



Evaluation Report for Category A, Subcategory 1.3 Application

Application Number: 2020-4760
Application: New Active Ingredient – Maximum residue Limits (MRLs) only
Product: Spiropidion Technical Insecticide
Registration Number: Not Applicable
Active ingredient (a.i.): Spiropidion
PMRA Document Number: 3369683

Purpose of Application

The purpose of this submission is to establish maximum residue limits (MRLs) for residues of spiropidion, a new active ingredient to Canada, in/on imported potato, soybean, tomato, pepper, cucumber, squash, watermelon and cantaloupe.

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance Spiropidion

Function Insecticide

Chemical name

1. International Union of Pure and Applied Chemistry (IUPAC) 3-(4-chloro-2,6-dimethylphenyl)-8-methoxy-1-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-en-4-yl ethyl carbonate

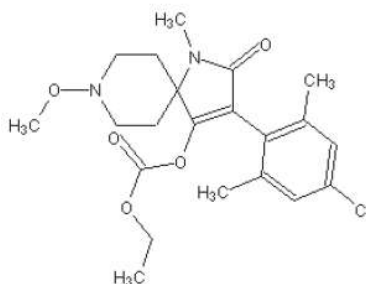
2. Chemical Abstracts Service (CAS) 3-(4-chloro-2,6-dimethylphenyl)-8-methoxy-1-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-en-4-yl ethyl carbonate

CAS number 1229023-00-0

Molecular formula C₂₁H₂₇ClN₂O₅

Molecular weight 422.9

Structural formula



Purity of the active ingredient 97.9%

1.2 Physical and Chemical Properties of the Active Ingredient

Technical Product— Spiropidion Technical Insecticide

Property	Result																
Colour and physical state	Off-white solid																
Odour	Odourless																
Melting range	134.26°C																
Boiling point	The product is a solid.																
Density	1.29 g/mL at 20°C																
Vapour pressure at 25°C	5×10^{-12} mPa																
Ultraviolet (UV)-visible spectrum	No significant absorption above 300 nm.																
Solubility in water at 25°C	0.046 g/ L																
Solubility in organic solvents at 25°C	<table border="1"><thead><tr><th>Solvent</th><th>Solubility (g/L)</th></tr></thead><tbody><tr><td>Acetone</td><td>360</td></tr><tr><td>Dichloromethane</td><td>>500</td></tr><tr><td>Ethyl acetate</td><td>300</td></tr><tr><td>Hexane</td><td>3.4</td></tr><tr><td>Methanol</td><td>250</td></tr><tr><td>Octanol</td><td>50</td></tr><tr><td>Toluene</td><td>320</td></tr></tbody></table>	Solvent	Solubility (g/L)	Acetone	360	Dichloromethane	>500	Ethyl acetate	300	Hexane	3.4	Methanol	250	Octanol	50	Toluene	320
Solvent	Solubility (g/L)																
Acetone	360																
Dichloromethane	>500																
Ethyl acetate	300																
Hexane	3.4																
Methanol	250																
Octanol	50																
Toluene	320																

<i>n</i> -Octanol-water partition coefficient (K_{ow})	$\log K_{ow} = 3.3$
Dissociation constant (pK_a)	The active ingredient will be unionized at environmental pH range of 4 to 10
Stability (temperature, metal)	<p>The active ingredient is stable when stored in a steel drum with inner varnish, polyethylene bags, high-density polyethylene (HDPE) packs, paper/PETP/Al/PE bags for 2 weeks at 54°C and for a year at 20°C.</p> <p>The active ingredient is stable for 2 weeks at 54°C when stored in glass.</p> <p>The active ingredient was not observed to be corrosive when the test samples were exposed to metals (aluminum & iron) and metals ions (aluminum acetate & iron (II) acetate) for 7 and 14 days at 20°C ± 2°C and at 40°C ± 2°C.</p> <p>The active ingredient was not observed to be corrosive when the test samples were exposed to tin, galvanized metals, steel and stainless steel for 7 days at 54°C ± 2°C.</p>

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.

2.2 Methods for Residue Analysis

A high performance liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS; QuEChERS) was developed and proposed for data generation and enforcement purposes for plant matrices. This 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. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstrating that extraction efficiency using bioincurred samples was not required.

3.0 Impact on Human and Animal Health

3.1 Hazard Assessment

3.1.1 Toxicology Summary

Spiropidion, also known as SYN546330, is a pro-insecticide belonging to the tetramic acid chemical class. As a pro-insecticide, the enol ethyl carbonate group on spiropidion is cleaved in vivo to release the active principle (SYN547305) which binds to the target site in insects. The insecticidal mode of action (MOA) of spiropidion is through the inhibition of the acetyl CoA carboxylase enzyme, leading to the inhibition of lipid biosynthesis.

A detailed review of the toxicology database for spiropidion was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The applicant also submitted an in vitro thyroid peroxidase activity study and a 90-day dietary study in rats investigating the induction of uridine 5'-diphospho-glucuronosyltransferase (UDP-GT). Additional toxicokinetic analyses for spiropidion and metabolite SYN547305 were conducted on blood samples collected from several short-term oral toxicity studies, and an in vitro study comparing the metabolism of spiropidion by rat and human liver microsomes was also provided. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The human health risk assessment also considered any relevant information found in the published literature. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with spiropidion.

Metabolism and toxicokinetic studies were conducted via gavage in both intact and bile duct-cannulated rats. In addition to the assessment of the absorption, metabolism, distribution, and elimination of spiropidion following single gavage dose administration, the database included limited toxicokinetic investigations in rats following repeated gavage dosing, and some studies incorporated a single dose via intravenous injection. For the studies that used radiolabelling, spiropidion was radiolabelled on the phenyl ring or the spirodecanone portion of the molecule. Absorption was rapid and moderate to high, ranging from 69-86% of the administered dose based on radioactive residues in urine, bile, cage wash and tissues. In the tissues, the highest concentrations of the radiolabel were detected in the liver and kidney. Excretion was fairly rapid, and occurred predominantly via the urine. The main components detected in the excreta were unchanged spiropidion as well as metabolites SYN548430, SYN547305 and hydroxyl oxidized desmethoxy SYN547305.

In a supplemental study, the toxicokinetics of the metabolite SYN547305 following single oral or intravenous dosing was also investigated. Levels of SYN547305 in blood were approximately two to five times higher than levels following administration of spiropidion. Absorption of SYN547305 was demonstrated to be higher in females when compared to males. From the

toxicokinetic investigations in the repeat dosing studies in the rat, mouse and dog, unchanged spiropidion was largely not quantifiable in the blood, and there is evidence that it was rapidly transformed to the metabolite SYN547305. From these studies, a higher concentration of SYN547305 was also observed in blood collected from females compared to males. Although the toxicokinetic analyses from some studies provided evidence for a lack of proportionality between systemic exposure and external dose, no definitive conclusions could be drawn regarding the relevance of these findings to the overall hazard characterization. In the supplemental in vitro study comparing the metabolism of spiropidion by rat and human liver microsomes, the metabolism was qualitatively similar between rat and human microsomes and was extensive for microsomes from both species, with slightly greater metabolism by rat microsomes compared to those from human liver cells.

In acute toxicity testing, spiropidion was of low acute toxicity via the oral route in rats. The metabolite SYN547435 was also of low acute toxicity in rats. Repeat-dose oral toxicity studies of short- and/or long-term duration with spiropidion were available in mice (dietary), rats (dietary), and dogs (capsule). In these studies, the most sensitive species appeared to be the dog, with severe toxicity including death or early sacrifice noted in studies of 28 days, 90 days, and 1- year in duration. Clinical signs observed in dogs prior to death included incoordination, ataxia, salivation, tremors, subdued behaviour, twitching, and abnormal respiration. It is noted that the method of dose administration (capsule in dogs versus dietary in rodents) could have contributed in part to this apparent sensitivity.

