environmental half-life at the worst case site (solar conditions at Phoenix/USA): **236 days**	Minor: M01, M02, M03, M05	Not expected to be a major route of dissipation for spiroxamine.	2331270
Biotransformation					
Bio-transformation in aerobic water/ sediment systems	[cyclohexyl-1-^{14}C]- Spiroxamine	**1 EU and 1 USA water/sediment system** Hönninger (Germany), silt loam (4.4% OC, pH 6.2, 20°C) $DT_{50\ water}$: 9.6 hours (PMRA calculated IORE) $DT_{90\ water}$: 4.25 days (PMRA calculated IORE) $t_{rep\ water}$: 1.28 days (PMRA calculated IORE) $DT_{50\ system}$: 76.3 days (PMRA calculated DFOP with combined M03) $DT_{90\ system}$: 761 days (PMRA calculated DFOP with combined M03) $t_{rep\ system}$: 295 days (PMRA calculated DFOP with combined M03) Stilwell (Kansas, USA), silty clay loam	Major: M03 (transient) Minor: M01, M02, M05, M06, unknown	Spiroxamine was rapidly distributed from the water layer to the sediment. Transformation products were also mainly distributed to the sediment. Spiroxamine is non-persistent to moderately persistent in the total system.	2331564

Property	Test substance	Value	Transformation products	Comments	Reference
		(1.6% OC, pH 7.8, 20°C) DT_{50} water: 1.03 days (PMRA calculated DFOP) DT_{90} water: 6.67 days (PMRA calculated DFOP) t_{rep} water: 2.43 days (PMRA calculated DFOP) DT_{50} system: 2.89 days (PMRA calculated DFOP with combined M03) DT_{90} system: 294 days (PMRA calculated DFOP with combined M03) t_{rep} system: 166 days (PMRA calculated DFOP with combined M03)			
	[1,3-dioxolane-4-^{14}C]-Spiroxamine	**2 EU water/sediment systems** 118-day study Anglerweiher (Germany), sand (0.8% OC, pH 6.6-7.2, 20°C) DT_{50} water: 0.8 days (DFOP) DT_{90}: 4.1 days DT_{50} system: 6.33 days (PMRA calculated DFOP) DT_{90} system: 150 days (PMRA calculated DFOP) t_{rep} system: 74.9 days (PMRA calculated DFOP) Hoenniger Weiher (Germany), sandy loam (3.8% OC, pH 5.2-5.5, 20°C) DT_{50} water: 0.7 days (FOMC) DT_{90}: 3.6 days DT_{50} system: 14 days (PMRA calculated DFOP) DT_{90} system: 450 days (PMRA calculated DFOP) t_{rep} system: 189 days (PMRA calculated DFOP)	Major: M06 Minor: unknowns	Spiroxamine is non-persistent in the total system.	2331567
	[cyclohexyl-1-^{14}C]-Spiroxamine-N-oxide **(M03)**	**1 EU water/sediment systems** 6-day study Hoenniger Weiher (Germany), silt loam (4.4% OC, pH 5.6, 20°C) **M03** DT_{50} water: 3.53 days (PMRA calculated IORE) t_{rep} water: 2.34 days (PMRA calculated IORE) DT_{50} whole system: < 6 days	Major: Spiroxamine Minor: M01, M02, M06, M11, M12, M15	**Study length of only six days.** This study was performed to determine if M03 transforms into spiroxamine. M03 is non-persistent in the total system.	2331565

Property	Test substance	Value	Transformation products	Comments	Reference
Bio-transformation in anaerobic water/ sediment systems	[cyclohexyl-1-^{14}C]- Spiroxamine	**1 USA water/sediment systems** 360-day study Stilwell (Kansas, USA), silty clay loam (1.22% OC, pH 7.8, 20°C) $DT_{50\ water}$: 5.74 days (PMRA calculated SFO and used means) $DT_{90\ water}$: 19.1 days (PMRA calculated SFO and used means) $DT_{50\ system}$: 690 days (PMRA calculated DFOP with combined M03) $DT_{90\ system}$: 3,321 days (PMRA calculated DFOP with combined M03) $t_{rep\ system}$: 1130 days (PMRA calculated DFOP with combined M03)	Minor: M01, M02, M03, M05, M06, M11, M12, M15	No additional transformation products formed compared with those occurring under aerobic conditions. Spiroxamine is persistent in the total system.	2331539 2358501
Field Studies (Mesocosm Studies)					
Mesocosm "Fatocosm" 56-day study Four enclosures in an experimental ditch (two enclosures each, with and without macrophytes and an upper layer of sediment rich in organic matter); Single application at 3.5 and 35 µg a.i./L	Spiroxamine EC 500	Macrophytes sorb a large proportion of the a.i. (up to 32-41%). Ditches with macrophytes and organic-rich detritus layer: DT_{50}: 0.9 - 2.0 days in water DT_{50}: 10.1 days in one total system Ditches without macrophytes and organic-rich detritus layer: DT_{50}: 3.1 - 5.9 days in water DT_{50}: 9.6 days in total system	Not identified		2331606
Mesocosm Natural sediment and water; natural communities emerged; introduced: three macrophyte species: *Callitriche pallustris, Myriophyllum spicatum*, *Potamogeton crispus*	Spiroxamine EC 500 Application rates: Control, 1.0, 2.1, 4.4, 9.3, and 19.4 µg a.i./L 3 applications with 7-day intervals Duration: 2 weeks before and 14 weeks after treatment (static)	DT_{50wate}: 3.8 days $DT_{50whole\ system}$: 7.2 days	Not identified		2331607

Property	Test substance	Value	Transformation products	Comments	Reference
Bioconcentration/bioaccumulation					
Bioconcentration/ bioaccumulation in fish	^{14}C-Spiroxamine	Whole body steady state bioconcentration factor: 87		Did not bioconcentrate in large amounts in fish under the test conditions of the study. When exposure ceased, the residue was depurated very quickly with a half-life of approximately 13 to 19 hours	2331597, 2331598

UK, Unknown compound

Table 11 Toxicity of Spiroxamine to Non-Target terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Invertebrates					
Earthworm (*Eisenia fetida*)	14 days (acute)	Spiroxamine (91.5%)	LC_{50} > 1000 mg a.i./kg dw soil (highest concentration tested); LOEC = 562 mg/kg substrate (weight loss)	Not applicable	2331635
	56 days (chronic), Reproduction	Spiroxamine EC 500 (494 g a.i./L)	NOEC: 3000 g a.i./ha equivalent to 4.0 mg a.i./kg dw soil; no effects on reproduction or growth of juveniles	Not applicable	2332411
	56 days (chronic), Reproduction	Spiroxamine EC 500 (488.9 g a.i./L)	NOEC 3750 g a.i./ha equivalent to 5.0 mg a.i./kg dw soil; no effects on reproduction	Not applicable	2332412
	56 days (chronic), Reproduction	**Spiroxamine-desethyl (M01)** (98%w/w)	NOEC: 100 mg M01/kg dw soil (growth and number of juveniles)	Not applicable	2331636
	56 days (chronic), Reproduction	**Spiroxamine-N-oxide (M03)** (86.6%w/w)	NOEC: 100 mg M03/kg dw soil (growth); NOEC: 316 mg a.i./kg dw soil (number of juveniles)	Not applicable	2331637
Bee (*Apis mellifera*)	48 hours (acute) Oral and contact	Spiroxamine (technical, 97.8%)	Oral LD_{50} > 100 µg/bee Contact LD_{50}: 4.2 µg/bee	Oral: Relatively non-toxic Contact: Moderately toxic	2331631

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
	48 hours (acute) Oral and contact	Spiroxamine EC 500 (491.4 g a.i./L)	Oral LD_{50} > 12.5 µg EP[b]/bee, equivalent to > 6.1 µg a.i./bee (highest test concentration) Contact LD_{50}: 30 µg EP/bee, equivalent to 15 µg a.i./bee	Relatively non-toxic	2332383
	48 hours (acute) Oral and contact	Spiroxamine EC 500 (505.5 g a.i./L)	Oral LD_{50} > 77 < 191 µg EP/bee, equivalent to > 39 < 96 µg a.i./bee Contact LD_{50}: > 200 µg EP/bee, equivalent to > 100 µg a.i./bee	Relatively non-toxic	2332384
	Semi-field test (tents/cages)	Spiroxamine EC 500 (491.4 g a.i./L)	From a single application rate of 3 L *KWG 4168 EC 500*/ha (Late morning application on *Phacelia* during bee foraging), equivalent to 1500 g a.i./ha: No signs of toxicity. No effects on mortality or brood of bees.	Not applicable	2332385
	Semi-field test (tents/cages)	Spiroxamine EC 500 (491.4 g a.i./L)	From a single application rate of 1.5 L *KWG 4168 EC 500*/ha (Late morning application on *Phacelia* during bee foraging), equivalent to 750 g a.i./ha: No significant increase in mortality. No effect on colony size or condition	Not applicable	2332387
	3 weeks, Field test	Spiroxamine EC 500 (500 g a.i./L nominal)	From a single application rate of 1.5 L *EP*/ha (Late morning application on *Phacelia* during bee foraging), equivalent to 750 g a.i./ha: No mortalities No effects on bee colonies or brood	Not applicable	2332388
Beneficial arthropods					
Collembola (*Folsomia candida*)	28 days (chronic)	Spiroxamine technical (95.1%w/w)	NOEC: 32 mg a.i./kg dw soil (reproduction, mean number of juveniles)	Not applicable	2331644
	28 days (chronic)	**Spiroxamine-desethyl (M01)** (98%w/w)	NOEC: 316 mg M01/kg dw soil (number of juveniles and adult mortality)	Not applicable	2331645
	28 days (chronic)	**Spiroxamine-despropyl (M02) (97%w/w)**	NOEC: 316 mg M02/kg dw soil (number of juveniles and adult mortality)	Not applicable	2331646
Aphidius rhopalosiphi (Parasitic wasp)	48 hours, Laboratory test, glass plates	Spiroxamine EC 500 (498.5 g a.i./L)	LR_{50} : 80.1 g a.i./ha ER_{50} : reproduction reduced up to 62% at 60 g a.i./ha;	Not applicable	2332395
	Extended laboratory test	Spiroxamine EC 500 (494.0 g a.i./L)	Exposure to residues on barley seedling: LR_{50} and ER_{50} > 750 g a.i./ha (adult mortality and fecundity) Exposure of parasitized mummies to direct spray at 750 g a.i./ha: 78.6% of treated mummies failed to emerge	Not applicable	2331633
	Extended laboratory test, barley plants	Spiroxamine EC 500 (49.8% w/w)	LR_{50} > 900 g a.i./ha (highest rate tested); no clear treatment-related effects on reproduction were established (85.4% repellency at 900 g a.i./ha)	Not applicable	2332399

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Typhlodromus pyri (Predatory mite)	7 days, Laboratory test, glass plates	Spiroxamine EC 500 (494 g a.i./L)	Test concentration, 741 g a.i./ha: juvenile mortality was 99.2% and 95.7%	Not applicable	2332391
	7 days, Laboratory test, glass cages	Spiroxamine EC 500 (509.5 g a.i./L)	LR_{50} : 240 g a.i./ha (juveniles) Fecundity at 180 g a.i./ha was reduced by 46% relative to controls (statistically significant)	Not applicable	2332394
	Field test EP applied at 109, 215, 278, 337, 381 and 449 g a.i./ha at the 1st, 2nd, 3rd, 4th, 5th, and 6th treatment date (approx. 7 day intervals).	Spiroxamine EC 500 (505.5 g a.i./L)	No treatment related effects.	Not applicable	2332404
	Field test EP applied at 154, 144, 384, 387, 374 and 391 g a.i./ha at the 1st, 2nd, 3rd, 4th, 5th, and 6th treatment date (approx. 7 day intervals).	Spiroxamine EC 500 (508.5 g a.i./L)	No treatment related effects.	Not applicable	2332405
	Field test EP applied at 153, 367, 375, and 372 g a.i./ha at the 1st, 2nd, 3rd, and 4th treatment date (approx. 7 day intervals).	Spiroxamine EC 500 (508.5 g a.i./L)	No treatment related effects.	Not applicable	2332406
	Field test EP applied at 165, 275, 330, 440 g a.i./ha at the 1st, 2nd, 3rd, and 4th treatment date (4 to 18 day intervals).	Spiroxamine EC 500 (501 g a.i./L)	No treatment related effects.	Not applicable	2332407
Amblyseius aberrans (Predatory mite)	Field test 3 applications at 300 g a.i./ha each (roughly 2 week intervals between applications)	Spiroxamine EC 500 (501 g a.i./L)	No treatment related effects.	Not applicable	2332409
Coccinella septempunctata (Seven pointed ladybird beetle)	Extended laboratory test (Full life-cycle), glass plates, larvae	Spiroxamine EC 500 (487.5 g a.i./L)	• 98% mortality at 731 g a.i./ha; • 100% mortality at 1463 g a.i./ha	Not applicable	2332393
	Laboratory test (full life-cycle), glass plates, larvae	Spiroxamine EC 500 (502.5 g a.i./L)	LR_{50}: ~ 1500 g a.i./ha (56% mortality at highest concentration) NOEC: 750 g a.i./ha	Not applicable	2332396
	Semi-field test, larvae	Spiroxamine EC 500 (491.4 g a.i./L)	No treatment related effects on larvae exposed to two applications of 737 g a.i./ha, field and lab.	Not applicable	2332403
Chrysoperla	Extended laboratory test,	Spiroxamine EC 500	75.6% mortality at 737 g a.i./ha	Not applicable	2332392