Decreases in body weight, body weight gain and food consumption were observed in repeat-dose oral toxicity studies in the rat, mouse and dog. The thyroid gland was a target organ in the rat after short- and long-term oral dosing, with findings of increased weight, follicular cell hypertrophy and colloid contractions. Based on the supplemental thyroid peroxidase activity study, neither spiropidion nor its metabolite SYN547305 inhibit rat thyroid peroxidase activity in vitro. Results from a special 90-day dietary study demonstrated that spiropidion was capable of UDP-GT enzyme induction in rats. Changes in clinical chemistry consistent with the insecticidal MOA of spiropidion, including decreased cholesterol, protein, and triglycerides, were observed in rats and mice. After long-term dosing, the bile duct was affected in male rats, with effects such as enlargement, luminal dilation, and inflammation noted, and gallstones were observed in male mice. These studies demonstrated some evidence of increased toxicity with increased duration of dosing in mice, rats and dogs.

Spiropidion was negative in several genotoxicity studies, including two bacterial reverse mutation assays, an in vitro mammalian cell forward mutation assay in mouse lymphoma cells, an in vitro micronucleus assay using human lymphocytes, and two in vivo micronucleus assays in rats. A positive finding was observed in an in vitro chromosome aberration test using human lymphocytes, but an in vivo chromosome aberration assay in rats yielded negative results. Based on the overall weight of evidence, spiropidion was considered to be negative for potential genotoxicity.

There was no evidence of tumorigenicity in the 2-year dietary combined chronic toxicity/oncogenicity study in rats or in the 80-week dietary carcinogenicity study in mice. In the 2-year rat study, there were no adverse effects observed in females at any dose level, calling into question the adequacy of the dose level selection for the assessment of tumorigenicity in female rats. However, a point of departure for chronic toxicity was able to be established. Furthermore, the overall level of concern for carcinogenic potential for spiropidion was low based on the conclusion that spiropidion does not have genotoxic potential and the lack of neoplastic lesions in the mouse carcinogenicity study or preneoplastic lesions in the other available studies. Therefore, it was concluded that the dose level selection in the 2-year rat study did not impact the hazard assessment.

In a 2-generation reproductive toxicity study conducted in rats via dietary dosing, the systemic toxicity observed in the parental females was generally consistent with findings reported in other repeat-dose toxicity studies in rats, including thyroid hypertrophy and increased thyroid weight. There were no treatment-related effects observed in the offspring or treatment-related effects on reproductive endpoints assessed (including ovarian follicle counts, estrous cycle or sperm parameters).

For the assessment of developmental toxicity, the database for spiropidion included dose tolerability studies with non-pregnant females, dose range-finding studies with pregnant animals, and main developmental toxicity studies in the rat and rabbit. Effects observed in adult animals in the tolerability and dose range-finding studies were consistent with those in the main studies. In the main rat developmental toxicity study, body weight loss that occurred early in the dosing period, lower overall body weight gain and lower food consumption were observed in maternal rats at the highest dose tested. At the same dose level, a higher incidence of accessory liver lobes was observed in rat fetuses. At the mid-dose level, a higher incidence of bifurcation of the sternum xiphoid cartilage, as well as ossified phalanges and incomplete ossification of the fifth sternebra, was observed in rat fetuses in the absence of maternal toxicity. Similarly, in the main rabbit developmental toxicity study, early body weight loss was observed in maternal animals at the highest dose tested. At the same dose level, reduced fetal body weight and increased incidences of several developmental variations (increased size of anterior and posterior fontanelle, non-ossified pubis, interrupted costal cartilage of the ribs, extra thirteenth rib with costal cartilage) were observed. At the mid-dose level, increased incidences of incomplete cartilaginous dorsal plate of the second cervical vertebra and incomplete sternum xiphoid cartilage were observed in the absence of maternal toxicity. Thus, there was evidence of sensitivity of the young in rats and rabbits as skeletal variations and effects on ossification were observed in the absence of maternal toxicity.

In an acute neurotoxicity study in rats in which spiropidion was administered via gavage, effects on body weight were observed at the mid- and high-dose levels shortly after dosing, with more severe impacts in female rats when compared to males. At the highest dose level, lower activity

counts were observed in males during the motor activity assessment and convulsions were noted in females on the day of dosing. There was no treatment-related neuropathology. Overall, the effects observed in this study were considered to be due to generalized toxicity; therefore, there was no evidence of selective neurotoxicity following acute exposure. Information was provided by the applicant to demonstrate that the criteria related to the conditional requirements for both a short-term neurotoxicity and a short-term immunotoxicity study were met. A request to waive the conditional requirement for a short-term neurotoxicity study was granted based on toxicokinetic considerations, and the lack of neurotoxic effects in other studies conducted with spiropidion and with other compounds in the same class of chemistry as spiropidion. Similarly, a request to waive the conditional requirement for a short-term immunotoxicity study was granted based on the absence of consistent effects on immune-related parameters in the available repeat-dose studies with spiropidion and the lack of immunotoxicity with other insecticidal compounds in the same class of chemistry as spiropidion.

The identification of select metabolites is presented in Appendix I, Table 1. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with spiropidion and relevant metabolites are summarized in Appendix I, Table 3.

3.1.2 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* (PCPA) 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 data¹.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including gavage developmental toxicity studies in the rabbit and rat, and a dietary 2-generation reproductive toxicity study in the rat.

With respect to potential prenatal and postnatal toxicity, there were no treatment-related effects in offspring in the reproductive toxicity study. However, there was evidence of increased sensitivity of the young in both the rat and rabbit developmental toxicity studies. In the rat developmental toxicity study, a higher incidence of bifurcation of the sternum xiphoid cartilage, as well as ossified phalanges and incomplete ossification of the fifth sternebra, was observed in rat fetuses in the absence of maternal toxicity.

¹ SPN2008-01. *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.*

Similarly, in the rabbit developmental toxicity study, increased incidences of incomplete cartilaginous dorsal plate of the second cervical vertebra and incomplete sternum xiphoid cartilage were observed in the absence of maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young. Sensitivity of the young was evident in the rat and rabbit developmental toxicity studies in the form of an increased incidence of skeletal variations occurring in the absence of maternal toxicity. Although these effects occurred in the absence of maternal toxicity, they were not considered serious in nature. On the basis of the information assessing potential sensitivity of the young, the PCPA factor was reduced to 3-fold for scenarios in which the endpoint of the variations from the rat or rabbit developmental toxicity study was used to establish the point of departure for assessing risk to women of reproductive age. For exposure scenarios involving other sub-populations, including children, the risk was considered well characterized and the PCPA factor was reduced to 1-fold.

3.2 Toxicology Reference Values

3.2.1 Route and Duration of Exposure

Potential exposure to spiropidion may occur via the diet (food only).