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
carnea (green lacewing)	glass plates, 1st instar	(491.4 g a.i./L)	100% mortality at 1464 g a.i./ha		
	Extended laboratory test, glass plates, larvae and adults	Spiroxamine EC 500 (509.5 g a.i./L)	7-day LR_{50} > 1600 g a.i./ha (larvae); effects on reproduction and hatching were <10% in all treatments	Not applicable	2332397
Pardosa spp. (wolf spider)	25 days, Extended laboratory test, Quartz sand as the substrate, adults	Spiroxamine EC 500 (487.5 g a.i./L)	Two direct oversprays (7-day interval) of Spiroxamine 500 EC at 750 g a.i./ha; no mortality after first spray and 80% mortality after second by 18 days	Not applicable	2332390
	25 days, Extended laboratory test, Silty sand soil, adults	Spiroxamine EC 500 (487.5 g a.i./L)	Two direct oversprays (7-day interval) of Spiroxamine 500 EC at 750 g a.i./ha: no harmful effects on survival or feeding activity.	Not applicable	2332398
Bembidion tetracolum (Carabid beetle)	35 days, Extended laboratory test, Quartz sand as the substrate, 4-8 week adults	Spiroxamine EC 500 (494.0 g a.i./L)	Appl. rate (g a.i./ha) / Mortality / Feeding rate reduction 2 × 375 / 6% / 0% 2 × 750 / 43% / -75% 2 × 1500 / 100% / 100%	Not applicable	2332389
	35 days, Extended laboratory test, Silty sand soil as the substrate, 4-8 week adults	Spiroxamine EC 500 (494.0 g a.i./L)	Appl. rate (g a.i./ha) / Mortality / Feeding rate reduction 2 × 750 / 3.3% / 16% 2 × 1500 / 6.6% / 16%	Not applicable	2331634
Birds					
Bobwhite quail	Acute, oral	Spiroxamine (97.8%)	LD_{50}: 565 mg a.i./kg bw	Slightly toxic	2331576
	Acute, oral	Spiroxamine EC 500 (491.4 g a.i./L)	LD_{50}: 971 mg formulation/kg bw, equivalent to 477 mg a.i./kg bw	Slightly toxic (formulation-based endpoint)	2332363
	5-day acute, dietary	Spiroxamine (96.6%)	LC_{50} > 5000 mg a.i./kg feed, equivalent to LD_{50} > 358 mg a.i./kg bw/day[c]	Practically non-toxic	2331577
	21-week feeding, reproduction	Spiroxamine (≥97.0%)	NOAEC: 78.6 mg a.i./kg feed, equivalent to a NOAEL of 11.1 mg a.i./kg bw/day[c] (significant reduction in bw of 14 day old survivors) LOEC: 204 mg a.i./kg feed, equivalent to a LOEL of 28.3 mg a.i./kg bw/day	Not applicable	2331580 2331581 2331582
Mallard duck	5-day acute, dietary	Spiroxamine (96.6%)	LC_{50}: > 5000 mg a.i./kg feed, equivalent to LD_{50} > 874 mg a.i./kg bw/day[c]	Practically non-toxic	2331578
	20-week feeding, reproduction	Spiroxamine (100%)	NOEC: 78.8 mg a.i./kg feed, equivalent to a NOEL of 10.6 mg a.i./kg bw/day[c] (slight but non-significant reduction in egg production, number of hatchlings and 14 day old survivors + significant reduction in bw of hatchlings) LOEC: 205 mg a.i./kg feed, equivalent to a LOEL of 24.0 mg a.i./kg bw/day	Not applicable	2331583

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Mammals					
Mouse	Acute, oral	Spiroxamine (93.6%)	LD_{50}: ♂ = 460, ♀ =561 mg/kg bw	Highly toxic	2331384
Rat	Acute, oral	Spiroxamine (93.6%)	LD_{50}: ♂ = 595, ♀ ~500 mg/kg bw	Moderately toxic	2331383
	2-Generation reproductive toxicity	Spiroxamine (94.3-95.3%)	NOEC: 80 ppm, equivalent to a NOEL of 9.2 mg a.i./kg bw/day (decreased pup survival, decreased litter size at birth) LOEL: 300 ppm, equivalent to a LOEL of 35.9 mg a.i./kg bw/day	Not applicable	2331433 2331427
	2-Generation reproductive toxicity	Spiroxamine (95.1%)	NOEC: 80 ppm, equivalent to a NOEL of 5.5 mg a.i./kg bw/day (decreased pup bw) LOEL: 300 ppm, equivalent to a LOEL of 21 mg a.i./kg bw/day	Not applicable	2331434
Vascular plants					
Abutilon theophrasti (Velvetleaf); *Amaranthus retroflexus* (Redroot pigweed)	28-day Tier II seedling emergence; 25, 50, 100, 200, and 400 g a.i./ha	Spiroxamine EC 500 (501 g a.i./L)	Survival: ER_{50} and ER_{25}: > 400 g a.i./ha (both species); Biomass reduction (necrosis and stunting): ER_{50} >400 g a.i./ha and ER_{25} < 25 g a.i./ha (both species)	Not applicable	2332424
	21-day Tier II Vegetative vigour; 25, 50, 100, 200, and 400 g a.i./ha	Spiroxamine EC 500 (501 g a.i./L0)	Survival: ER_{50} and ER_{25}: > 400 g a.i./ha (both species); Biomass reduction: ER_{50} >400 g a.i./ha and ER_{25} > 100 g a.i./ha (redroot pigweed)	Not applicable	2332421
<u>Monocots</u>: Corn, wild oat, cockspur, black twitch, and green blistlegrass <u>Dicots</u>: White mustard, sugarbeet, cleavers, common amaranth, Indian mallow, and Ivyleaf morningglory	Pre-emergence application; screening 250 to 2250 g a.i./ha	Spiroxamine EC 500 (50.6% w/w)	Indian mallow and common amaranth (18 % of all tested species) showed relevant phytotoxic effects (≥ 50 %) at 750 g a.i./ha	Not applicable	2332419
	Postemergence application; screening 250 to 2250 g a.i./ha		64 % of the species showed relevant (≥ 50 %) phytotoxic effects at 750 g a.i./ha.		
<u>Monocots</u>: oat, onion <u>Dicots</u>: Sugarbeet, turnip, carrot, soybean	21-day Tier II Seedling emergence; 150, 300, 600, 1200 and 2400 g a.i./ha	Spiroxamine EC 500 (488.9 g a.i./L)	ER_{50} and ER_{25}: > 2400 g a.i./ha (all species tested; shoot height, fresh weight, seedling emergence)	Not applicable	2332422
	21-day Tier II Vegetative vigour; 150, 300, 600, 1200 and 2400 g a.i./ha	Spiroxamine EC 500 (485.9 g a.i./L)	<u>Most sensitive monocot:</u> onion ER_{50}: > 2400 g a.i./ha (dry weight) ER_{25}: 926 g a.i./ha <u>Most sensitive dicot:</u> turnip ER_{50}: 960 g a.i./ha (dry weight) ER_{25}: 278 g a.i./ha	Not applicable	2332420

[a] United States Environmental Protection Agency classification, where applicable
[b] EP = end-use product

[c] The avian dietary and reproduction endpoints were converted from concentration to daily dose using the following equation: Daily Dose = Concentration in food × (FIR/BW) where: Concentration in food: Toxicity endpoint (for example, LC_{50} or NOEC), in mg a.i./kg diet
FIR: Food ingestion rate (equivalent to food consumption), in g diet/day
BW: Body weight, in g

Table 12 Screening Level and Refined Risk Assessment of Spiroxamine to Beneficial Arthropods

Organism	Exposure	Endpoint value	EEC	RQ (EEC/endpoint)	LOC exceeded? (LOC = 1 unless otherwise stated)	Implications for further refinements
Arthropods						
Aphidius rhopalosiphi (Parasitic wasp)	48 hours, Laboratory test, glass plates Spiroxamine EC 500 (498.5 g a.i./L)	LR_{50} : 80.1 g a.i./ha	In field - 413.7 g a.i./ha*	5.2	Yes **(LOC > 2 for screening level)**	Refine by examining results of higher tier parasitic wasp studies
			Off field (early season airblast 74%)- 306.1 g a.i./ha	3.8	Yes **(LOC > 2 for screening level)**	
			Off field (late season airblast 59%)- 244.1 g a.i./ha	3.0	Yes **(LOC > 2 for screening level)**	
			Off field (field sprayer 6%)- 24.8 g a.i./ha	0.3	No **(LOC > 2 for screening level)**	
	Extended laboratory test Spiroxamine EC 500 (494.0 g a.i./L)	Exposure to residues on barley seedling: LR_{50} and ER_{50} > 750 g a.i./ha (adult mortality and fecundity)	In field - 413.7 g a.i./ha*	<0.55	No	Negligible risk to parasitic wasps both on and off field
Typhlodromus pyri (Predatory mite)	7 day, Laboratory test, glass cages Spiroxamine EC 500 (509.5 g a.i./L)	LR_{50} : 240 g a.i./ha (juveniles) Fecundity at 180 g a.i./ha was reduced by 46% relative to controls (statistically significant)	In field - 413.7 g a.i./ha*	1.7	No **(LOC > 2 for screening level)**	No refinement required. Negligible risk to predatory mites both on and off field. Results of field studies showed no treatment related effects after multiple applications of up to 449 g a.i./ha with as little as 7 day intervals between applications.
	Extended laboratory test, barley plants Spiroxamine EC 500 (49.8% w/w)	LR_{50} > 900 g a.i./ha (highest rate tested); no clear treatment-related effects on reproduction were established (85.4% repellency at 900 g a.i./ha)	In field - 413.7 g a.i./ha*	<0.46	No	
Coccinella septempunctata (Seven pointed ladybird beetle)	Laboratory test (full life-cycle), glass plates, larvae	LR_{50}: ~ 1500 g a.i./ha (56% mortality at highest concentration) NOEC: 750 g a.i./ha	In field - 413.7 g a.i./ha*	~0.28	No	No refinement required. Negligible risk to ladybird beetle

Organism	Exposure	Endpoint value	EEC	RQ (EEC/endpoint)	LOC exceeded? (LOC = 1 unless otherwise stated)	Implications for further refinements
	Spiroxamine EC 500 (502.5 g a.i./L)					both on and off field
Chrysoperla carnea (green lacewing)	Extended laboratory test, glass plates, 1st instar Spiroxamine EC 500 (491.4 g a.i./L)	75.6% mortality at 737 g a.i./ha 100% mortality at 1464 g a.i./ha	In field - 413.7 g a.i./ha*	N/A	N/A	No RQ value could be calculated as no endpoint was available. Refine by examining results of higher tier green lacewing studies
	Extended laboratory test, glass plates, larvae and adults Spiroxamine EC 500 (509.5 g a.i./L)	7-day LR_{50} > 1600 g a.i./ha (larvae); effects on reproduction and hatching were <10% in all treatments	In field - 413.7 g a.i./ha*	<0.26	No	No refinement required. Negligible risk to green lacewing both on and off field
Pardosa spp. (wolf spider)	25 day, Extended laboratory test, Quartz sand as the substrate, adults Spiroxamine EC 500 (487.5 g a.i./L)	Two direct oversprays (7-day interval) of Spiroxamine 500 EC at 750 g a.i./ha; no mortality after first spray and 80% mortality after second by 18 days	In field - 413.7 g a.i./ha*	N/A	N/A	No RQ value could be calculated as no endpoint was available. Refine by examining results of higher tier wolf spider studies
	25 day, Extended laboratory test, Silty sand soil, adults Spiroxamine EC 500 (487.5 g a.i./L)	Two direct oversprays (7-day interval) of Spiroxamine 500 EC at 750 g a.i./ha: no harmful effects on survival or feeding activity.	In field - 413.7 g a.i./ha*	N/A	N/A	No refinement required. Negligible risk to wolf spiders both on and off field since there were no effects observed following applications at a rate higher than the maximum proposed cumulative seasonal rate in Canada.
Bembidion tetracolum (Carabid beetle)	35 day, Extended laboratory test, Quartz sand as the substrate, 4-8 week adults Spiroxamine EC 500 (494.0 g a.i./L)	After 2 applications of 750 g a.i./ha, mortality was 43%.	In field - 413.7 g a.i./ha*	N/A	N/A	No RQ value could be calculated as no endpoint was available. Refine by examining results of higher tier carabid beetle studies
	35 day, Extended laboratory test, Silty sand soil	3.3 % mortality and 16% reduction in feeding rate after 2 applications of 750 g a.i./ha 6.6 % mortality and 16% reduction in	In field - 413.7 g a.i./ha*	N/A	N/A	No refinement required. Negligible risk to carabid beetles

Organism	Exposure	Endpoint value	EEC	RQ (EEC/endpoint)	LOC exceeded? (LOC = 1 unless otherwise stated)	Implications for further refinements
	as the substrate, 4-8 week adults Spiroxamine EC 500 (494.0 g a.i./L)	feeding rate after 2 applications of 1500 g a.i./ha				both on and off field since there were no significant effects observed following applications at a rate higher than the maximum proposed cumulative seasonal rate in Canada.

*cumulative application rate calculated using 2 applications of 300 g a.i./ha, 14 days apart and a default foliar dissipation time (DT_{50}) of 10 days.

Table 13 Screening Level Risk Assessment of Spiroxamine to Earthworms, Collembola, Bees and Terrestrial Vascular Plants

Organism	Exposure (Endpoint): Substance	Endpoint Value	EEC	RQ	Level of Concern
Invertebrates					
Earthworm (*Eisenia foetida*)	Acute Mortality (14-day LC_{50}/2): Spiroxamine	> 500 mg a.i./kg soil	0.259 mg a.i./kg soil[1]	< 0.001	Not Exceeded
	Chronic (8-week NOEC): Spiroxamine	4 mg a.i./kg soil	0.259 mg a.i./kg soil[1]	0.065	Not Exceeded
	Chronic (8-week NOEC): M01	100 mg a.i./kg soil	0.235 mg a.i./kg soil[2]	0.002	Not Exceeded
	Chronic (8-week NOEC): M03	100 mg a.i./kg soil	0.273 mg a.i./kg soil[2]	0.003	Not Exceeded
Collembola (*Folsomia candida*)	Chronic (28-day NOEC): Spiroxamine	32 mg a.i./kg soil	0.259 mg a.i./kg soil[1]	0.008	Not Exceeded
	Chronic (28-day NOEC): M01	316 mg a.i./kg soil	0.235 mg a.i./kg soil[2]	0.001	Not Exceeded
	Chronic (28-day NOEC): M02	316 mg a.i./kg soil	0.222 mg a.i./kg soil[2]	0.001	Not Exceeded
Bees (*Apis mellifera*)	Acute Contact (48-hour LC_{50}): Spiroxamine	4.2 µg a.i./bee	0.72 µg a.i./bee[3]	0.171	Not Exceeded
	Acute Oral (48-hour LD_{50}): Spiroxamine	> 100 µg a.i./bee	8.70 µg a.i./bee[4]	< 0.09	Not Exceeded
Vascular plants					
Onion	Seedling Emergence (21 day, ER_{50}/2): Spiroxamine EC 500	> 1200 g a.i./ha	413.7 g a.i./ha[5]	< 0.34	Not Exceeded
Turnip	Vegetative Vigour (21 day, ER_{50}/2): Spiroxamine EC 500	480 g a.i./ha	413.7 g a.i./ha[5]	0.86	Not Exceeded

1 EEC calculated using 2 applications of 300 g a.i./ha, 14 days apart and a soil half-life of 156 days (90 percent confidence bound on the mean of spiroxamine and M03 combined half-life values adjusted to 25°C, from aerobic soil lab data), assuming soil density of 1.5 g/cm^3 and soil depth of 15 cm.

2 EEC converted for transformation products by assuming 100% conversion of parent to transformation product:
EEC (M01) = (0.259 mg a.i./kg soil × 269.4 M01/mol) ÷ 297.5 g spiroxamine/mol = 0.235 mg M01/kg soil
EEC (M02) = (0.259 mg a.i./kg soil × 255.4 M02/mol) ÷ 297.5 g spiroxamine/mol = 0.222 mg M01/kg soil
EEC (M03) = (0.259 mg a.i./kg soil × 313.5 M03/mol) ÷ 297.5 g spiroxamine/mol = 0.273 mg M01/kg soil

3 the proposed upper-bound residue value for estimating exposure to bees is based on a maximum residue value: 0.3 kg a.i./ha × 2.4 µg a.i./bee per kg/ha = 0.72 µg a.i./bee.

4 the oral exposure estimate for adult bees is calculated by multiplying the direct single rate by 29 µg a.i./bee per kg/ha: 0.3 kg a.i./ha × 29 µg a.i./bee per kg/ha = 8.7 µg a.i./bee.

5 cumulative application rate calculated using 2 applications of 300 g a.i./ha, 14 days apart and a default foliar dissipation time (DT_{50}) of 10 days

Table 14 Estimated Environmental Concentrations (EEC) in Vegetation and Insects

Food item	EEC (mg a.i./kg fw)		Fresh / dry weight ratios	EEC (mg a.i./kg dw)	
	Maximum Residues	Mean Residues		Maximum Residues	Mean Residues
Short range grass	89	31	3.3	292	104
Long grass	41	13	4.4	178	58
Broadleaf plants	50	17	5.4	270	89
Pods with seeds	5	3	3.9	21	10
Insects	35	24	3.8	132	91
Grain and seeds	5	3	3.8	20	10
Fruit	5	3	7.6	41	19

Table 15 Screening Level Risk Assessment of Spiroxamine to Birds and Mammals

	Toxicity (mg a.i./kg bw/day)	Feeding Guild (food item)	Estimated Daily Exposure (mg a.i./kg bw/day)	RQ
Small Bird (0.02 kg)				
Acute	56.5	Insectivore (insects)	33.67	0.60
Reproduction	10.6	Insectivore (insects)	33.67	3.18
Medium Sized Bird (0.1 kg)				
Acute	56.5	Insectivore (insects)	26.28	0.47
Reproduction	10.6	Insectivore (insects)	26.28	2.48
Large Sized Bird (1 kg)				
Acute	56.5	Herbivore (short grass)	16.97	0.30
Reproduction	10.6	Herbivore (short grass)	16.97	1.60
Small Mammal (0.015 kg)				
Acute	46	Insectivore (insects)	19.37	0.42
Reproduction	5.5	Insectivore (insects)	19.37	3.52
Medium Sized Mammal (0.035 kg)				
Acute	46	Herbivore (short grass)	37.56	0.82
Reproduction	5.5	Herbivore (short grass)	37.56	6.83
Large Sized Mammal (1 kg)				
Acute	46	Herbivore (short grass)	20.07	0.44
Reproduction	5.5	Herbivore (short grass)	20.07	3.65

Food Ingestion Rates - For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$. For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g) $^{0.822}$
Estimated dietary exposure is calculated using the following formula: (FIR/BW) × EEC.
At the screening level, food items representing the most conservative EEC for each size guild are used. Shaded cells indicate that the level of concern is exceeded (LOC = 1).

Table 16 Further Characterization of the Reproductive Risk to Birds and Mammals Using the NOEL

Toxicity (mg a.i./kg bw/day)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
		On-field		Off Field		On-field		Off Field	
		EDE (mg a.i./kg bw/day)	RQ	EDE (mg a.i./kg bw/day)	RQ	EDE (mg a.i./kg bw/day)	RQ	EDE (mg a.i./kg bw/day)	RQ
Small Bird (0.02 kg)									
10.6	Insectivore (insects)	33.7	3.2	24.9	2.4	23.3	2.2	17.2	1.6
	Granivore (grain and seeds)	5.2	0.5	3.9	0.4	2.5	0.2	1.8	0.2
	Frugivore (fruit)	10.4	1.0	7.7	0.7	5.0	0.5	3.7	0.3
Medium Sized Bird (0.1 kg)									
10.6	Insectivore (insects)	26.3	2.5	19.4	1.8	18.1	1.7	13.4	1.3
	Granivore (grain and seeds)	4.1	0.4	3.0	0.3	1.9	0.2	1.4	0.1
	Frugivore (fruit)	8.1	0.8	6.0	0.6	3.9	0.4	2.9	0.3
Large Sized Bird (1 kg)									
10.6	Insectivore (insects)	7.7	0.7	5.7	0.5	5.3	0.5	3.9	0.4
	Granivore (grain and seeds)	1.2	0.1	0.9	0.1	5.3	0.5	0.4	0.0
	Frugivore (fruit)	2.4	0.2	1.8	0.2	1.1	0.1	0.8	0.1
	Herbivore (short grass)	17.0	1.6	12.6	1.2	6.0	0.6	4.5	0.4
	Herbivore (long grass)	10.4	1.0	7.7	0.7	3.4	0.3	2.5	0.2
	Herbivore (broadleaf plants)	15.7	1.5	11.6	1.1	5.2	0.5	3.8	0.4
Small Mammal (0.015 kg)									
5.5	Insectivore (insects)	19.4	3.5	14.3	2.6	13.4	2.4	9.9	1.8
	Granivore (grain and seeds)	3.0	0.5	2.2	0.4	1.4	0.3	1.1	0.2
	Frugivore (fruit)	6.0	1.1	4.4	0.8	2.9	0.5	2.1	0.4
Medium Sized Mammal (0.035 kg)									
5.5	Insectivore	17.0	3.1	12.6	2.3	11.7	2.1	8.7	1.6
	Granivore (grain and seeds)	2.6	0.5	1.9	0.4	1.3	0.2	0.9	0.2
	Frugivore (fruit)	5.3	1.0	3.9	0.7	2.5	0.5	1.9	0.3
	Herbivore (short grass)	37.6	6.8	27.8	5.1	13.3	2.4	9.9	1.8
	Herbivore (long grass)	22.9	4.2	17.0	3.1	7.5	1.4	5.5	1.0
	Herbivore (Broadleaf plants)	34.8	6.3	25.7	4.7	11.5	2.1	8.5	1.5
Large Sized Mammal (1 kg)									
5.5	Insectivore	9.1	1.6	6.7	1.2	6.3	1.1	4.6	0.8
	Granivore (grain and seeds)	1.4	0.3	1.0	0.2	0.7	0.1	0.5	0.1
	Frugivore (fruit)	2.8	0.5	2.1	0.4	1.3	0.2	1.0	0.2
	Herbivore (short grass)	20.1	3.6	14.9	2.7	7.1	1.3	5.3	1.0
	Herbivore (long grass)	12.3	2.2	9.1	1.6	4.0	0.7	3.0	0.5
	Herbivore (Broadleaf plants)	18.6	3.4	13.7	2.5	6.1	1.1	4.5	0.8

Shaded cells indicate that the level of concern is exceeded (LOC = 1).

Table 17 Further Characterization of the Reproductive Risk to Birds and Mammals Using the LOEL

Toxicity (mg a.i./kg bw/day)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
		On-field		Off Field		On-field		Off Field	
		EDE[2] (mg a.i./kg bw/day)	RQ	EDE (mg a.i./kg bw/day)	RQ	EDE (mg a.i./kg bw/day)	RQ	EDE (mg a.i./kg bw/day)	RQ
Small Bird (0.02 kg)									
24	Insectivore (insects)	33.7	1.4	24.9	1.0	23.3	1.0	17.2	0.7
	Granivore (grain and seeds)	5.2	0.2	3.9	0.2	2.5	0.1	1.8	0.1
	Frugivore (fruit)	10.4	0.4	7.7	0.3	5.0	0.2	3.7	0.2
Medium Sized Bird (0.1 kg)									
24	Insectivore (insects)	26.3	1.1	19.4	0.8	18.1	0.8	13.4	0.6
	Granivore (grain and seeds)	4.1	0.2	3.0	0.1	1.9	0.1	1.4	0.1
	Frugivore (fruit)	8.1	0.3	6.0	0.3	3.9	0.2	2.9	0.1
Large Sized Bird (1 kg)									
24	Insectivore (insects)	7.7	0.3	5.7	0.2	5.3	0.2	3.9	0.2
	Granivore (grain and seeds)	1.2	0.0	0.9	0.0	5.3	0.2	0.4	0.0
	Frugivore (fruit)	2.4	0.1	1.8	0.1	1.1	0.0	0.8	0.0
	Herbivore (short grass)	17.0	0.7	12.6	0.5	6.0	0.3	4.5	0.2
	Herbivore (long grass)	10.4	0.4	7.7	0.3	3.4	0.1	2.5	0.1
	Herbivore (broadleaf plants)	15.7	0.7	11.6	0.5	5.2	0.2	3.8	0.2
Small Mammal (0.015 kg)									
21	Insectivore (insects)	19.4	0.9	14.3	0.7	13.4	0.6	9.9	0.5
	Granivore (grain and seeds)	3.0	0.1	2.2	0.1	1.4	0.1	1.1	0.1
	Frugivore (fruit)	6.0	0.3	4.4	0.2	2.9	0.1	2.1	0.1
Medium Sized Mammal (0.035 kg)									
21	Insectivore	17.0	0.8	12.6	0.6	11.7	0.6	8.7	0.4
	Granivore (grain and seeds)	2.6	0.1	1.9	0.1	1.3	0.1	0.9	0.0
	Frugivore (fruit)	5.3	0.3	3.9	0.2	2.5	0.1	1.9	0.1
	Herbivore (short grass)	37.6	1.8	27.8	1.3	13.3	0.6	9.9	0.5
	Herbivore (long grass)	22.9	1.1	17.0	0.8	7.5	0.4	5.5	0.3
	Herbivore (Broadleaf plants)	34.8	1.7	25.7	1.2	11.5	0.5	8.5	0.4
Large Sized Mammal (1 kg)									
21	Insectivore	9.1	0.4	6.7	0.3	6.3	0.3	4.6	0.2
	Granivore (grain and seeds)	1.4	0.1	1.0	0.0	0.7	0.0	0.5	0.0
	Frugivore (fruit)	2.8	0.1	2.1	0.1	1.3	0.1	1.0	0.0
	Herbivore (short grass)	20.1	1.0	14.9	0.7	7.1	0.3	5.3	0.3
	Herbivore (long grass)	12.3	0.6	9.1	0.4	4.0	0.2	3.0	0.1
	Herbivore (Broadleaf plants)	18.6	0.9	13.7	0.7	6.1	0.3	4.5	0.2

[1] Shaded cells indicate that the level of concern is exceeded (LOC = 1).

[2] EDE = estimated daily exposure

Table 18 Toxicity of Spiroxamine to Non-Target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Freshwater fish species					
Daphnia magna	48 hour, static	Spiroxamine (97.8%)	EC_{50}: 6.1 mg a.i./L	Moderately toxic	2331599
	48 hour, static	Spiroxamine (96.3%) + [1,3-dioxolan-4-^{14}C]-labeled a.i.	EC_{50}: 6.8 mg a.i./L	Moderately toxic	2331601
	48 hour, flow-through	Spiroxamine (96.5%) + [cyclohexyl-1-^{14}C]-labeled a.i.	EC_{50}: 3.0 mg a.i./L	Moderately toxic	2331602
	48 hour, static	Spiroxamine 500 EC (494 g a.i./L)	EC_{50}: 5.1 mg a.i./L	Moderately toxic	2332374
	48 hour, static, range-finding test	Spiroxamine-N-oxide (M03; 93%)	EC_{50} > 100 mg M03/L	Practically non-toxic	2331600
	21 day (chronic), semi-static	Spiroxamine (97.8%)	NOEC: 0.1 mg a.i./L (number of offspring)	No classification	2331603
	21 day (chronic), flow-through	Spiroxamine (96.5%) + [cyclohexyl-1-^{14}C]-labeled a.i.	NOEC: 0.034 mg a.i./L (number of offspring per parent per reproduction day)	No classification	2331604
	21 day (chronic), static-renewal	Spiroxamine (96.3%) + [1,3-dioxolan-4-^{14}C]-labeled a.i.	NOEC: 0.047 mg a.i./L (number of offspring per parent per reproduction day)	No classification	2331605
Sediment dwelling invertebrate (*Chironomus riparius*)	28 day, static, spiked water	Spiroxamine (96.3%) + [cyclohexyl-1-^{14}C]-labeled a.i.	NOEC: 3.2 mg a.i./L (development rate)	Moderately toxic	2331625
	28 day, static, spiked water artificial + natural sediment	Spiroxamine EC 500 (494.0 g a.i./L)	NOEC: 0.0025 mg a.i./L (highest concentration tested)	No classification	2332378
Rainbow trout (*Oncorhynchus mykiss*)	96 hour, static	Spiroxamine (97.8%)	LC_{50}: 18.5 mg a.i./L	Slightly toxic	2331585
	96 day (chronic), flow-through, Early-life stage	Spiroxamine (96.7%) + [1,3-dioxolan-4-^{14}C]-labeled a.i.	NOEC: 0.0142 mg a.i./L (measured concentrations; hatchling length)	No classification	2331590
	93 day (chronic), flow-through, Early-life stage	Spiroxamine (97.8%)	NOEC: 0. 0625 mg a.i./L (hatchling length)	No classification	2331589
	56 day (chronic), static, Early-life stage, water/artificial sediment systems, and 3 pulse applications, 10 day intervals	Spiroxamine (97.0%)	NOEC: 0.060 mg a.i./L (standard length, dry weight) (results were difficult to interpret due to turbidity in the test system and potential adsorption to sediment)	No classification	2331591
Bluegill sunfish *(Lepomis macrochirus)*	96 hour, static	Spiroxamine (97.8%)	LC_{50}: 7.13 mg a.i./L	Moderately toxic	2331586
Fathead minnow (*Pimephales promelas*)	21 day, Fish Screening Assay (FSA)	Spiroxamine (95.1%)	NOEC: 0.0189 mg a.i./L (decreased vitellogenin in females)	No classification	2331588
Zebra fish (*Danio rerio)*	96 hour, static	Spiroxamine (97%)	LC_{50}: 2.41 mg a.i./L	Moderately toxic	2331587