3.2.2 Acute Reference Dose (ARfD)

Females 13-49 Years of Age

The rat developmental toxicity study and the rabbit developmental toxicity study were selected as co-critical studies to estimate the acute dietary risk for females 13-49 years of age. The developmental NOAEL of 10 mg/kg bw/day from the rat and rabbit developmental toxicity studies was selected. At the developmental LOAEL of 30 mg/kg bw/day in the rat study, higher incidences of ossified phalanges, bifurcated sternum xiphoid cartilage and incomplete ossification of the fifth sternebra were observed. At the developmental LOAEL of 30 mg/kg bw/day in the rabbit study, higher incidences of incomplete cartilaginous dorsal plate of the second cervical vertebra and incomplete sternum xiphoid cartilage were observed. These developmental findings all occurred in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. The composite assessment factor (CAF) is thus 300. The ARfD is calculated according to the following formula:

$$\text{ARfD (females 13-49 years of age)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw of spiropidion}$$

General Population (excluding females 13-49 years of age)

To estimate the acute dietary risk for the general population, the maternal NOAEL of 30 mg/kg bw/day from the rat and rabbit developmental toxicity studies was selected. At the maternal LOAEL of 60 mg/kg bw/day, body weight loss was observed within the first few days of dosing in both studies. The selection of this point of departure is also supported by the effects in the supplemental 28-day oral toxicity study in the dog, in which no adverse effects were observed at the mid-dose level of 30 mg/kg bw/day, whereas animals administered the high dose of 100 mg/kg bw/day were euthanized after one or two doses due to adverse clinical signs. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The CAF is thus 100. The ARfD is calculated according to the following formula:

$$\text{ARfD (general population)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{30 \text{ mg/kg bw/day}}{100} = 0.3 \text{ mg/kg bw of spiropidion}$$

3.2.3 Acceptable Daily Intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 3 mg/kg bw/day from the 1-year oral toxicity study in the dog was selected. At the LOAEL of 10 mg/kg bw/day, lower body weights and body weight gains were observed in females. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The CAF is thus 100. The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{3 \text{ mg/kg bw/day}}{100} = 0.03 \text{ mg/kg bw/day of spiropidion}$$

The ADI provides a margin of 300 to the NOAEL for the variations observed in the absence of maternal toxicity in the rat and rabbit developmental toxicity studies.

3.2.4 Cancer Assessment

There was no evidence of tumourigenicity and therefore, a cancer risk assessment is not required.

3.2.5 Aggregate Toxicology Reference Values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). For spiropidion, exposure is limited to the dietary route; therefore, an aggregate assessment is not required.

3.3 Occupational/Residential Exposure

Occupational/residential exposure assessments were not required for this application.

3.4 Food Residues Exposure Assessment

3.4.1 Residues in Plant Foodstuffs

The residue definition for risk assessment in plant commodities is spiropidion and the metabolites SYN547305, SYN547435, and SYN548430, expressed as spiropidion equivalents and the residue definition for enforcement in plant commodities is spiropidion and the metabolite SYN547305, expressed as spiropidion equivalents. The data gathering/enforcement analytical method is valid for the quantitation of spiropidion, SYN547305, SYN547435, and SYN548430 residues in crop matrices. The residues of spiropidion and the metabolites SYN547305, SYN547435, and SYN548430 are stable in representative matrices from five commodity categories (high water, high oil, high protein, high starch and high acid content) for up to 24 months when stored at $\leq -13^{\circ}\text{C}$. Therefore, spiropidion residues are considered stable in all frozen crop matrices for up to 24 months. Residues of spiropidion and/or SYN547305 (residue definition for enforcement) concentrated in the following processed commodities: potato flakes (SYN547305 (3.49x)), tomato paste (spiropidion (0.3x), SYN547305 (3.7x)), and dried tomato (spiropidion (2.9x), SYN547305 (12.2x)). Crop field trials conducted in Canada and the United States using end-use products containing spiropidion in or on potatoes, soybeans, tomatoes, bell and non-bell peppers, cucumber, and cantaloupe are sufficient to support the proposed maximum residue limits.

3.4.2 Dietary Risk Assessment

Acute and chronic non-cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 4.02), which uses food consumption data from the National Health and Nutrition Examination Survey and the What We Eat In America dietary survey for the years 2005-2010.

3.4.2.1 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the refined acute analysis for spiropidion: highest average field trial (HAFT) residues of spiropidion and the metabolites SYN547305, SYN547435, and SYN548430, expressed as spiropidion equivalents, and anticipated highest residues in processed commodities, where applicable. The refined acute dietary exposure (food alone) for all supported spiropidion registered commodities is estimated to be 17.4% (0.005210 mg/kg bw/day) of the ARfD for females 13–49 years old (95th percentile, deterministic) and ranges from 1.6-5.4% (0.005-0.016 mg/kg bw/day) for all other subpopulations (95th percentile, deterministic) and are considered acceptable.

3.4.2.2 Chronic Non-Cancer Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic analysis for spiropidion: supervised trial median residue (STMdR) values of spiropidion and the metabolites SYN547305, SYN547435, and SYN548430, expressed as spiropidion equivalents, and anticipated median residues in processed commodities, where applicable. The refined chronic dietary exposure from all supported spiropidion food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 5.0% of the acceptable daily intake (ADI). The PMRA estimates that chronic dietary exposure to spiropidion from food is 2.2% (0.0006 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 at 5.0% (0.0015 mg/kg bw/day) of the ADI.

3.4.3 Maximum Residue Limits

The recommendation for maximum residue limits (MRLs) for spiropidion was based upon the submitted field trial data from the exporting country, and the guidance provided in the [OECD MRL Calculator](#). MRLs to cover residues of spiropidion and the metabolite SYN547305 in/on crops and processed commodities are proposed as shown in Table 3.4-1 Residues in processed commodities not listed in Table 3.4-1 are covered under the proposed MRLs for the raw agricultural commodities (RACs).

Table 3.4-1 Summary of Field Trial and Processing Data Used to Support Maximum Residue Limits (MRLs)

Commodity	Application Method/ Total Application Rate (g a.i./ha)	PHI (days)	Residues (ppm)		Experimental Processing Factor	Recommended MRL (ppm)
			LAFT	HAFT		
Potato	Foliar applications/ 343-373	6-8	0.02	0.896	Potato Flakes: Spiropidion: Not calculated SYN547305: 3.49x	5.0 (potato flakes) 1.5 (potatoes)
Soybean seed	Foliar applications/ 348-375	10-16	0.02	1.765	---	3.0
Tomato	Foliar applications/ 530-565	1	0.029	0.503	Tomato paste: Spiropidion: 0.3x SYN547305: 3.7x Dried tomato: Spiropidion: 2.9x, SYN547305: 12.2x	7.0 (dried tomato) 1.5 (tomato paste) 0.8 (tomato)
Bell pepper	Foliar applications/ 539-563	1	0.106	0.493	---	1.0
Non-bell pepper	Foliar applications/ 534-554	1	0.073	0.693	---	
Cucumber	Foliar applications/ 532-550	1	0.115	0.440	---	0.8

Commodity	Application	PHI	Residues (ppm)		Experimental	Recommended
Cantaloupe	Foliar applications/ 536-558	1	0.117	0.526	---	0.9 (winter squash, pumpkin, cantaloupe, muskmelon, watermelon)

LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial

3.5 Cumulative Assessment

The PCPA requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for spiropidion. Spiropidion acts to control insects by inhibiting acetyl CoA carboxylase and interfering with lipid metabolism. Other structurally-related insecticides with this same insecticidal MOA include spiroadiclofen, spiromesifen, and spirotetramat.

It is not known if these insecticides share the same mammalian MOA. However, in the available mammalian toxicity studies, the thyroid gland was identified as a target tissue with each of these insecticides, with hypertrophy common to spiropidion and spiromesifen, and hormone alterations noted with spiroadiclofen, spirotetramat, and spiromesifen. The database for spiropidion did not include measurements of thyroid hormones. Additionally, effects on cholesterol metabolism, consistent with the insecticidal MOA, were evident with three of these insecticides (spiropidion, spiroadiclofen, and spiromesifen). These common effects were not the most sensitive endpoints in the toxicology databases, as human health reference values were based on other endpoints such as reduced body weight or effects on other organs (brain, thymus, adrenal gland) that occurred at lower dose levels. Although adequate data is not available to establish the key events in the pathway that lead to the effects in the thyroid and on cholesterol metabolism, there was sufficient information to suggest a pattern of common effects across this structurally-related group of chemicals that share an insecticidal mode of action. Based on the available information, it is not possible to rule out that these insecticides share a common mode of action related to thyroid or cholesterol metabolism, and thus were considered at this time to form a common assessment group.