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
	chronic, full life-cycle flow-through	Spiroxamine (97.0%)	NOEC values: F0 early life - 0.0026 mg a.i./L (reduction in hatching); F0 juvenile – 0.0064 mg a.i./L (length); F0 adult – 0.064 mg a.i./L (length of males); F0 adult – 0.0026 mg a.i./L (reduced vitellogenin in females and reduced F1-ELS fish larvae survival); F1 early life – 0.0026 mg a.i./L (hatching rate)	No classification	2331596
Freshwater algae					
Green algae (*Pseudokirchneriella subcapitata, a.k.a. Selenastrum capricornutum*)	120 hour, static	Spiroxamine (96.4%)	E_rC_{50}: 0.01943 mg a.i./L E_bC_{50}: 0.00542 mg a.i./L	No classification	2331614
	96 hour, static	^{14}C-Spiroxamine (98.2%)	E_rC_{50}: 0.0411 mg a.i./L E_bC_{50}: 0.0055 mg a.i./L E_dC_{50}: 0.0057 mg a.i./L	No classification	2331616
	Recovery study; 120-hour exposure followed by observations up to 528 hours; transfer to fresh medium and cell counts at 72 and 192 hour.	Spiroxamine (96.4%) Initial concentrations: 0, 1.0, 1.8, 3.2, 5.6, 10.0, 18.0, and 32.0 µg a.i./L	E_rC_{50}: 0.0193 mg a.i./L Pre-exposure of algal cells to highest two concentrations of Spiroxamine had no lasting influence on the rates at which these cells could grow in the absence of the compound.	No classification	2331615
Green algae (*Desmodesmus subspicatus, a.k.a. Scenedesmus subspicatus*)	72 hour, static	Spiroxamine (97.5%)	E_rC_{50}: 0.175 mg a.i./L E_bC_{50}: 0.0369 mg a.i./L	No classification	2331618
	72 hour, static	Spiroxamine (96.4%)	E_rC_{50}: 0.012 mg a.i./L E_bC_{50}: 0.0032 mg a.i./L	No classification	2331613
	72 hour, static	Spiroxamine EC 500 (491.4 g a.i./L)	E_rC_{50}: 0.0143 mg a.i./L E_bC_{50}: 0.0059 mg a.i./L	No classification	2332375
	72 hour, static	Spiroxamine-desethyl (M01; 98%)	E_rC_{50}: 0.737 mg M01/L E_bC_{50}: 0.133 mg M01/L	No classification	2331622
	72 hour, static	Spiroxamine-N-oxide (M03; 86.6%)	E_rC_{50}: 31.680 mg M03/L E_bC_{50}: 9.977 mg M03/L	No classification	2331623
	Recovery study: 22-day exposure, Further 7 days after transfer in fresh medium	Spiroxamine (97.8%) Initial concentrations: 1.0, 1.8, 3.2, 5.6, 10.0, 18.0, 32.0 µg/L	Algal cells from previous exposure levels up to at least 32 µg a.i./L are able to recover completely after elimination of the compound.		2331619
Blue-green algae (*Anabaena flos-aquae*)	96 hour, static Limit test	Spiroxamine (96.3%) + [cyclohexyl-1-^{14}C]-labeled a.i.	EC_{50}: > 0.99 mg a.i./L (only concentration tested)	No classification	2331620
Freshwater diatom (*Navicula pelliculosa*)	96 hour, static	Spiroxamine (96.3%) + [cyclohexyl-1-14C]-labeled a.i.	72-hour E_rC_{50}: 0.0119 mg a.i./L 96-hour E_dC_{50}: 0.01185 mg a.i./L	No classification	2331624 2331621
Freshwater algae	Species Sensitivity Distribution using acute, static toxicity values	Spiroxamine	HC_5: 0.00018 mg a.i./L (PMRA calculated)	No classification	Multiple algae studies (listed above)

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Freshwater vascular plants					
Monocot vascular plant, duckweed (*Lemna gibba*)	14 day, static Dissolved	Spiroxamine (95.3%)	14-day $EC_{50,\text{frond count}}$: 1.91 mg a.i./L 14-day E_rC_{50}: 2.65 mg a.i./L 7-day $E_rC_{50,\text{frond count}}$: 6.78 mg a.i./L	No classification	2331626 2331628
	14 day, static	^{14}C-Spiroxamine (>99%)	14-day $EC_{50,\text{frond count}}$: 2.76 mg a.i./L 14-day $E_bC_{50,\text{dry weight}}$: 9.38 mg a.i./L 7-day $EC_{50,\text{frond count}}$: 5.60 mg a.i./L 14-day $E_rC_{50,\text{dry weight}}$: 21.2 mg a.i./L	No classification	2331627 2331629
Mesocosm Study					
Artificial tanks: Natural sediment and water; natural communities emerged; introduced: 3 macrophyte species: *Callitriche pallustris*, *Myriophyllum spicatum*, *Potamogeton crispus*	Application rates: Control, 1.0, 2.1, 4.4, 9.3, and 19.4 µg a.i./L Three applications with 7-day intervals Mesocosms were monitored/sampled 2 weeks before and 14 weeks after treatment (static)	Spiroxamine EC 500 (501 g a.i./L) Concentrations of the test substance in water were below the limit of detection by four weeks (two lowest treatments) and 70 days (highest treatment).	NOEC based on recovery: 0.0194 mg a.i./L (this is max concentration tested) NOEC without recovery: 0.0021 mg a.i./L Pronounced effects on phytoplankton and zooplankton; recovery occurred for populations.	No classification	2331607
Marine species					
Saltwater diatom (*Skeletonema costatum*)	96 hour, static	^{14}C-Spiroxamine (98.2%)	E_rC_{50}: 0.0063 mg a.i./L E_bC_{50}: 0.0013 mg a.i./L E_dC_{50}: 0.0013 mg a.i./L	No classification	2331640

a. United States Environmental Protection Agency classification, where applicable

Table 19 Screening Level Risk Assessment of Spiroxamine for Aquatic Organisms

Organism	Exposure (Endpoint): Substance	Endpoint Value	EEC	RQ	Level of Concern
Freshwater species					
Daphnia magna	Acute (48-hour EC_{50}/2): Spiroxamine	1500 µg a.i./L	73	0.05	Not Exceeded
	Chronic (21-day NOEC): Spiroxamine	34 µg a.i./L	73	2.1	Exceeded
	Acute (48-hour EC_{50}/2): M03	> 50000 µg a.i./L	76.93	< 0.002	Not Exceeded
Benthic Invertebrate (chironomid)	Chronic (28-day NOEC): Spiroxamine	3200 µg a.i./L	73	0.02	Not Exceeded
Zebrafish	Acute (96-hour LC_{50}/10): Spiroxamine	241 µg a.i./L	73	0.30	Not Exceeded
	Chronic (full-life cycle NOEC): Spiroxamine	2.6 µg a.i./L	73	28.08	Exceeded
Amphibians (most sensitive fish)	Acute (96-hour LC_{50}/10): Spiroxamine	241 µg a.i./L	387	1.61	Exceeded
	Chronic (full-life cycle NOEC): Spiroxamine	2.6 µg a.i./L	387	149	Exceeded
Freshwater alga (green - *Desmodesmus subspicatus*)	Acute (72-hour EC_{50}/2): M01	66.5 µg a.i./L	66.10	0.99	Not Exceeded
	Acute (72-hour EC_{50}/2): M03	4989 µg a.i./L	76.93	0.02	Not Exceeded

	Acute (72-hour EC_{50}/2): M06	> 1600 µg a.i./L	80.36	< 0.05	Not Exceeded
Freshwater algae (SSD)	Species Sensitivity Distribution (HC_5): Spiroxamine	0.18 µg a.i./L	73	405.56	Exceeded
Mesocosm	Chronic (NOEC): Spiroxamine EC 500	2.1 µg a.i./L	73	34.76	Exceeded
Vascular plant (duckweed - *Lemna gibba*)	Acute (14-day EC_{50}/2): Spiroxamine	955 µg a.i./L	73	0.08	Not Exceeded
Marine Species					
Marine algae (diatom-(*Skeletonema costatum*)	Acute (96-hour EC_{50}/2): Spiroxamine	0.65 µg a.i./L	73	112.3	Exceeded

Table 20 Risk Quotients for Aquatic Organisms Determined for Drift of Spiroxamine

Estimated Environmental Concentrations	Airblast early (74% drift)	Airblast late (59% drift)	Ground boom (6% drift)
EEC (80 cm depth for freshwater invertebrates, fish, algae and marine algae)	54.0 µg a.i./L	43.1 µg a.i./L	4.38 µg a.i./L
EEC (15 cm depth for amphibians)	286.4 µg a.i./L	228.3 µg a.i./L	23.22 µg a.i./L
Risk Quotients (RQ)			
Freshwater invertebrates: Chronic risk RQ (NOEC: 34 µg a.i./L)	1.59	1.27	0.13
Freshwater Fish: Chronic risk RQ (NOEC: 2.6 µg a.i./L)	20.78	16.57	1.69
Amphibians: Acute risk RQ (LC_{50}/10: 241 µg a.i./L)	1.19	0.95	0.10
Amphibians: Chronic risk RQ (NOEC: 2.6 µg a.i./L)	110.15	87.82	8.93
Freshwater Algae: Acute risk RQ (HC_5: 0.18 µg a.i./L)	300.11	239.28	24.33
Mesocosm: Chronic risk RQ (NOEC: 2.1 18 µg a.i./L)	25.72	20.51	2.09
Marine Algae: Acute risk RQ (EC_{50}/2: 0.65 µg a.i./L)	83.11	66.26	6.74

Level of concern exceeded for highlighted values (RQ > 1)

Table 21 Risk Quotients for Aquatic Organisms Determined for Runoff of Spiroxamine Combined with M03 in Water Bodies 80 or 15 cm Deep

Organism (exposure)	Endpoint value	EEC concentrations (time-frame, water body)	RQ	Level of Concern
Freshwater invertebrates (Chronic risk)	NOEC: 34 µg a.i./L	21 day, 80 cm water body: 27 µg a.i./L	0.8	Not exceeded
Freshwater Fish (Chronic risk)	NOEC: 2.6 µg a.i./L	90 day, 80 cm water body: 26 µg a.i./L	1.8	Exceeded
Amphibians (Acute risk)	LC_{50}/10: 241 µg a.i./L	96 hour, 15 cm water body: 93 µg a.i./L	0.4	Not exceeded
Amphibians (Chronic risk)	NOEC: 2.6 µg a.i./L	90 day, 15 cm water body: 70 µg a.i./L	26.9	Exceeded
Freshwater Algae (Acute risk)	HC_5: 0.18 µg a.i./L	Peak, 80 cm water body: 28 µg a.i./L	155.6	Exceeded

Organism (exposure)	Endpoint value	EEC concentrations (time-frame, water body)	RQ	Level of Concern
Mesocosm (Chronic risk)	NOEC: 2.1 µg a.i./L	90 day, 80 cm water body: 26 µg a.i./L	12.4	Exceeded
Marine Algae (Acute risk)	EC_{50}/2: 0.65 µg a.i./L	96 hour, 80 cm water body: 28 µg a.i./L	43.1	Exceeded

Table 22 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Spiroxamine Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]	Soil	Half-life ≥ 182 days	DT_{50} of 39.3 – 134 days in aerobic soil systems.
	Water	Half-life ≥ 182 days	DT_{50} of 0.4 – 5.74 days in aqueous phase of aerobic and anaerobic water/sediment systems.
	Sediment	Half-life ≥ 365 days	DT_{50} of 2.89 – 690 days in total system of aerobic and anaerobic water/sediment systems.
	Air	Half-life ≥ 2 days or evidence of long range transport	Spiroxamine may dissipate in air (vapour pressure: 9.7×10^{-3} Pa at 20°C, Henry's Law Constant: 2.53×10^{-3} Pa m^3 mol^{-1} (isomer A) and 4.99×10^{-3} Pa m^3 mol^{-1} (isomer B)) but has a DT_{50} of < 3 hours in air and is therefore very unlikely to undergo long-range atmospheric transport.
Bioaccumulation[4]	Log $K_{ow} \geq 5$		1.28 – 5.08
	Bioconcentration factor ≥ 5000		87
	Bioaccumulation factor ≥ 5000		Value not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (in other words, all other TSMP criteria are met).

[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4]Field data (for example, bioaccumulation factors) are preferred over laboratory data (for example, bioconcentration factors) which, in turn, are preferred over chemical properties (for example, *n*-Octanol/water partition coefficient (log K_{ow})).

Table 23 Registered Alternative Products (as of August 2014) for Powdery Mildew on Grape

Active ingredient	Mode of Action Group (or indicated as not classified)
Non-conventional alternatives	
Streptomyces lydicus strain WYEC 108	Not classified
Mineral oil	Not classified
Plant extract of *Reynoutria sachalinensis*	Not classified
Potassium bicarbonate	Not classified
Bacillus subtilis strain QST 713	44
Tea tree oil	46
Conventional alternatives	
Copper	M1
Sulphur	M2
Metrafenone	U8
Difenoconazole	3
Myclobutanil	3
Tetraconazole	3
Boscalid	7
Fluopyram + Pyrimethanil	7 + 9
Boscalid + Pyraclostrobin	7 + 11
Kresoxim-methyl	11
Trifloxystrobin	11
Quinoxyfen	13
Zoxamide	22

Table 24 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Use claim	Supported / Not Supported
To control powdery mildew (*Uncinula necator*) on grape, Impulse 500 EC Fungicide is applied at 400-600 mL/ha (200-300 g a.i./ha) in a minimum of 500 L water/ha anytime between shoot emergence until 35 days prior to harvest, and prior to disease development as part of a preventative spray schedule. Application may be made using ground application equipment (field sprayer or airblast). The interval between applications is 14 days. The maximum seasonal application rate is 1.2 L/ha, which permits up to two applications per growing season at the maximum rate. Other fungicides registered for control of powdery mildew are to be applied in conjuction with Impulse 500 EC Fungicide to achieve season long control of this disease.	Supported at proposed rates and timings The instruction is added that the higher rate be applied when conditions favour the development of heavy disease pressure or in vineyards with a history of heavy disease pressure.