For the purposes of this import MRL submission, a qualitative approach to assessing risks from cumulative exposure was undertaken for the pesticides within this common assessment group. As exposure to spiropidion will be limited to food residues, the current cumulative assessment focused on exposure via the diet, as well as drinking water for those active ingredients registered in Canada. The current cumulative assessment also focused on chronic exposure as the common toxic effects are only relevant to repeated exposure scenarios. When considering the estimated

risks from the individual dietary exposure assessments using the most conservative points of departure, exposure was low, and represented less than 10% of the ADI in the refined chronic dietary exposure assessments for spiropidion, spirotetramat and spirodiclofen and 31% of the ADI in a basic assessment for spiromesifen.

Therefore, based on this qualitative assessment, the cumulative risks from potential co-exposure to spiropidion and other inhibitors of acetyl CoA carboxylase through food, and drinking water where relevant, are acceptable.

3.6 Health Incident Reports

As of June 18, 2022, no human or domestic animal incidents involving spiropidion had been submitted to the PMRA.

4.0 Toxic Substances Management Policy (TSMP) Considerations

No TSMP-implicated substances were identified.

5.0 Value and Environmental Assessments

Value and environmental assessments were not required for this application.

6.0 Summary

6.1 Human Health and Safety

The nature of the residues in plants is adequately understood. The residue definition for enforcement in plant products is spiropidion and the metabolite SYN547305, expressed as spiropidion equivalents. The importation of spiropidion-treated potatoes, soybeans, cantaloupe/muskmelon, watermelon, cucumber, winter squash, tomatoes, bell peppers, and non-bell peppers does not constitute a risk of concern for acute or chronic dietary exposure (food alone) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs on imported commodities. The PMRA recommends that the following MRLs be specified for residues of spiropidion.

Table 6.1-1 Proposed Canadian MRL to Cover Residues of Spiropidion in/on Imported Food Commodities

Commodity	Recommended MRL (ppm)
Dried tomato	7.0
Potato flakes	5.0

Dry soybeans	3.0
Potatoes	1.5
Tomato paste	1.5
Bell peppers	1.0
Non-bell peppers	1.0
Winter squash	0.9
Pumpkins	0.9
Cantaloupe	0.9
Muskmelons (other than those listed in this item)	0.9
Watermelons	0.9
Tomatoes	0.8
Cucumbers	0.8

List of abbreviations

↑	increased
↓	decreased
♂	male
♀	female
μM	micromolar
μg	microgram(s)
AD	administered dose
ADI	acceptable daily intake
A/G	albumin/globulin ratio
Al	Aluminum
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
AUC	area under the curve
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
Cmax	maximum plasma concentration
F1	first filial generation
fc	food consumption
g	gram(s)
GD	gestation day
GIT	gastrointestinal tract
HDPE	High Density Polyethylene
hr(s)	hour(s)
i.v.	intravenous
kg	kilogram(s)
L	litre(s)
LD ₅₀	dose estimated to be lethal to 50% of the test population
LOAEL	lowest observed adverse effect level
mg	milligram(s)
min	minute
mL	millilitre(s)
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MOA	mode of action
NOAEL	no observed adverse effect level
NZW	New Zealand White
P	parental generation

PCPA	<i>Pest Control Product Act</i>
PE	Polyethylene
PETP	Polyethylene Terephthalate Polyester
PMRA	Pest Management Regulatory Agency
Tmax	time of maximum plasma concentration
UDP-GT	uridine diphosphate glucuronyltransferase
wt	weight

Appendix I Tables and figures

Table 1 Identification of Select Metabolites of Spiropidion

Code	Chemical Name	Source
SYN547305	3-(4-chloro-2,6-dimethyl-phenyl)-4-hydroxy-8-methoxy-1-methyl-1,8-diazaspiro[4.5]dec-3-en-2-one	Rat (major plasma metabolite, major excreted metabolite), growing crops
SYN548430	3-(4-chloro-2,6-dimethyl-phenyl)-4-hydroxy-1-methyl-1,8-diazaspiro[4.5]dec-3-en-2-one	Rat (major plasma metabolite, major excreted metabolite)
SYN547435	3-(4-chloro-2,6-dimethyl-phenyl)-4-hydroxy-8-methoxy-1,8-diazaspiro[4.5]dec-3-en-2-one	Rat (minor metabolite in urine), growing crops

Table 2 Toxicology Reference Values for Use in Health Risk Assessment for Spiropidion

Exposure Scenario	Study	Point of Departure and Endpoint	CAF ¹
Acute dietary general population	Rat and rabbit developmental toxicity studies	Maternal NOAEL = 30 mg/kg bw/day Body weight loss	100
	ARfD (general population) = 0.3 mg/kg bw		
Acute dietary females 13-49 years of age	Rat and rabbit developmental toxicity studies	Developmental NOAEL = 10 mg/kg bw/day Variations in the absence of maternal toxicity	300
	ARfD (females 13-49 years of age) = 0.03 mg/kg bw		
Repeated dietary	1-year oral toxicity study in dogs	NOAEL = 3 mg/kg bw/day Decreased body weight and body weight gain in females	100
	ADI = 0.03 mg/kg bw/day		
Cancer	No treatment-related tumours were observed, therefore a cancer risk assessment is not required.		

¹ CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments. **Table 3. Toxicity Profile of Technical Spiropidion**

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights 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
Toxicokinetic Studies	
<p>Absorption, distribution, excretion (gavage and i.v.; single dose)</p> <p>Rat (Wistar); intact and bile duct-cannulated</p> <p>PMRA 3161295</p>	<p>[¹⁴C]-labelled spiropidion (labelled on the phenyl-U) was administered via gavage as a single dose at 5 or 250 mg/kg bw, as well as via i.v. as a single dose at 1 mg/kg bw.</p> <p>Absorption: At each dose level, the absorption was similar in both sexes, with oral absorption ranging from 69-86% of the AD (based on radioactive residues in urine, bile, cage wash, and carcass). Calculation of the ratio of urinary excretion in gavage-dosed to i.v.-dosed intact ♂ rats as an estimate of the fraction of dose absorbed gave values of 82% of the AD at 5 mg/kg bw and 78% of the AD at 250 mg/kg bw.</p> <p>Excretion: Following a single oral administration at 5 mg/kg bw to intact rats, the majority of the AD (94%) was excreted in the first 48 hrs. The routes and rates were similar for both sexes, with the majority of the dose excreted in the urine (57-61% of the AD by 168 hrs). Fecal excretion accounted for 29-36% of the AD by 168 hrs. Following a single oral administration of 250 mg/kg bw to intact rats, the majority of the AD (97-100%) was excreted in the first 48 hrs. The routes and rates were similar for both sexes, with 49-53% of the AD excreted in the urine and 45-47% of the AD in the feces by 168 hrs. Excretion was essentially complete in all animals by 168 hrs post dose with 0.2% or less remaining in the carcass and GIT.</p> <p>In bile duct-cannulated rats, the majority of the dose was excreted in the urine (45-64% of the AD). Elimination via the feces and bile accounted for 19-30% and 13-14% of the AD, respectively.</p> <p>Following a single i.v. administration at 1 mg/kg bw to intact ♂ rats, the majority of the AD (97%) was excreted in the first 24 hrs. After 96 hrs, the majority of the dose was excreted in the urine and feces (64% and 30% of the AD, respectively).</p> <p>Distribution: Seven days after administration of 5 or 250 mg/kg bw,</p>