Appendix II Supplemental Maximum Residue Limit Information – International Situation and Trade Implications

Spiroxamine is a new active ingredient which is being registered in Canada.

Currently, there are no Codex Maximum Residue Limits[9] (MRLs) listed for spiroxamine in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1 compares the MRLs proposed for spiroxamine in Canada with corresponding American tolerances and Codex MRLs. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity.

Table 1 Comparison of Canadian Maximum Residue Limits, American Tolerances and Codex Maximum Residue Limits (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Raisins	4	Not Established	Not Established
Bananas	3	3	Not Established
Grapes	2	1	Not Established

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data.

Under the North American Free Trade Agreement, Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

[9] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2331226	2008, Document J-II - Confidential data and information for spiroxamine (KWG 4168) - Tier 2 summary of the identity, analytical methods and validation of the active substance, DACO: 2.11.2 CBI
2331237	1995, Material accountability of KWG 4168, DACO: 2.13.3, IIA 1.11.1, IIA 1.11.2 CBI
2331238	2001, Analytical profile of batches (material accountability) of spiroxamine (KWG 4168 D techn.), DACO: 2.13.3, IIA 1.11.1 CBI
2331243	1993, Thermal stability of the active ingredient KWG 4168, DACO: 2.14.13, 2.14.5, IIA 2.1.2, IIA 2.1.3
2331245	1993, Density of KWG 4168, DACO: 2.14.6, IIA 2.2
2331246	1994, Vapour pressure curve of KWG 4168, DACO: 2.14.9, 8.2.3.3.3, 8.2.4.5, IIA 2.3.1, IIA 7.10, IIA 7.4.9
2331250	1998, Aspect and odour as well as oxidation and reduction characteristics of KWG 4168, DACO: 2.14.1, 2.14.2, 2.14.3, IIA 2.4.1, IIA 2.4.2
2331254	2007, Spectral data set of spiroxamine (KWG 4168), DACO: 2.13.2, 2.14.12, IIA 2.5.1.1, IIA 2.5.1.2, IIA 2.5.1.3, IIA 2.5.1.4, IIA 2.5.1.5
2331264	1992, Water solubility of KWG 4168, DACO: 2.14.7, IIA 2.6
2331265	1993, Solubility of KWG 4168 in representative organic solvents, DACO: 2.14.8, IIA 2.7
2331267	1995, Partition coefficient of KWG 4168 in octanol - water as function of pH, DACO: 2.14.11, IIA 2.8.2
2331272	1992, Dissociation constant and pH value of KWG 4168, DACO: 2.14.10, 8.2.3.2, IIA 2.9.5
2331280	1991, pH of KWG 4168, DACO: 2.16, IIA 2.16
2331281	2003, Storage stability of spiroxamine techn. (Article-no.: 05395674) - Final report, DACO: 2.14.14, IIA 2.17.1
2331282	2010, Annex B - Spiromaine - B-2: Physical and chemical properties, DACO: 12.5.2, 12.5.3, 2.16, IIA 2.18
2331293	2000, KWG 4168 techn.; Content - Capillary gas chromatography, DACO: 2.13.1, IIA 4.2.1
2331294	2004, Validation of GC-method 2201-0329801-00 - Determination of the assay (diastereomer A and B) in KWG 4168 (spiroxamine) techn.grade active ingredient, DACO: 2.13.1, IIA 4.2.1
2331297	2005, By-products - capillary gas chromatography, standard per cent, DACO: 2.13.4, IIA 4.2.3 CBI

2331299	2005, Validation of GC-method AM000205DB1- Determination of the by-products in KWG 4168 (spiroxamine) techn.grade active ingredient, DACO: 2.13.4, IIA 4.2.3 CBI
2331300	2005, Determination of [CBI removed] - Capillary gas chromatography, standard per cent, DACO: 2.13.4, IIA 4.2.3 CBI
2331301	2005, Validation of GC-method AM000805DB1 - Determination of [CBI removed] in KWG 4168 (spiroxamine) tech. grade active ingredient, DACO: 2.13.4, IIA 4.2.3 CBI
2429482	1995, Determination of [CBI removed], DACO: 2.13.1 CBI
2429483	1997, Validation report of study KWG-4168 (22-06-1995), MA-study no. 15920 2017 Sample-no. 17002-90, determination of N-[CBI removed], DACO: 2.13.1 CBI
2429484	1995, Determination of [CBI removed] GC/TEA method for solid and liquid matter without sample cleanup, DACO: 2.13.1 CBI
2429485	1997, Validation report of study KWG-4168 (22-06-1995), MA-study no. 15920 2017 sample-no. 17002-90, determination of [CBI removed], DACO: 2.13.1 CBI
2429487	2007, Certificate of analysis of spiroxamine D techn, DACO: 2.13.2 CBI
2437273	2014, Spectral data (NMR and MS) of organic impurities specified in spiroxamine (BCS-AA28732) technical material, DACO: 2.13.2 CBI
2445297	2014, Spectra data (NMR and MS) of organic impurities specified in spiroxamine (BCS-AA28732) technical material, DACO: 2.13.2 CBI
2445298	1995, Material accountability of KWG 4168, DACO: 2.13.1 CBI
2332291	1995, KWG 4168 EC 500 (0168478) - Appearance, DACO: 3.5.1, 3.5.2, 3.5.3, IIIA 2.1
2332292	1995, Determination of safety-relevant parameters of KWG 4168 EC 500 (Identification No: 94/00307), DACO: 3.5.11, 3.5.12, IIIA 2.2.1, IIIA 2.3.1, IIIA 2.3.3
2332294	2008, Determination of safety-relevant data of Spiroxamine EC 500 (500 g/L), DACO: 3.5.8, IIIA 2.2.2
2332296	1995, KWG 4168 EC 500 (0122915) - pH, DACO: 3.5.7, IIIA 2.4.2
2332297	1995, KWG 4168 EC 500 (0168478) - pH, DACO: 3.5.7, IIIA 2.4.2
2332300	2005, Storage stability of Spiroxamine EC 500 further code name: Impulse EC 500 [packaging material: HDPE], DACO: 3.5.10, 3.5.14, 3.5.5, 3.5.7, 8.2.3.6, IIIA 2.4.2, IIIA 2.7.1, IIIA 2.7.3, IIIA 2.7.4, IIIA 2.8.2, IIIA 2.8.7.1, IIIA 2.8.7.2, IIIA 2.8.7.3
2332302	1995, KWG 4168 EC 500 (0168478) - Viscosity, DACO: 3.5.9, IIIA 2.5.1, IIIA 2.5.2
2332303	1995, KWG 4168 EC 500 (0122915) - Viscosity, DACO: 3.5.9, IIIA 2.5.2
2332309	1995, KWG 4168 EC 500 (0122915) - Relative density of liquid preparations, DACO: 3.5.6, IIIA 2.6.1
2332310	1995, KWG 4168 EC 500 (0168478) - Relative density of liquid preparations, DACO: 3.5.6, IIIA 2.6.1
2332315	1995, KWG 4168 EC 500 (0122915) - Shelf life at ambient temperatures, DACO: 3.5.10, IIIA 2.7.5
2332326	1997, Determination of KWG 4168 in formulations, DACO: 3.4.1, IIIA 5.2.1

2332327	1993, Determination of KWG 4168 in formulations, DACO: 3.4.1, IIIA 5.2.1
2332328	1995, Validation-report GLC-method 2001-0034401-93, DACO: 3.4.1, IIIA 5.2.1
2332329	1997, Validation supplement report VS1.1-2001-0034402E (+Chromatogram), DACO: 3.4.1, IIIA 5.2.1
2332332	2001, Validation of GLC-method 2001-0034402-97 - Determination of spiroxamine in formulations-, DACO: 3.4.1, IIIA 5.2.1
2332428	2008, Tier 2 summary of the identity of the plant protection product for Spiroxamine EC 500 (500 g/L), DACO: 12.7, 3.1.2, 3.1.3, 3.1.4, 3.5.4
2429459	2014, BCS response to clarification request, DACO: 0.8
2429466	2005, Product specification manufacturing procedure Impulse EC 500, DACO: 3.2.2 CBI
2429472	1997, Validation supplement report VS1/1-2001-0034402E, GLC method 2001-0034402-97, DACO: 3.4.1 CBI
2437631	2014, Specification for co-formulant benzylalcohol, DACO: 3.2 CBI
2437632	2014, Specification for co-formulant emulsogen PSI 100, DACO: 3.2 CBI
2437633	2014, Specification for co-formulant geronol PSI , DACO: 3.2 CBI
2437634	2014, Specification for co-formulant tanemul PSI 100, DACO: 3.2 CBI
2331366	2008, Analytical method 01088 for the determination of residues of KWG 4168 (spiroxamine) in soil and sediment by HPLC-MS/MS, DACO: 8.2.2.1, 8.2.2.2 ,IIA 4.4, IIA 4.6
2331368	1997, Method 00433 (MR-248/96) for liquid chromatographic determination of KWG 4168 and the metabolites KWG 4557, KWG 4669 and WAK 6301 in soil, DACO: 8.2.2.1, IIA 4.4
2331371	1999, Enforcement and confirmatory method for determination of KWG 4168 in drinking water and surface water by GC/MS, DACO: 8.2.2.3, IIA 4.5
2331372	2001, Method for the determination of KWG 4168 in water by HPLC-MS/MS, DACO: 8.2.2.3, IIA 4.5

2.0 Human and Animal Health

PMRA Document Number	Reference
2332352	1994, [1,3-dioxolane-4-^{14}C] KWG 4168 - Dermal absorption study in the rat. DACO: 5.8, IIIA 7.6.1
2332354	1994, *In vitro* skin penetration of KWG 4168. DACO: 5.8, IIIA 7.6.2
2332355	2008, Impulse EC 500 ([^{14}C]-Spiroxamine - Comparative i*n vitro* dermal absorption study using human and rat skin. DACO: 5.8, IIIA 7.6.2
2332357	2003, Dissipation of dislodgeable foliar residues from grapes treated with BAY KWG 4168 Fungicide. DACO: 5.9, IIIA 7.7.1

2331311	1997, Independent laboratory validation for the determination of the total residue of KWG 4168 in grapes (Bayer report no.107714), DACO: 7.2.3, IIA 4.2.6
2331318	1996, Method for the gas-chromatographic determination of the total residue of KWG 4168 in grapes and processed commodities, DACO: 7.2.1, 7.2.4, IIA 4.3
2331335	1996, Extraction efficiency testing of the residue method for the determination of KWG 4168 residues in grapes using aged radioactive residues, DACO: 7.2.1, 7.2.4, IIA 4.3
2331337	2002, Supplement E002 to method 00407 for the determination of total residue of KWG 4168 in/on sample materials of banana and hops by GC-MS, DACO: 7.2.1, 7.2.4, IIA 4.3
2331339	2001, Extraction efficiency testing of the residue methods 00721 and 00407/E002 for the determination of KWG4168 residues in banana using aged radioactive residues, DACO: 7.2.1, 7.2.4, IIA 4.3
2331347	2008, Analytical method 01089 for the determination of spiroxamine (KWG 4168) and of the total residue of spiroxamine (as aminodiol) in/on grapes by HPLC-MS/MS, DACO: 7.2.1, 7.2.4, IIA 4.3
2331353	1998, Analytical method verification for the determination of KWG4168 residues in grapes and grape foliage, DACO: 7.2.1,7.2.4,IIA 4.3
2331377	2010, Annex B - Spiromaine - B-5: Methods of analysis, DACO: 12.5.2, 12.5.3, 12.5.7, 12.5.8, 2.16, 8.6, IIA 4.9
2331489	1997, Storage stability of KWG 4168 in/on grapes and processed commodities, DACO: 7.3, IIA 6.1.1
2331490	2004, Determination of the storage stability of KWG 4168 and aminodiol residues in fortified analytical samples of hops and banana during frozen storage, DACO: 7.3, IIA 6.1.1
2331492	1996, Metabolism of [Cyclohexyl-1-14C] KWG 4168 in grapes, DACO: 6.3, IIA 6.2.1
2331493	1996, Metabolism of [1,3-Dioxolane-4-14C] KWG 4168 in grapes, DACO: 6.3, IIA 6.2.1
2331495	2000, Metabolism of [14C]-KWG 4168 in banana (In-life phase), DACO: 6.3, IIA 6.2.1
2331496	2002, Metabolism of [cyclohexyl-1-14C]KWG4168 in banana (analytical part), DACO: 6.3, IIA 6.2.1
2331497	2001, Metabolism of [1,3-dioxolane-4-14C]KWG4168 in banana (analytical part), DACO: 6.3, IIA 6.2.1
2331502	1996, Determination of residues of KWG 4168 (500 EC) on grape in the Federal Republic of Germany, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3

2331503	1996, Determination of residues of KWG 4168 (500 EC) and KWG 4168 (800 EC) in/on grape in the Federal Republic of Germany, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331504	1998, Determination of residues of KWG 4168 & HWG 1608 (500 EC) on grape in the field in Federal Republic of Germany and France, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331505	2000, Determination of residues of KWG 4168 & Quinoxyfen 480 SE (A.S.: spiroxamine, Quinoxyfen) in/on grape in the field following spray application in France and Germany, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331506	1999, Determination of residues of KWG 4168 500 EC (A.S.: spiroxamine) in/on grape following spray application in France and Germany, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331507	2008, Determination of the residues of KWG 4168 in/on grape after low-volume spraying and spraying of KWG 4168 (500 EC) in the field in Northern France and Germany, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331508	1996, Determination of residues of KWG 4168 500 EC on grape and table grape in France, Portugal, Spain and Italy, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331509	1996, Determination of residues of KWG 4168 (500 EC) and KWG 4168 (800 EC) in/on grape in France, Portugal, Greece and Italy, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331510	1997, Determination of residues of KWG 4168 in/on table grape following spray application with different formulations (500 EC, 800 EC) in Italy, Portugal and France, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331511	2001, Determination of residues of Spiroxamine in/on grapes after spray application of KWG 4168 300 CS and KWG 4168 500 EC to grape vines in the field in Italy and Spain, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.3
2331512	2008, Determination of the residues of KWG 4168 in/on grape after low-volume spraying and spraying of KWG 4168 (500 EC) in the field in Southern France, Italy, Spain and Greece, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331517	2000, KWG 4168 300 CS (OXA) - Magnitude of the residues in grapes, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.3
2331518	2002, KWG 4168 800 EC - magnitude of the residue in bananas, DACO: 7.7, IIA 6.3.4
2331520	2002, Determination of residues of spiroxamine after ultra low volume application of KWG 4168 800 EC in/on banana in Martinique, DACO: 7.7, IIA 6.3.4
2331523	1996, Determination of residues of KWG 4168 500 EC / 800 EC on grape and table grape and in processed commodities, DACO: 7.4.5, IIA 6.5.4