Study Type/ Animal/ PMRA #	Study Results
	<p>radioactive residues were not detectable in the majority of tissues, with 0.2% of the AD or less remaining in the carcass and GIT. The highest mean tissue concentration was observed in the liver, with the tissue distribution of radioactivity being similar in both sexes and following both dose levels.</p>
<p>Distribution (gavage; single dose)</p> <p>Rat (Wistar)</p> <p>PMRA 3161299</p>	<p>[¹⁴C]-labelled spiropidion (labelled on the phenyl-U) was administered via gavage as a single dose at 5 or 250 mg/kg bw.</p> <p>Distribution: At 5 mg/kg bw, radioactivity was widely distributed to the tissues in both sexes. Peak mean tissue concentrations were observed at the first sampling time of 2 hrs post dose. The highest mean tissue concentrations were obtained in the liver and kidneys. All other tissue concentrations were similar or lower than the blood and plasma concentrations. Thereafter, all tissue concentrations declined steadily up to 96 hrs post dose. All tissue concentrations, with the exception of those in liver and kidney, were below that of circulating blood or were below the limit of detection. The total mean residues in tissues and carcass at 96 hrs accounted for 2.5% of the AD in both sexes.</p> <p>At 250 mg/kg bw, radioactivity was widely distributed to the tissues in both sexes. Peak mean tissue concentrations were attained at the first sampling time of 4 hrs post dose in ♂ and 2 hrs post dose in ♀. The highest mean tissue concentrations were observed in the liver and kidneys. Thereafter, all tissue concentrations declined steadily up to 96 hrs post dose, where, with the exception of liver, all tissue concentrations were below that of circulating blood or were below the limit of detection. The total mean residues in tissues and carcass at 96 hrs accounted for 1.6% and 1.3% of the AD in ♂ and ♀, respectively.</p> <p>Throughout the study, the majority of mean tissue concentrations were, in general, broadly similar between the sexes at both dose levels. Consistent with this, estimates for tissue depletion half-life appeared similar in ♂ and ♀. The tissue depletion half-life of dose-related radioactivity in the majority of tissues was either similar or estimated to be shorter than in plasma. However, longer estimates were obtained in whole blood. Consistent with this, circulating concentrations of total radioactivity were initially more associated with the plasma fraction and then generally became increasingly associated with the cellular fraction at later time points.</p>

Study Type/ Animal/ PMRA #	Study Results
<p>Metabolism (gavage; single dose)</p> <p>Rat (Wistar; ♂); bile duct- cannulated</p> <p>PMRA 3161300</p>	<p>[14C]-labelled spiropidion (labelled on the phenyl-U) was administered via gavage as a single dose at 5 or 250 mg/kg bw.</p> <p>Excretion: Most of the AD (95 to 98%) was eliminated by 48 hrs post dose with excretion essentially complete by 96 hrs.</p> <p>Metabolite identification: Unchanged spiropidion and three metabolites (SYN548430, SYN547305, and hydroxy oxidised desmethoxy SYN547305) were detected in the excreta which accounted for >5% of the AD. The main circulating metabolites detected in plasma were confirmed as SYN548430, SYN547305, and hydroxy oxidised desmethoxy SYN547305. A further four components were detected and identified (SYN547305 glucuronide, reduced SYN547305, SYN547435 and desmethoxy spiropidion) in the excreta as minor components. At least nine other unidentified radiolabelled components were detected in the excreta, but no single component accounted for >1.9% of the AD in the individual matrices. At least five other unidentified radiolabelled circulatory components were detected in the plasma.</p>
<p>Toxicokinetics (gavage and i.v.; single dose)</p> <p>Rat (Wistar)</p> <p>PMRA 3161297</p>	<p>[14C]-labelled spiropidion (labelled on the phenyl-U) was administered via gavage as a single dose at 5 or 250 mg/kg bw, as well as via i.v. as a single dose at 1 mg/kg bw.</p> <p>Single oral dose: Following a single oral administration of 5 mg/kg bw, absorption was rapid with peak blood and plasma concentrations observed at 1-2 hrs. At the higher dose (250 mg/kg bw) absorption was also rapid, with Tmax observed 1-4 hrs post dose. Overall total systemic exposure was comparable between whole blood and plasma within the same dose level. Systemic exposure to total radioactivity (based on AUC(0-t) estimates) increased in a broadly proportional manner between the 5 and 250 mg/kg bw dose levels with no obvious trend for non-proportionality. In general there were no consistent sex-related differences noted in the toxicokinetics of total radioactivity. In the oral dose groups, no significant differences were observed between the blood and plasma concentrations of total radioactivity. Blood to plasma ratios suggested that total radioactivity remained predominantly in plasma rather than the cellular component of whole blood at earlier time points. The blood to plasma ratio appeared to increase at later time points, becoming either evenly distributed or greater in the cellular fraction.</p> <p>Single i.v. dose: Following a single i.v. dose, the concentration of</p>

Study Type/ Animal/ PMRA #	Study Results
	<p>radioactivity in blood steadily declined to 72 hrs post dose. The AUC was comparable irrespective of sex. The estimated half-life of elimination of total radioactivity following i.v. administration was longer in ♂ (42 hrs) than ♀ (22 hrs).</p>
<p>Toxicokinetics (repeated gavage and single i.v. dose)</p> <p>Rat (strain not reported)</p> <p>PMRA 3161298</p>	<p>Supplemental</p> <p>Rats were administered multiple (daily for 7 days) gavage doses of 3, 30 or 300 mg/kg bw/day or a single i.v. dose of 1 mg/kg bw of non-radiolabelled spiropidion. Additional groups of rats were administered a single gavage dose of 3 mg/kg bw or a single i.v. dose of 1 mg/kg bw of the metabolite SYN547305.</p> <p>All animals in the repeat oral high dose group (300 mg/kg bw/day spiropidion) showed bw loss and vocalisation/aggression during handling over the first several days of dosing. More severe effects were observed in ♀. Two ♀ animals were removed from the study as they appeared thin, with a hunched posture, piloerection, red staining around the mouth, an unsteady gait, and were subdued.</p> <p>After oral or i.v. administration of spiropidion, blood concentrations of unchanged spiropidion were generally very low and often not quantifiable.</p> <p>After repeated oral administration of spiropidion for 7 days, unchanged spiropidion concentrations in blood were generally low and variable (likely due to its rapid hydrolysis to SYN547305), preventing the evaluation of toxicokinetic parameters.</p> <p>After i.v. dosing of spiropidion, concentrations of SYN547305 at 1 hr post-dosing in ♂ (C_{max} of 107 ng/mL) were higher than those in ♀ (C_{max} of 21 ng/mL). The AUC was also higher in ♂ (279 ng.h/mL) than in ♀ (152 ng.h/mL), suggesting that SYN547305 is cleared from blood faster in ♀.</p> <p>After the first oral administration of spiropidion, the C_{max} for SYN547305 was observed approximately 2 hrs post-dosing, supporting the rapid hydrolysis of spiropidion. The C_{max} of SYN547305 increased in both sexes from 85 ng/mL at 3 mg/kg bw to 4000 ng/mL at 300 mg/kg bw. Due to the variability in the data, no obvious correlation can be drawn regarding proportionality of AUC or C_{max} with dose level. No</p>

Study Type/ Animal/ PMRA #	Study Results
	<p>sex-specific differences were evident.</p> <p>Following i.v. administration of SYN547305, C_{max} values of 239 and 92 ng/mL were observed in ♂ and ♀, respectively. This is higher when compared to i.v. dosing with spiropidion, but reflects the same pattern with higher concentrations observed in ♂. The exposure to SYN547305 after oral administration of SYN547305 was approximately 3- to 4-fold higher than after administration of spiropidion. However, exposure in ♀ was higher than that in ♂, which is contrary to the i.v. dose and following administration of spiropidion. No obvious correlation can be drawn regarding proportionality of AUC or C_{max} with dose.</p> <p>Limitations: limited and sometimes contradictory reporting.</p>
<p>Preliminary study - absorption, metabolism, excretion (gavage and i.v.; single dose)</p> <p>Rat (Wistar)</p> <p>PMRA 3161301</p>	<p>Supplemental</p> <p>A single gavage dose of 5 or 250 mg/kg bw of [14C]-spiropidion (labelled on the phenyl-U), or a single gavage dose of 1000 mg/kg bw of [14C]-spiropidion (labelled on the spirodecanone) was administered by gavage. A single dose of 1 mg/kg bw of spiropidion was administered by i.v.</p> <p>Elimination: The majority of the AD (91-95%) was eliminated by 48 hrs post dose with excretion essentially complete by 168 hrs. There were no marked differences observed in urinary or fecal excretion between sexes after either dose. The major route of elimination was via the urine. Elimination via expired air was negligible.</p> <p>Toxicokinetics: Following a single i.v. dose, blood concentrations steadily declined over 48 hrs, with apparent terminal phase half-lives < 38 hrs. No differences between radiolabel positions or between sexes were noted.</p> <p>Following oral administration of the phenyl label (5 mg/kg bw) and the spirodecanone label (5 and 250 mg/kg bw), the dose was rapidly absorbed with C_{max} observed at around 2 hrs. Concentrations of total radioactivity then declined over 72 hrs, with apparent terminal phase half-lives < 38 hrs.</p> <p>Absorption: Systemic exposure appeared to increase approximately proportionally to the dose of the spirodecanone label. Absorption</p>

Study Type/ Animal/ PMRA #	Study Results
	<p>approached completion with urinary excretion being similar after both oral and i.v. administration, with bioavailability estimates of > 71% of the AD.</p> <p>Metabolite Identification: Spiropidion was readily metabolized, with approximately 75 to 82% of an orally AD and 79 to 84% of an i.v. AD assigned to identified metabolites. The most abundant metabolite, desmethoxy SYN547305, was detected in all urine and feces samples and accounted for up to 78% of the AD following oral administration and up to 84% of the AD following i.v. administration. Two other metabolites, (hydroxy oxidised desmethoxy SYN547305 and hydroxyl desmethoxy SYN547305a) accounted for greater than 5% of the AD in excreta. Hydroxy oxidised desmethoxy SYN547305 accounted for up to 19% of the AD and hydroxy desmethoxy SYN547305a accounted for up to 7.8% of the AD. Circulating components detected in the blood were tentatively identified as desmethoxy SYN547305, hydroxy desmethoxy SYN547305, and SYN547305.</p>
<p>In vitro rat and human liver microsomal metabolism (non-guideline)</p> <p>Rat (Wistar) microsomes, human microsomes</p> <p>PMRA 3161296</p>	<p>Supplemental</p> <p>[14C]-spiropidion (radiolabeled on the phenyl-U ring or on the spirodecanone portion of the molecule) was administered at 10 µM to human or rat microsomes.</p> <p>In the absence of liver microsomes, [phenyl-U-14C]-spiropidion was slightly unstable with approximately 90% of unchanged spiropidion detected at the initiation of the experiment (0 min). After the 60 min incubation in the absence of liver microsomes, approximately 78% of [phenyl-U-14C]-spiropidion was detected. In the presence of rat and human liver microsomes, spiropidion was relatively unstable at the initiation of the experiment (0 min) with 87% (rat) and 86% (human) of unchanged spiropidion detected, respectively. After the 60 min incubation period, metabolism was extensive in rat and human liver microsomes with 1% and 6% of unchanged spiropidion detected, respectively. Seven metabolite fractions (M1, M2, M4, M10, M11, M16 and M17) were consistently detected above the limit of quantification (≥ 1%) in rat and human liver microsomes. All the metabolite fractions observed with human microsomes were also observed with rat microsomes.</p> <p>Similarly, [spirodecanone-5-14C]-spiropidion was slightly unstable with</p>

Study Type/ Animal/ PMRA #	Study Results
	<p>approximately 80% of unchanged spiropidion detected at the initiation of the experiment (0 min) in the absence of liver microsomes. After 60 min incubation in the absence of liver microsomes, approximately 72% of unchanged spiropidion was detected. In the presence of rat and human liver microsomes, spiropidion was relatively unstable at the initiation of the experiment (0 min) with 90% of unchanged spiropidion detected. After the 60 min incubation period, metabolism was extensive in rat and human liver microsomes with 3% and 6% of unchanged spiropidion detected, respectively. Seven metabolite fractions (M1, M2, M4, M10, M11, M16 and M17), which had similar retention times to [phenyl-U-14C]-spiropidion, were consistently detected above the limit of quantification ($\geq 1\%$). All the metabolite fractions observed with human microsomes were also observed with rat microsomes.</p>
Acute Toxicity Studies	
<p>Acute oral (gavage) Rat (Wistar) PMRA 3161304</p>	<p>LD₅₀ > 2000 mg/kg bw (♀) Clinical signs of toxicity included vocalization, incoordination, ↓ activity, irritability, hunched back, piloerection, intermittent tremors, and liquid feces. Low acute toxicity</p>
<p>Acute oral (gavage) – Metabolite SYN547435 Rat (Wistar) PMRA 3161305</p>	<p>LD₅₀ > 2000 mg/kg bw (♀) No clinical signs of toxicity were observed. Low acute toxicity</p>
Short-Term Toxicity Studies	
<p>28-day oral (dietary) Mice (CD-1) PMRA 3161312</p>	<p>NOAEL = 117/126 mg/kg bw/day (♂/♀) LOAEL = 449/465 mg/kg bw/day (♂/♀) Effects at LOAEL: mortality (2 ♂, 3 ♀), bw loss, ↓ fc (♂/♀); hunched posture rolling gait, partially closed eyes, tremors, piloerection, slow respiration (♀) Toxicokinetics: There were no quantifiable levels of spiropidion in plasma at any dose level. At most time points and dose levels, exposure to SYN547305 in ♀ appeared to be higher than in ♂.</p>

Study Type/ Animal/ PMRA #	Study Results
90-day oral (dietary) Mouse (CD-1) PMRA 3161318, 3161316	NOAEL = 105/115 mg/kg bw/day (♂/♀) LOAEL = 236/252 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bwg, ↓ albumin, ↓ A/G ratio (♂/♀); ↑ urea, ↑ BUN, ↑ liver wt (♂); ↓ bw, ↑ ALP (♀) Toxicokinetics: While spiropidion was found to be present in very few blood samples, systemic exposure to metabolite SYN547305 appeared to increase sub-proportionally across the dose ranges in both sexes, suggesting that spiropidion was readily converted to this metabolite. Following repeated administration, exposure estimates were generally comparable between sample days. There were no appreciable differences in systemic exposure to SYN547305 between sexes. However, where a difference was noted, exposure was greater in ♀ than in ♂.
28-day oral (dietary) Rat (Wistar) PMRA 3161314	NOAEL = 44 mg/kg bw/day (♂/♀) LOAEL = 177/178 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bwg, ↓ cholesterol, ↓ triglycerides, thyroid follicular cell hypertrophy (♂/♀); ↓ albumin (♂); ↑ ALT (♀) Toxicokinetics: There were no quantifiable levels of spiropidion in plasma at any dose level, while systemic exposure to SYN547305 appeared to increase supra-proportionally in ♂ and sub-proportionally in ♀ on Day 2, suggesting that spiropidion was readily converted to SYN547305. There was no appreciable difference in mean AUC estimates on Day 28 when compared to Day 9. There were no clear and consistent differences in systemic exposure between sexes.
90-day oral (dietary) Rat (Wistar) PMRA 3161317, 3161315	NOAEL = 6.2/7.0 mg/kg bw/day (♂/♀) LOAEL = 32/36 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ cholesterol (♂/♀); ↑ phosphorous, ↓ adrenal wt (♂); ↓ triglycerides, ↑ ALT, ↓ ALP, ↓ spleen wt (♀) Toxicokinetics: Toxicokinetic parameters of spiropidion were unable to be determined as all samples contained concentrations below the limit of quantification. A higher AUC of SYN547305 was observed in ♀ compared to ♂. For both sexes, the AUC was higher on Day 91 (repeat dosing) compared to Day 2 (single dose).