2331531	2010, Annex B - Spiroxamine - B-7: Residue data, DACO: 12.5.6, 12.5.7, 12.5.7 (OECD), 6.4,7.8, IIA 6.10
2331739	2010, Draft re-assessment report - Spiroxamine - Volume 3 - Annex B - Summary, scientific - Evaluation and assessment - Rapporteur member state: Germany - Co-rapporteur member state: Hungary, DACO: 12.5 (OECD), 12.7, Document N
2331483	1997, KWG 4168 - Position paper on the toxicological no-observed effect level which is relevant for the calculation of a systemic AOEL, Report MO-99-010330, DACO: 4.1, IIA 5.11
2331383	1991, KWG 4168 - Study for acute oral toxicity in rats, Report 20416, MRID 45090125, DACO: 4.2.1, IIA 5.2.1
2331384	1991, KWG 4168 - Study for acute oral toxicity in mice, Report 20418, DACO: 4.2.1, IIA 5.2.1
2331385	1991, KWG 4168 - Study for acute dermal toxicity in the rat, Report 20417, MRID 45090128, DACO: 4.2.2, IIA 5.2.2
2331386	1990, KWG 4168 - Study for acute inhalation toxicity in the rat, Report 19806, MRID 45090130, DACO: 4.2.3, IIA 5.2.3
2331387	1990, KWG 4168 - Study for skin and eye irritation/corrosion in rabbits, Report 19584, DACO: 4.2.4, 4.2.5, IIA 5.2.4, IIA 5.2.5
2331388	1998, Spiroxamine (KWG 4168) - Results of eye irritation tests with active ingredient and EC 500 formulation, Report MO-99-009355, DACO: 4.2.4, IIA 5.2.5
2331389	1992, KWG 4168 - Studies on skin sensitizing effect in guinea pigs (maximization test according to Magnusson and Kligman), Report 21687, DACO: 4.2.6, IIA 5.2.6
2331390	1992, KWG 4168 - Study for skin-sensitizing effects in guinea pigs (Buehler Patch Test), Report 21716, MRID 45090205, DACO: 4.2.6, IIA 5.2.6
2331391	2001, A patch test procedure to facilitate the expression and detection of the irritating and sensitizing propensities of KWG 4168, Report 107791, DACO: 4.2.6, IIA 5.2.6
2331466	2008, Occupational medical experiences with spiroxamine, DACO: 4.2.8, IIA 5.9.1
2331438	1995, Combined report of embryotoxicity screening study (including teratogenicity) and supplementary study to the embryotoxicity screening study (including teratogenicity) with KWG 4168 technical in the rat, Report R6355, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.2, 4.5.8, 4.8, IIA 5.1
2331439	1995, Range-finding studies with KWG 4168 technical in the rat, Report R6343, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.2, 4.5.8, 4.8, IIA 5.10, IIA 5.6.10

2331442	1993, Embryotoxicity study (including teratogenicity) with KWG 4168 technical in the rat (dermal application), Report R5952, MRID 45090218, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.2, 4.5.8, 4.8, IIA 5.10, IIA 5.6.10
2331477	2009, Spiroxamine - Annex I renewal - Further information requested by the BfR to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex I, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8
2331478	2009, Spiroxamine - Annex I renewal - Further information requested by the BfR to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex I, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8
2331467	1991, KWG 4168 - Study for acute intraperitoneal toxicity in rats, Report 20419, MRID 45090229,DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331468	1991, KWG 4168 - Studies of sensory irritation potential in rats (determination of the median irritation dose ID50), Report 20375, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331469	1991, KWG 4168 - Study for sensory irritant potential in the mouse (RD50 determination), Report 20370, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331470	2008, Spiroxamine - Investigation on potential in vitro aromatase (CYP19) inhibition, Report AT04594, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331471	2008, Spiroxamine - Investigation on potential in vitro steroidgenesis inhibition, Report AT04646, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331472	1992, KWG 4168 - Study for immunostimulation potential in rats and mice - 1st revision to report no. 21616 of August 05, 1992, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331473	1991, KWG 4168 - Liver foci test with promotion, Report 106890, MRID 45090305, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331479	2009, Response of BCS to requests raised by BfR after submission of the dossier for Annex I Renewal, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331482	2009, Response of BCS to requests raised by BfR after submission of the dossier for Annex I Renewal, DACO: 4.2.9, 4.3.8, 4.4.5, 4.5.8, 4.8, IIA 5.10
2331395	1992, KWG 4168 - Subchronic toxicity study in Wistar rats (thirteen-week administration in the diet with a four-week recovery period), Report 21627, DACO: 4.3.1, IIA 5.3.2
2331396	1992, KWG 4168 - Subchronic range-finding testing for a two-year study in B6C3F1 mice (administration in the diet over a period of about 13 weeks), Report 21022, DACO: 4.3.1, IIA 5.3.2

2331397	1992, KWG 4168 - Subchronic toxicologic study in B6C3F1 mice to examine effects on the skin, kidneys, liver and urinary bladder (thirteen-week administration by gavage and eight-week recovery period), Report 21330, DACO: 4.3.1, IIA 5.3.2
2331399	1994, KWG 4138 - 13-week subchronic feeding study in beagle dogs, Report BC7442, MRID 45090209, DACO: 4.3.2, IIA 5.3.3
2331400	1997, Technical grade KWG 4168: A subchronic toxicity study in the beagle dog, Report BC8105, MRID 45090210, DACO: 4.3.2, IIA 5.3.3
2331402	1995, Technical grade KWG 4168 - A chronic toxicity feeding study in the beagle dog, Report BC7461, MRID 45090214, DACO: 4.3.2, IIA 5.3.4
2399853	2014, Response to Spiroxamine-PMRA-HPRT-Question 6-March-2014, DACO: 4.3.2, IIA 5.3.4
2331392	1992, KWG 4168 - Subacute oral toxicity study in rats (feeding study), Report 21644, DACO: 4.3.3, IIA 5.3.1
2331393	1992, KWG 4168 - Subacute oral toxicity study in rats, Report 21841, DACO: 4.3.3, IIA 5.3.1
2331394	1996, Spiroxamine - Position paper on the no-observed adverse effect level of the subacute feeding study in rats, Report MO-99-009351, DACO: 4.3.3, IIA 5.3.1
2331407	1995, KWG 4168 - Subacute dermal toxicity study on the rabbit, Report 24357, DACO: 4.3.5, IIA 5.3.7
2331404	1992, KWG 4168 Aerosol - Study for subacute inhalation toxicity in the rat (according to OECD guideline no. 412, Report 21785, DACO: 4.3.7, IIA 5.3.5
2331405	1990, KWG 4168 - Pilot study for subacute inhalation toxicity in the rat, Report 103973, MRID 45090301, DACO: 4.3.7, IIA 5.3.5
2331425	1994, KWG 4168 - Investigations of chronic toxicity and carcinogenicity in Wistar rats (administration in diet over 2 years), Report 23580, DACO: 4.4.1, 4.4.2, 4.4.4, IIA 5.5.1, IIA 5.5.2
2331426	2000, Spontaneous tumors in Wistar rats in 2-year studies performed at Bayer AG, Report MO-00-000946, DACO: 4.4.1, 4.4.4, IIA 5.5.1
2331427	1991, KWG 4168 : Range-finding study for a two-generation study in rats, Report 20320, MRID 45254102, DACO: 4.4.1, 4.4.4, IIA 5.5.1
2331429	1995, KWG 4168 - Summary report of a oncogenicity study and a supplementary six-months chronic toxicity study in B6C3F1 mice, Report 23975, DACO: 4.4.3, IIA 5.5.3
2331430	1997, KWG 4168 - Supplementary oncogenicity study in B6C3F1 mice (Administration in diet over 2 years), Report 26780, DACO: 4.4.3, IIA 5.5.3

2331433	1993, KWG 4168 - Two generation Study on rats, Report 23115, DACO: 4.5.1, IIA 5.6.1
2331434	2008, Technical grade Spiroxamine (BAY KWG 4168): A two generation reproductive toxicity study in the Wistar rat, Report 201823, MRID 47526301, DACO: 4.5.1, IIA 5.6.1
2331453	1994, Historical control and method validation studies in rats for acute and subchronic neurotoxicity screening battery, Report 23337, DACO: 4.5.12, 4.5.13, IIA 5.7.1, IIA 5.7.4
2331452	1994, KWG 4168 - Acute oral neurotoxicity screening study in rats, Report 23503, DACO: 4.5.12, IIA 5.7.1
2331455	1995, KWG 4168 - Subchronic neurotoxicity sreening study in Wistar rats (thirteen-week administration in the diet), Report 24089, MRID 45090212, DACO: 4.5.13, IIA 5.7.4
2331437	1992, Embryotoxicity study (including teratogenicity) with KWG 4168 technical in the rat, Report R5574, DACO: 4.5.2, IIA 5.6.10
2331440	1993, Dose range-finding embryotoxicity study (including teratogenicity) with KWG 4168 technical in the rat, Report R6072, DACO: 4.5.2, IIA 5.6.10
2331441	1995, Historical control data of rats - Rat Wist Hanlbm: Wist (SPF) - Data from prenatal developmental toxicity studies performed during 1991 to 1995, DACO: 4.5.2, IIA 5.6.10
2331444	1993, Dose range-finding embryotoxicity study (including teratogenicity) with KWG 4168 technical in rat (dermal application), Report 106820, MRID 45090216, DACO: 4.5.2, IIA 5.6.10
2331446	Golub, M. S.; Campbell, M. A.; Kaufmann, F. L.; Iyer, P.; Li, L. H.; Donald, J. M.; Morgan, J. E., 2004, Effects of restraint stress in gestation: Implications for rodent developmental toxicology studies, Birth Defects Research (Part B), 71: 26-36, DACO: 4.5.2, IIA 5.6.10
2331447	1994, FCR 1272 - Explantory report on results and mechanistic studies for embryortoxicity effects in rats after inhalation, Report 23219, DACO: 4.5.2, IIA 5.6.10
2331448	1995, KWG 4168 - Studies for embryotoxic effects in rabbits following oral administration, Report 23662, DACO: 4.5.3, IIA 5.6.11
2331449	2000, Pilot developmental study on rabbits cited in report 23662: KWG 4168 - Studies for embryotoxic effects in rabbits following oral administration dated 1995-01-20, amended 2000-10-10), DACO: 4.5.3, IIA 5.6.11
2331450	1996, Historical control data of malformations in control and treated groups of rabbits CHBB:HM - Data from prenatal developmental toxicity studies performed during 1989 and 1996, DACO: 4.5.3, IIA 5.6.11

2331409	1990, KWG 4168 - Salmonella/microsome test, Report 106811, MRID 45090223, DACO: 4.5.4, IIA 5.4.1
2331411	1995, KWG 4168-Bisadduct - Salmonella/microsome test plate incorporation and preincubation method - revised final report, first revision of report 24104, Report 109436, MRID 45254113, DACO: 4.5.4, IIA 5.4.1
2331413	1995, Spiroketal - Salmonella/microsome test plate incorporation and preincubation method, Report 109437, MRID 45254114, DACO: 4.5.4, IIA 5.4.1
2331415	1999, EP-Amin (intermediate for KWG 4168) - Special study - Ames test screening, Report 109435, MRID 45254112, DACO: 4.5.4, IIA 5.4.1
2331419	1991, KWG 4168 - Mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay in vitro, Report 20682, DACO: 4.5.5, IIA 5.4.3
2331420	1991, KWG 4168 - Mutagenicity test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro, Report 20446, DACO: 4.5.5, IIA 5.4.3
2399852	2003, EPA DER of (1998) KWG 4168-N-Oxide. V79-HPRT Test *In Vitro* for the Detection of Induced Forward Mutations, MRID 45254110, DACO: 4.5.5, IIA 5.4.3
2331417	1995, KWG 4168 - *In vitro* mammalian chromosome aberration test with Chinese hamster ovary (CHO) cells, Report 24216, DACO: 4.5.6, IIA 5.4.2
2331423	1991, KWG 4168 - Micronucleus test on the mouse, Report 106813, MRID 45090225, DACO: 4.5.7, IIA 5.4.4
2331379	1992, [Cyclohexyl-1-14C] KWG 4168: Investigation on the distribution of the total radioactivity in the rat by whole-body autoradiography, Report PF3779, DACO: 4.5.9, IIA 5.1.1
2331380	1995, KWG 4168: Investigations on the existence and behaviour of the N-oxide in the warm-blooded animal under in vivo- and in vitro-conditions, Report PF4026, DACO: 4.5.9, IIA 5.1.1
2331381	1996, [1,3-dioxolan-4-14C]KWG 4168: Biokinetic behaviour and metabolism in rats, Report PF4153, DACO: 4.5.9, IIA 5.1.1, IIA 5.1.2
2331378	1995, [Cyclohexyl-1-14C] KWG 4168: General rat metabolism study, Report PF4032, MRID 45090228, DACO: 4.5.9, IIA 5.1.1, IIA 5.1.2, IIA 5.1.3
2331457	1995, KWG 4168-N-Oxide - Pilot study for acute oral toxicity in female rats, Report 23716, DACO: 4.8, IIA 5.8
2331458	1995, KWG 4168-N-Oxid - Salmonella/microsome test plate incorporation and preincubation method, Report 24105, DACO: 4.8, IIA 5.8
2331459	1998, KWG 4168-N-Oxid - *In vitro* chromosome aberration test with chinese hamster V79 cells, Report 27715, DACO: 4.8, IIA 5.8