Study Type/ Animal/ PMRA #	Study Results
<p>28-day oral (capsule) – dose range-finding</p> <p>Dog (Beagle)</p> <p>PMRA 3161313</p>	<p>Supplemental</p> <p>NOAEL and LOAEL not established.</p> <p>After two days of dosing at 100 mg/kg bw/day, dosing was stopped due to severe clinical signs. Following a 26-day recovery period animals were dosed at 65 mg/kg bw/day for four days before the study was terminated due to severe clinical signs.</p> <p>Effects at 100/65 mg/kg bw/day: 3 dogs euthanized early for humane reasons (1 ♀ after 2 doses at 100 mg/kg bw/day, 1 ♀ after 1 dose of 100 mg/kg bw/day and then 2 doses of 65 mg/kg bw/day, 1 ♂ after 2 doses of 100 mg/kg bw/day and then 4 doses of 65 mg/kg bw/day).</p> <p>Clinical signs in surviving dogs included: subdued and uncoordinated behaviour, unsteadiness, unawareness of surroundings.</p> <p>Clinical signs in dogs that were euthanized were similar to survivors but more severe and included: salivation, unsteadiness, ataxia, tremors, subdued behaviour, twitching, abnormal respiration, falling over.</p> <p>Toxicokinetics: There were no quantifiable levels of spiropidion in blood. For SYN547305, Tmax at 10 or 30 mg/kg bw/day was shorter on Day 28 than on Day 1. Cmax and AUC were approximately 2-3.5-fold and 1.5-fold higher on Day 28 than on Day 1 at 10 and 30 mg/kg bw/day, respectively. Tmax at 100/65 mg/kg bw/day was shorter on Day 1 when compared with Tmax for animals receiving 10 or 30 mg/kg bw/day.</p>
<p>90-day oral (capsule)</p> <p>Dog (Beagle)</p> <p>PMRA 3161319</p>	<p>NOAEL = 30/15 mg/kg bw/day (♂/♀) LOAEL = not determined/30 mg/kg bw/day (♂/♀)</p> <p>Effects at LOAEL: mortality (1 ♀ sacrificed in extremis on Day 13 after exhibiting clinical signs of toxicity including being unaware of surroundings, body tremors, no coordination of hind limbs, subdued behaviour, and unresponsiveness to stimulation) (♀).</p> <p>Toxicokinetics: No quantifiable levels of spiropidion were detected in blood. Systemic exposure to metabolite SYN547305 increased with dose on Day 1. This increase in exposure appeared to be proportional in ♂ between 5 and 30 mg/kg bw/day. However, there was no appreciable</p>

Study Type/ Animal/ PMRA #	Study Results
	<p>increase in exposure estimates between 5 and 15 mg/kg bw/day in ♂. In ♀, systemic exposure to SYN547305 appeared to be supra-proportional relative to dose. Tmax was observed at 24 hrs for all dose groups. Systemic exposure to SYN547305 was between 1.7-fold and 5.3-fold greater at Week 13 than Day 1 in both sexes. Systemic exposure to SYN547305 was comparable between the sexes on Day 1 and Week 13 in the 5 and 30 mg/kg bw/day dose groups. In the 15 mg/kg bw/day dose group, exposure estimates were greater in ♀ than in ♂ by approximately 2.5-fold on Day 1 and 1.7-fold at Week 13.</p>
<p>1-year oral (capsule) Dog (Beagle) PMRA 3161321</p>	<p>NOAEL = 10/3 mg/kg bw/day (♂/♀) LOAEL = 30/10 mg/kg bw/day (♂/♀)</p> <p>Effects at LOAEL: mortality (1 ♂ sacrificed in extremis on Day 14 with clinical signs of incoordination, salivation and lying on side) (♂); ↓ fc, ↓ bw/bwg (♀).</p>
Chronic Toxicity/Oncogenicity Studies	
<p>2-year combined chronic toxicity /oncogenicity (dietary) Rat (Wistar) PMRA 3161331, 3161332</p>	<p>NOAEL = 4.7/19 mg/kg bw/day (♂/♀) LOAEL = 24 mg/kg bw/day/not determined (♂/♀)</p> <p>Effects at LOAEL: ↓ bw, ↓ bwg, slight ↓ fc, ↓ food utilization, ↓ cholesterol, ↑ fibrinogen, ↓ ALP, bile duct enlargement, luminal dilation and inflammation (♂)</p> <p>No evidence of tumourigenicity</p>
<p>80-week carcinogenicity (dietary) Mouse (CD-1) PMRA 3161334, 3161333</p>	<p>NOAEL = 6.4/7.0 mg/kg bw/day (♂/♀) LOAEL = 32/37 mg/kg bw/day (♂/♀)</p> <p>Effects at LOAEL: ↓ bw, ↓ bwg ↓ food utilization (♂/♀); ↑ incidence of gallstones (♂)</p> <p>No evidence of tumourigenicity</p>
Developmental/Reproductive Toxicity Studies	
<p>2-generation reproductive toxicity (dietary) Rat (Wistar)</p>	<p>Parental NOAEL = 31/8.1 mg/kg bw/day (♂/♀) Parental LOAEL = not determined/24 mg/kg bw/day (♂/♀)</p> <p>Effects at LOAEL: ↑ thyroid wt (P), thyroid hypertrophy (P and F1) (♀)</p>

<p>PMRA 3161339, 3161340</p>	<p>Offspring NOAEL = 24 mg/kg bw/day Offspring LOAEL not established</p> <p>No treatment-related effects in offspring</p> <p>Reproductive NOAEL = 31/24 mg/kg bw/day (♂/♀) Reproductive LOAEL not established</p> <p>No treatment-related reproductive effects (including ovarian follicle counts, estrous cycle, sperm parameters)</p> <p>No evidence of sensitivity of the young</p>
<p>Developmental toxicity (gavage) – 7-day tolerability study in non-pregnant animals</p> <p>Rat (Wistar)</p> <p>PMRA 3161343</p>	<p>Supplemental</p> <p>NOAEL and LOAEL not established</p> <p>Effects at ≥ 75 mg/kg bw/day: \downarrow bw, \downarrow fc</p> <p>Effects at 200 mg/kg bw/day: agitation</p> <p>Toxicokinetics: Spiropidion was detected in a negligible number of samples at low levels; concentrations of the remaining samples were below the quantifiable limit. For the metabolite SYN547305, C_{max} \uparrow proportionally with dose between 75 and 150 mg/kg bw/day while AUC \uparrow supra-proportionally on Day 1; on Day 7 C_{max} were sub-proportional and AUC were proportional to external dose. Between 75 and 200 mg/kg bw/day, AUC \uparrow sub-proportionally with dose on Days 1 and 7. C_{max} \uparrow sub-proportionally with dose on Day 1 and no \uparrow was seen on Day 7. Both C_{max} and AUC were higher at 150 mg/kg bw/day than at 200 mg/kg bw/day.</p>
<p>Developmental toxicity (gavage) – dose range-finding</p> <p>Rat (Wistar)</p> <p>PMRA 3161341</p>	<p>Supplemental</p> <p>NOAEL and LOAEL not established</p> <p>Maternal effects at ≥ 75 mg/kg bw/day: \downarrow bwg, \downarrow fc (\downarrow fc only on GD 6-9 at this dose level)</p> <p>Maternal effects at 100 mg/kg bw/day: \downarrow fc</p> <p>Maternal effects at ≥ 125 mg/kg bw/day: unscheduled sacrifice of all animals due to severe bw loss (GD 8-9 and 18-19 at 125 and 150 mg/kg bw/day, respectively)</p>