2331460	1998, KWG 4168 N-Oxide - Study for subchronic oral toxicity in rats (feeding study over 13 weeks), Report 27475, MRID 45254116, DACO: 4.8, IIA 5.8
2331461	1998, KWG 4168-N-Oxid - V79-HPRT test in vitro for the detection of induced forward mutations, Report 28143, DACO: 4.8, IIA 5.8
2331462	1998, KWG 4168 N-Oxide - Study for subacute oral toxicology in rats (feeding study over 4 weeks) - 1st revised version of report no. 28161 from Nov. 17, 1998-, Report 28161A, MRID 45254128, DACO: 4.8, IIA 5.8
2409970	2014, Spiroxamine-PMRA-HPRT-question-4Apr-14.ppt, DACO: 4.8, IIA 5.8
2332344	1994, KWG 4168 500 EC 04023/0021 - Study on the acute oral toxicity in rats, Lab Report 22956, DACO: 4.6.1, IIIA 7.1.1
2332345	1998, KWG 4168 500 EC 04023/0626 - Study for acute oral toxicity in rats, Lab Report 27457, DACO: 4.6.1, IIIA 7.1.1
2332346	1994, KWG 4168 500 EC 04023/0021 - Study on the acute dermal toxicity in rats, Lab Report 22957, DACO: 4.6.2, IIIA 7.1.2
2332347	2000, KWG 4168 500 EC 04023/0626 (c.n.: spiroxamine) - Study on acute inhalation toxicity in rats according to OECD no. 403, Lab Report 29759, DACO: 4.6.3, IIIA 7.1.3
2332348	1992, KWG 4168 EC 00500 04023/0021 - Study for skin and eye irritation/corrosion in rabbits, Lab Report 21260, DACO: 4.6.4, 4.6.5, IIIA 7.1.4, IIIA 7.1.5
2332349	1993, KWG 4168 500 EC 04023/0021- Studies on skin sensitizing effect on guinea pigs (Buehler Test), Lab Report 22546, DACO: 4.6.6, IIIA 7.1.6
2388647	2008, Spiroxamine EC 500 G (Project: Spiroxamine (KWG 4168)) - Local lymph node assay in mice (LLNA/IMDS), Lab Report AT04681, DACO: 4.6.6, IIIA 7.1.6
2004944	Agricultural Handler Exposure Task Force (AHETF), 2010. Agricultural Handler Exposure Scenario Monograph: Open Cab Airblast Application of Liquid Sprays. Report Number AHE1006. Submission #2005-2695. DACO: 5.3, 5.4.
2115788	Agriculture Re-entry Task Force (ARTF), 2008. Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients. Submission #2006-0257.

3.0 Environment

PMRA Document Number	Reference
2331268	1995, Hydrolysis of KWG 4168 in sterile aqueous buffer solutions, DACO: 7.4.5,8.2.3.2,IIA 2.9.1,IIA 6.5.1,IIA 7.5
2331269	1997, Hydrolysis of KWG 4168 (Spiroxamine, proposed) as a function of pH, DACO: 7.4.5,8.2.3.2,IIA 2.9.1,IIA 6.5.1,IIA 7.5
2331270	1995, Photolysis of KWG 4168 in aqueous solution, DACO: 8.2.3.3.2,IIA 2.9.2,IIA 7.6
2331276	1994, Calculation of the chemical lifetime of KWG 4168 in the troposphere, DACO: 8.2.3.3.3,IIA 2.10,IIA 7.10
2331365	1996, Storage stability of KWG 4168 and the metabolites KWG 4557 (desethyl-KWG 4168) and KWG 4669 (despropyl-KWG 4168) in soil, DACO: 8.2.2.1,IIA 4.4,IIA 7.3.1
2331526	1994, [Cyclohexyl-1-14C] KWG 4168 residues in following crops, DACO: 7.4.4,8.2.3.4.2,IIA 6.6.2,IIA 7.1.1
2331535	1995, Aerobic degradation and metabolism of KWG 4168 in soil, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.1,IIA 7.2.2
2331536	1994, Aerobic degradation of KWG 4168 in BBA soil 2.2, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.1
2331537	1997, Degradation and metabolism of KWG 4168 in soil aerobic soil metabolism, DACO: 8.2.3.4.2,IIA 7.1.1
2331538	2008, [1,3-Dioxolane-4-14C]spiroxamine: Metabolic screening for degradation pathways under aerobic conditions in soil, DACO: 8.2.3.4.2,IIA 7.1.1
2331539	1997, Anaerobic aquatic metabolism of the active ingredient KWG 4168, DACO: 8.2.3.4.4,8.2.3.6,IIA 7.1.2,IIA 7.8.3
2331541	1995, Photolysis of KWG 4168 on soil surfaces (according to EPA guidelines), DACO: 8.2.3.3.1,IIA 7.1.3
2331542	1995, Dissipation of KWG 4168 in soils under field conditions (Germany and Great Britain), DACO: 8.2.4.6,IIA 7.3.1,IIA 7.4.8
2331543	1995, Dissipation of KWG 4168 in soils under field conditions, DACO: 8.2.4.6,IIA 7.3.1,IIA 7.4.8
2331544	1995, Dissipation of KWG 4168 in soils under field conditions (Great Britain and France), DACO: 8.2.4.6,IIA 7.3.1,IIA 7.4.8
2331546	1997, Storage stability of KWG 4168 and the metabolites desethyl-KWG 4168 (KWG 4557) and despropyl-KWG 4168 (KWG 4669) in soil, DACO: 8.3.2,IIA 7.3.1
2331548	1998, Storage stability of KWG 4168 and the metabolites desethyl-KWG 4168 (KWG 4557), despropyl-KWG 4168 (KWG 4669) and KWG 4168 N-oxide (WAK 6301) in soil, DACO: 8.3.2,IIA 7.3.1
2331549	1996, Dissipation of KWG 4168 in soils under field conditions (France and Italy cropped soils), DACO: 8.3.2,IIA 7.3.1
2331550	1996, Dissipation of KWG 4168 in soils under field conditions (France and Italy bare soils), DACO: 8.3.2,IIA 7.3.1

2331554	1998, Terrestrial field dissipation of KWG 4168 in Fresno, California, 1995, DACO: 8.3.2,IIA 7.3.1
2331556	1995, Adsorption/Desorption of KWG 4168 on soils, DACO: 8.2.4.2,IIA 7.4.1
2331557	1996, Adsorption/desorption of KWG 4168 on five American soils, DACO: 8.2.4.2,IIA 7.4.1
2331558	1996, Adsorption/desorption of KWG 4557 on four different soils, DACO: 8.2.4.2,IIA 7.4.2
2331559	1996, Adsorption/Desorption of KWG 4669 on four different soils, DACO: 8.2.4.2,IIA 7.4.2
2331560	1997, Adsorption/desorption of [cyclohexyl-1-14C] WAK 6301 on four different soils, DACO: 8.2.4.2,IIA 7.4.2
2331561	1994, Leaching behaviour of KWG 4168 aged in soils, DACO: 8.2.4.3.2,IIA 7.4.5
2331562	1998, Leaching behaviour of KWG 4168 after aging in soil (aged leaching) in accordance with EPA requirements, DACO: 8.2.4.3.2,IIA 7.4.5
2331564	1995, Aerobic metabolism of KWG 4168 in an aquatic model ecosystem, DACO: 8.2.3.5.2,8.2.3.5.4,8.2.3.6,IIA 7.8.1,IIA 7.8.3
2331565	1996, Aerobic metabolism of KWG 4168-N-Oxide in an aquatic model ecosystem, DACO: 8.2.3.6,IIA 7.8.3
2331567	2008, [1,3-Dioxolane-4-14C]spiroxamine: Aerobic aquatic metabolism, DACO: 8.2.3.6,IIA 7.8.3
2331569	1994, Determination of the volatilization behaviour of KWG 4168 EC 500 in a field trial, DACO: 8.2.3.3.3,IIA 7.10
2331570	1998, Volatilisation behaviour of KWG 4168 EC 500 in a field trial, treatment of bare soil, DACO: 8.2.3.3.3,IIA 7.10
2331575	2010, Annex B - Spiromaine - B-8: Environmental fate and behaviour, DACO: 12.5.8, 12.5.8 (OECD), 8.2.3.6, 8.2.4.6, 8.5.1, 8.6, IIA 7.13
2331576	1994, KWG 4168 (technical grade): Acute oral toxicity to bobwhite quail, DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1
2331577	1994, KWG 4168 (technical grade): 5-day dietary LC50 to bobwhite quail, DACO: 9.6.2.4,9.6.2.5,IIA 8.1.2
2331578	1995, KWG 4168 (technical grade): 5-day dietary LC50 to mallard duck, DACO: 9.6.2.6,IIA 8.1.3
2331580	1995, Effects of a subchronic dietary exposure of KWG 4168 techn. on bobwhite quail including effects on reproduction and health, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2331581	2006, Comment on study SXR/REP 04 (GLP-No.: E 298 0738-7 by Schmuck; R. (1995): Effects of subchronic dietary exposure of KWG 4168 techn. on bobwhite quail including effects on reproduction and health, Bayer AG, Leverkusen, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2331582	2008, Evaluation of historical control data on bobwhite quail 14-d chick body weights to establish the NOAEL in the study SXR/REP 04 with spiroxamine, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2331583	1997, KWG 4168 Technical - A reproduction study with mallard (*Anas platyrhynchos*), DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2331585	1994, KWG 4168 techn.- Acute toxicity (96h) to rainbow trout in a static test, DACO: 9.5.2.1,9.5.2.3,IIA 8.2.1.1

2331586	1994, KWG 4168 techn.- Acute toxicity (96 h) to bluegill in a static test, DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2
2331587	2008, Acute toxicity of spiroxamine to zebra fish (*Danio rerio*) over 96 hours, DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2
2331588	2008, Spiroxamine - fish screening assay (FSA) with fathead minnow, DACO: 9.5.2.3,9.5.2.4,IIA 8.2.2
2331589	1994, KWG 4168 techn. -Early life stage toxicity to rainbow trout (*Oncorhynchus mykiss*) under flow-through conditions, DACO: 9.5.3.1,IIA 8.2.4
2331590	1996, 14C-KWG 4168 - Early life stage toxicity to rainbow trout (*Oncorhynchus mykiss*) under flow-through conditions (supplemental raw data), DACO: 9.5.3.1,IIA 8.2.4
2331591	2008, Effects of spiroxamine technical on selected early life stages of rainbow trout (*Oncorhynchus mykiss*) in a static water/sediment system, DACO: 9.5.3.1,IIA 8.2.4
2331596	2008, Zebra fish (*Danio rerio*), life cycle test, flow through conditions, DACO: 9.5.3.2,IIA 8.2.5
2331597	1995, KWG 4168: Bioconcentration in bluegill-sunfish, DACO: 9.5.6,IIA 8.2.6.1
2331598	1997, [Cyclohexyl-1-14C] KWG 4168: Metabolism in the edible parts of bluegill sunfish, DACO: 9.5.6,IIA 8.2.6.1
2331599	1994, Acute toxicity of KWG 4168 (tech.) to waterfleas (*Daphnia magna*), DACO: 9.3.2,IIA 8.3.1.1
2331600	1996, Orientating waterflea toxicity of N-oxide-KWG 4168, DACO: 9.3.2,IIA 8.3.1.1
2331601	1996, Acute toxicity of 14-C-KWG 4168 (tech.) to water fleas (*Daphnia magna*), DACO: 9.3.2,IIA 8.3.1.1
2331602	1997, Acute toxicity of 14C-KWG 4168 (tech.) to water fleas (*Daphnia magna*) under flow-through test conditions, DACO: 9.3.2,IIA 8.3.1.1
2331603	1994, Influence of KWG 4168 (techn.) on the reproduction rate of water fleas, DACO: 9.3.3,IIA 8.3.2.1
2331604	1998, Influence of 14C-KWG 4168 (technical) on the reproduction of water fleas under flow-through test conditions, DACO: 9.3.3,IIA 8.3.2.1
2331605	1996, Influence of 14C-KWG 4168 (techn.) on the reproduction rate of water Fleas, DACO: 9.3.3,IIA 8.3.2.1
2331606	2000, Fate of spiroxamine in enclosures of an experimental ditch, DACO: 9.4.7,IIA 8.3.3
2331607	2008, Biological effects and fate of Spiroxamine EC 500 in outdoor mesocosm ponds simulating actual exposure conditions in agricultural use, DACO: 9.4.7,IIA 8.3.3
2331613	1994, Influence of KWG 4168 on the growth of the green alga, *Scenedesmus subspicatus*, DACO: 9.8.2,9.8.3,IIA 8.4
2331614	1995, Influence of KWG 4168 on the growth of the green alga, *Selenastrum capricornutum*, DACO: 9.8.2,9.8.3,IIA 8.4
2331615	1995, Growth of *Selenastrum capriornutum* cells in nutrient medium containing high concentrations of KWG 4168, DACO: 9.8.2,9.8.3,IIA 8.4

2331616	1998, Toxicity of 14C-KWG 4168 to the green alga *Selenastrum capricornutum*, DACO: 9.8.2,9.8.3,IIA 8.4
2331618	2006, *Desmodesmus subspicatus* growth inhibition test with Spiroxamine, DACO: 9.8.2,9.8.3,IIA 8.4
2331619	2000, Growth of the green alga, *Scenedesmus subspicatus*, during and after exposure with spiroxamine (KWG 4168), DACO: 9.8.2,9.8.3,IIA 8.4
2331620	1997, Toxicity of KWG 4168 technical to the blue-green alga *Anabaena flos-aquae*, DACO: 9.8.2,9.8.3,IIA 8.4
2331621	2006, Non-GLP recalculation report *Navicula pelliculosa* growth inhibition test with 14 C - KWG 4168, DACO: 9.8.2,9.8.3,IIA 8.4
2331622	2007, *Desmodesmus subspicatus* growth inhibition test with spiroxamine - desethyl, DACO: 9.8.2,9.8.3,IIA 8.4
2331623	2007, *Desmodesmus subspicatus* growth inhibition test with spiroxamine - N - oxid, DACO: 9.8.2,9.8.3,IIA 8.4
2331624	1997, Toxicity of 14C-KWG 4168 to the freshwater diatom *Navicula pelliculosa*, DACO: 9.8.2,9.8.3,IIA 8.4
2331625	1998, Influence of 14C-KWG 4168 (techn.) on development and emergence of larvae of *Chironomus riparius* in a water-sediment stystem, DACO: 9.9,IIA 8.5.2
2331626	1996, KWG 4168 - toxicity (14 days) to *Lemna gibba* G3, DACO: 9.8.5,IIA 8.6
2331627	1997, 14C-KWG 4168- toxicity (14 days) to *Lemna gibba* G3, DACO: 9.8.5,IIA 8.6
2331628	2008, Non-GLP recalculation report: KWG 4168 - toxicity (14 days) to *Lemna gibba* G3, DACO: 9.8.5,IIA 8.6
2331629	2008, Non-GLP recalculation report: 14C-KWG 4168- toxicity (14 days) to *Lemna gibba* G3, DACO: 9.8.5,IIA 8.6
2331631	1994, KWG 4168 - Acute toxicity to honey bees (*Apis mellifera*), DACO: 9.2.4.2,IIA 8.7.1
2331633	1994, An laboratory evaluation of the side-effects of Fungicide KWG 4168, on the parasitic wasp *Aphidius rhopalosiphi*, when applied to barley seedlings, DACO: 9.2.6,IIA 8.8.2.1
2331634	1994, Acute effects of repeated spray application of KWG 4168 on carabid beetles (*Bembidion tetracolum*) under extended laboratory conditions, DACO: 9.2.5,IIA 8.8.2.3
2331635	1993, Toxicity of KWG 4168 (techn.) to earthworms, DACO: 9.2.3.1,IIA 8.9.1
2331636	2007, KWG 4168-Desethyl (technical): Effects on survival, growth and reproduction on the earthworm *Eisenia fetida* tested in artificial soil with 5 % peat, DACO: 9.2.3.1,IIA 8.9.2
2331637	2007, KWG 4168-N-Oxid (technical): Effects on survival, growth and reproduction on the earthworm *Eisenia fetida* tested in artificial soil with 5 % peat, DACO: 9.2.3.1,IIA 8.9.2
2331640	1998, Toxicity of 14C-KWG 4168 to the marine diatom *Skeletonema costatum*, DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1

2331644	2007, KWG 4168 tech.: Influence on the reproduction of the collembola species *Folsomia candida* tested in artificial soil with 5 % peat, DACO: 9.3.4,9.6.6,9.9,IIA 8.16.1
2331645	2007, KWG 4168-desethyl (Metabolite of KWG 4168): Influence on the reproduction of the collembola species *Folsomia candida* tested in artificial soil with 5 % peat, DACO: 9.3.4,9.6.6,9.9,IIA 8.16.1
2331646	2007, KWG 4168-despropyl (Metabolite of KWG 4168): Influence on the reproduction of the collembola species *Folsomia candida* tested in artificial soil with 5 % peat, DACO: 9.3.4,9.6.6,9.9,IIA 8.16.1
2331651	2010, Annex B - Spiromaine - B-9: Ecotoxicology, DACO: 12.5.9, 12.5.9 (OECD), 9.3.4, 9.6.6, 9.9, IIA 8.16.1
2332363	1995, KWG 4168 (EC 500): Acute oral toxicity to bobwhite quail, DACO: 9.6.4,IIIA 10.1.6
2332374	1994, Acute toxicity of KWG 4168 EC 500 to waterfleas (*Daphnia magna*), DACO: 9.3.2,IIIA 10.2.2.2
2332375	1994, Influence of KWG 4168 500 EC on the growth of the green alga, *Scenedesmus subspicatus*, DACO: 9.8.2,9.8.3,IIIA 10.2.2.3
2332378	1994, Influence of KWG 4168 EC 500 on development and emergence of larvae of *Chironomus riparius*, DACO: 9.3.5,IIIA 10.2.6.2
2332383	1994, KWG 4168 EC 500 - Acute toxicity to honey bees (*Apis mellifera*), DACO: 9.2.8,IIIA 10.4.2.1
2332384	1997, Testing toxicity to honeybee - *Apis mellifera* L. (laboratory) according to EPPO Guideline No. 170 (1992) KWG 4168 EC 500, DACO: 9.2.8,IIIA 10.4.2.1
2332385	1994, Toxicity testing of KWG 4168 EC 500 to honey bees (*Apis mellifera* L.) (Hymenoptera, Apidae) semi field study, DACO: 9.2.8,IIIA 10.4.4
2332387	1995, Field evaluation of the toxicity of KWG 4168 EC 500 to foraging honey bees (*Apis mellifera*) under cage test field conditions, DACO: 9.2.8,IIIA 10.4.4
2332388	1995, Testing toxicity to honeybee - *Apis mellifera* L. under field conditions - KWG 4168 EC 500, fungicid (BAY 12260 F), DACO: 9.2.9,IIIA 10.4.5
2332389	1994, Acute effects of a multiple spray application of the fungicide KWG 4168 (500 EC) on carabid beetles (*Bembidion tetracolum*) under laboratory conditions, DACO: 9.2.8,IIIA 10.5.1
2332390	1995, Acute effects of a repeated spray treatment with the fungicide KWG 4168 EC 500 on lycosid spiders (*Pardosa agricola*) under laboratory conditions, DACO: 9.2.8,IIIA 10.5.1
2332391	1994, Testing the effect of KWG 4168 on the predaceous mite *Typhlodromus pyri* Scheuten (*Acari: Phytoseiidae*) using ventilated glass cages (coffin cells), DACO: 9.2.8,IIIA 10.5.1
2332392	1994, Testing toxicity to beneficial arthropods - green lacewing - *Chrysopa carnea Steph*. according to modified IOBC guideline (Bigler 1988) KWG 4168 EC 500, DACO: 9.2.8,IIIA 10.5.1
2332393	1995, Effects of KWG 4168 EC 500 on the life cycle of ladybird beetles (*Coccinella septempunctata*) under laboratory conditions, DACO: 9.2.8,IIIA 10.5.1

2332394	2000, KWG 4168 EC 500: A laboratory dose-response study to evaluate the effects on the predaceous mite *Typhlodromus pyri Scheuten* (*Acari: Phytoseiidae*) in ventilated glass cages, DACO: 9.2.8,IIIA 10.5.1
2332395	2000, A laboratory test to determine the effects of spiroxamine EC 500 on the parasitic wasp, *Aphidius rhopalosiphi*, DACO: 9.2.8,IIIA 10.5.1
2332396	2000, Spiroxamine EC 500: A laboratory study to evaluate the effects on the ladybird *Coccinella septempunctata* (*Cucujoidea: Coccinellidae*), DACO: 9.2.8,IIIA 10.5.1
2332397	2001, KWG 4168 EC 500: A laboratory study to evaluate the effects on the green lacewing, *Chrysoperla carnea* (*Neuroptera: Chrysopidae*), DACO: 9.2.8,IIIA 10.5.1
2332398	1995, Acute effects of a repeated spray treatment with the fungicide KWG 4168 EC 500 on lycosid spiders *(Pardosa spp*., mainly *P. agricola*) under extended laboratory conditions, DACO: 9.2.8,IIIA 10.5.2
2332399	2007, Toxicity to the parasitoid wasp *Aphidius rhopalosiphi* (DESTEPHANI-PEREZ) (*Hymenoptera: Braconidae*) using an extended laboratory test Spiroxamine EC 500 g/l, DACO: 9.2.8,IIIA 10.5.2
2332403	1995, Effects of KWG 4168 EC 500 on the life cycle of ladybird beetles (*Coccinella septempunctata*) under semifield conditions, DACO: 9.2.9,IIIA 10.5.3
2332404	1998, Effects on *Typhlodrdomus pyri* predatory mites of 'KWG 4168 EC 500' under typical vine culture conditions on grape vines, Germany 1997, DACO: 9.2.9,IIIA 10.5.4
2332405	1999, Effects of 'spiroxamine EC 500' on predatory mites (*Typhlodromus pyri*) under typical vine culture conditions on grape vines (6 apps), Germany 1999, DACO: 9.2.9,IIIA 10.5.4
2332406	1999, Effects of 'spiroxamine EC 500' on predatory mites (*Typhlodromus pyri*) under typical vine culture conditions on grape vines (4 apps), Germany 1999, DACO: 9.2.9,IIIA 10.5.4
2332407	1996, A field experiment to determine the effects of KWG 4168 EC 500 on the predatory mite *Typhlodromus pyri* (*Acari, Phytoseiidae*) in vines in Germany, DACO: 9.2.9,IIIA 10.5.4
2332409	1996, A field experiment to determine the effects of KWG 4168 EC 500, on the predatory mite *Amblyseius aberrans* (*Acari: Phytoseiidae*) in vines in Southern Italy, DACO: 9.2.9,IIIA 10.5.4
2332411	1994, Influence of KWG 4168 EC 500 on the reproduction of earthworms (*Eisenia fetida*), DACO: 9.2.8,IIIA 10.6.3
2332412	2000, Influence of Spiroxamine EC 500 on the reproduction of earthworms (*Eisenia fetida*) tested with 5 % peat in the test substrate, DACO: 9.2.8,IIIA 10.6.3
2332419	1999, Herbicidal screening data for KWG 4168 EC 500, DACO: 9.8.7,IIIA 10.8.1.4
2332420	2001, Spiroxamine EC 500 - Terrestrial plants toxicity, vegetative vigor, tier II, DACO: 9.8.6,IIIA 10.8.1.2
2332421	2008, Spiroxamine EC 500 G: Effect on the vegetative vigour of two non crop species of non-target terrestrial plants (Tier 2), DACO: 9.8.6,IIIA 10.8.1.2

2332422	2001, Spiroxamine EC 500 - Terrestrial plants toxicity, seedling emergence, Tier II, DACO: 9.8.6,IIIA 10.8.1.3
2332424	2008, Spiroxamine EC 500 G: Effect on the seedling growth of two non crop species of non-target terrestrial plants (Tier 2), DACO: 9.8.6,IIIA 10.8.1.3
2358501	1997, Anaerobic Aquatic Metabolism pf the Active Ingredient KWG 4168, DACO: 8.2.3.5.5,8.2.3.5.6,IIA 7.8.2

4.0 Value

PMRA Document Number	Reference
2331288	2010, Annex B - Spiromaine - B-3: Data on application and further information, DACO: 10.6, 12.5.10, 2.16, 8.6, IIA 3.10
2332333	2010, Rationale supplementing relevance of European efficacy data for the registration of sprioxamine to combat disease on grapes in Canada, DACO: 10.2.1, 10.2.2, 10.2.3.3, 10.2.3.4, 10.3.2, IIIA 6.1.2, IIIA 6.1.3, IIIA 6.2.1
2332334	1996, Trial report - Prosper 500 EC on red and white wines; vinification studies, DACO: 10.3.2, IIIA 6.1.4.2
2332335	1992, Etude des effets non intentionnels de produits phytopharmaceutiques (anti-oidium) sur l'elaboration et la qualite des vins, DACO: 10.3.2, IIIA 6.1.4.2
2332336	1998, Etude des effets non intentionnels de produits phytopharmaceutiques (anti-oidium) sur l'elaboration et la qualite des vins, DACO: 10.3.2, IIIA 6.1.4.2
2332337	1997, Study of non-intentional effects of plant protection products (anti powdery mildew) on the confection and quality of wines, DACO: 10.3.2, IIIA 6.1.4.2
2332338	1997, Rapport d'etude des effects non intentionnels sur l'elaboration et la qualite des mouts et des vins, DACO: 10.3.2, IIIA 6.1.4.2
2332339	1997, Etude des effets non intentionnels de produits phytopharmaceutiques (anti-oidium) sur l'elaboration et la qualite des vins - Methode CEB 143, DACO: 10.3.2, IIIA 6.1.4.2
2332340	1997, Etude des effets non intentionnels de produits phytopharmaceutiques (anti-oidium) sur l'elaboration et la qualite des vins - Methode CEB no 143, DACO: 10.3.2, IIIA 6.1.4.2
2332341	1997, Rapport d'etude des effects non intentionnels sur l'elaboration et la qualite des mouts et des vins (campagne 1996-1997) - Rapport final, DACO: 10.3.2, IIIA 6.1.4.2
2332342	1998, Etude du produit antioidium BAY 9715 - Annee 1997 - Methode CEB 143 - Incidence organoleptique des produits de traitement sur la qualite des eaux-de-vie de Cognac, DACO: 10.3.2, IIIA 6.1.4.2
2332343	2008, Spiroxamine - Sensitivity monitoring and anti-resistance strategy, DACO: 10.5.3,IIIA 6.2.8

2332439	2008, Tier 2 summary of the efficacy data and information on the plant protection product for spiroxamine EC 500 (500 g/L), DACO: 10.2.1, 10.2.2, 12.7, Document M
2387231	2013, Compilation of trial report for SPX EC500 - Spiroxamine EC 500 (500 g/L) - Efficacy on powdery mildew - 9 trials BCS France - Grapes, DACO: 10.2.3.4, IIIA 6.1.3
2387232	2013, Compilation of trial report for SPX EC500 - Spiroxamine EC 500 (500 g/L) - Efficacy on powdery mildew - 9 trials BCS France - Grapes, DACO: 10.2.3.4, IIIA 6.1.3
2387233	2013, Summary of the efficacy data and information on the plant protection product for Spiroxamine EC 500 (500 g/L), DACO: 10.2.3.4, IIIA 6.1.3
2387234	2013, Compilation of trial report for Spiroxamine EC 500 (500 g/L) - Efficacy tests - Grapevine - KIIIA 6.1.3, DACO: 10.2.3.4, IIIA 6.1.3
2387235	2013, Registration report - Part B - Section 7: Efficacy data and information - Detailed summary - Spiroxamine EC 500 (500 g/l) - Southern zone - Zonal rapporteur member state: none - National addendum - France, DACO: 10.2.3.4, IIIA 6.1.3
2387236	2013, Summary of the efficacy data and information on the plant protection product Spiroxamine EC 500 (500 g/L), DACO: 10.2.3.4, IIIA 6.1.3
2387240	2013, Efficacy Trial Reports (supplement for M-367732-01-1), DACO: 10.2.3.4, IIIA 6.1.3
2389479	2005, Trial report FD0DEU920OZI4, DACO: 10.2.3.4,IIIA 6.1.3
2396653	1997, Procedura operative CEB 143 per la minivinificazione in bianco con defecazione a freddo del mosto, DACO: 10.3.2, IIIA 6.1.4.2