	<p>Developmental effects at 100 mg/kg bw/day: ↑ incidence of accessory liver lobes (developmental assessment limited to: external and visceral examinations)</p> <p>Toxicokinetics: There were no quantifiable concentrations of spiropidion in any of the blood samples analysed. The concentration of metabolite SYN547305 increased in a dose-related manner.</p>
<p>Developmental toxicity (gavage)</p> <p>Rat (Wistar)</p> <p>PMRA 3161342, 3161344</p>	<p>Maternal NOAEL = 30 mg/kg bw/day Maternal LOAEL = 100 mg/kg bw/day</p> <p>Effects at LOAEL: bw loss (GD 6-9), ↓ bwg, ↓ fc</p> <p>Developmental NOAEL = 10 mg/kg bw/day Developmental LOAEL = 30 mg/kg bw/day</p> <p>Effects at LOAEL: ↑ incidence (fetal and litter) of ossified phalanges on forelimb, ↑ incidence (fetal and litter) of bifurcated xiphoid cartilage on sternum, ↑ incidence (fetal and litter) of incomplete ossification of 5th sternebra.</p> <p>No treatment-related malformations</p> <p>Evidence of sensitivity of the young</p>
<p>Developmental toxicity (gavage) – 7-day tolerability study in non-pregnant animals</p> <p>Rabbit (NZW)</p> <p>PMRA 3161348</p>	<p>Supplemental</p> <p>NOAEL and LOAEL not established</p> <p>Effects at ≥ 50 mg/kg bw/day: bw loss</p> <p>Effects at ≥ 85 mg/kg bw/day: ↓ fc</p> <p>Toxicokinetics: Spiropidion was detected in a negligible number of samples at low levels; concentrations of the remaining samples were below the quantifiable limit. None of the blood samples analyzed from control animals were found to contain spiropidion. For the metabolite SYN547305, on Day 1 the increase in C_{max} and AUC₀₋₂₄ were sub-proportional to the increase in dose between 50 and 125 or 250 mg/kg bw/day and no change was observed between 50 and 85 mg/kg bw/day. On Day 7, there was no appreciable change in C_{max} with increasing dose. AUC appeared to increase proportionally with dose between 50 and 85 or 125 mg/kg bw/day</p>

	and sub-proportionally between 50 and 250 mg/kg bw/day. The AUC at 50, 85, 125 and 250 mg/kg bw/day was lower on Day 7 than Day 1.
Developmental toxicity (gavage) – dose range-finding Rabbit (NZW) PMRA 3161345	Supplemental NOAEL and LOAEL not established Maternal effects at ≥ 15 mg/kg bw/day: \downarrow fc Maternal effects at ≥ 50 mg/kg bw/day: bw loss (GD 6-9), \downarrow bwg (GD 6-15) Maternal effects at 75 mg/kg bw/day: mortality of one doe on GD 28 (fluid present in thoracic cavity, possibly result of dosing trauma), abortions in one doe on GD 26 No treatment-related developmental findings in the external and visceral evaluations conducted.
Developmental toxicity (gavage) Rabbit (NZW) PMRA 3161346, 3161350	Maternal NOAEL = 30 mg/kg bw/day Maternal LOAEL = 60 mg/kg bw/day Effects at LOAEL: \downarrow bwg, slightly \downarrow fc (non-adverse) Effects at 60 mg/kg bw/day: bw loss (GD 6-12) Developmental NOAEL = 10 mg/kg bw/day Developmental LOAEL = 30 mg/kg bw/day Effects at LOAEL: \uparrow incidence of incomplete 2 nd cartilaginous dorsal plate of the cervical vertebrae and incomplete xiphoid cartilage of the sternum. No treatment-related malformations Evidence of sensitivity of the young
Genotoxicity Studies	
Bacterial reverse mutation assay S. typhimurium (TA1535, TA1537, TA98, TA100) and E. Coli (WP2uvrA pKM101, WP2 pKM101)	Negative \pm metabolic activation Tested up to the limit concentration.

PMRA 3161323	
Bacterial reverse mutation assay S. typhimurium (TA1535, TA1537, TA98, TA100) and E. Coli (WP2uvrA pKM101, WP2 pKM101)	Negative ± metabolic activation Tested up to the limit concentration.
PMRA 3161324	
In vitro mammalian cell forward mutation assay Mouse Lymphoma L5178Y cells	Negative ± metabolic activation Tested up to cytotoxic concentrations.
PMRA 3161327	
In vitro chromosome aberration test Human lymphocytes	Positive ± metabolic activation Tested up to precipitating concentrations.
PMRA 3161325	
In vitro micronucleus assay Human lymphocytes	Negative ± metabolic activation Tested up to phase separating concentrations
PMRA 3161326	
In vivo chromosome aberration assay (gavage) Rat (Wistar)	Negative Tested up to the maximum tolerated dose Evidence of toxicity included slight bw loss, ano-genital soiling, ↓ activity, twitching.
PMRA 3161328	
In vivo micronucleus test (gavage) ♂ Rat (Wistar)	Negative Tested up to the maximum tolerated dose
PMRA 3161329	Clinical signs of toxicity included ↓ activity, intermittent twitching, unsteady gait, convulsions.
In vivo micronucleus test (gavage) ♂ Rat (Wistar)	Negative Tested up to the maximum tolerated dose
PMRA 3161330	Clinical signs of toxicity included ↓ activity, unsteady

	gait, laboured breathing, incoordination, piloerection, abnormal sensitivity to touch or disturbance.
Neurotoxicity Studies	
<p>Acute neurotoxicity (gavage)</p> <p>Rat (Wistar)</p> <p>PMRA 3161351, 3161352</p>	<p>NOAEL = 50 mg/kg bw (♂/♀)</p> <p>LOAEL = 150 mg/kg bw (♂/♀)</p> <p>Effects at LOAEL: ↓ bwg Days 1-2 (♂); bw loss Days 1-2 (♀)</p> <p>Effects at 500 mg/kg bw/day: ↓ bw (Days 1-8), bw loss (over first day following dosing), ↓ fc during week 1, ↓ activity counts during MA assessment on Day 1 (possibly secondary to bw loss) (♂); convulsions Day 1 (8 hrs post-dosing) resulting in unscheduled sacrifice (4 ♀)</p> <p>No evidence of selective neurotoxicity.</p>
<p>Short-term neurotoxicity - waiver request</p> <p>PMRA 3161354</p>	<p>The applicant's request to waive the conditional requirement for a short-term neurotoxicity study was based on a weight of evidence that included the following considerations: spiropidion is rapidly excreted with low tissue residues remaining in brain and fat, suggesting low exposure in the nervous system and low potential for neurotoxicity; there is a lack of evidence of treatment-related neurotoxicity following repeated oral exposures in rats, mice and dogs; and there is no concern for neurotoxicity for other compounds in the same class of chemistry as spiropidion. The request to waive this conditional data requirement was granted.</p>



Special Studies (non-guideline)	
In vitro thyroid peroxidase activity Rat thyroid gland microsomal preparation (Wistar) PMRA 3161338	Spiropidion and metabolite SYN547305 were administered. No evidence of inhibition of rat thyroid peroxidase activity in vitro with either spiropidion or SYN547305.
90-day UDP-glucuronosyltransferase induction (dietary) Rat (Wistar) PMRA 3161335	Spiropidion induced a significant increase in the rate of hepatic UDP-glucuronyl transferase activity in both ♂ and ♀ dosed at 159 and 110 mg/kg bw/day, respectively. When compared to controls, 2.5-fold and 2-fold increases in the rate of glucuronidation of [¹²⁵ I]-thyroxine were observed in ♂ and ♀, respectively.
Short-term immunotoxicity - waiver request PMRA 3161302	The applicant's request to waive the conditional requirement for a short-term immunotoxicity study was based on a weight of evidence that included the following considerations: there was no evidence of consistent spiropidion-related changes in any immune-related parameters in the available repeat-dose studies; and there is no evidence of functional immunotoxicity with other insecticidal compounds in the same class of chemistry as spiropidion. The request to waive this conditional data requirement was granted.

References

A. List of studies/Information submitted by registrant

Chemistry

PMRA References

Document Number

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- 3161283 2020, Analytical Method SA-134/1- Determination of Spiropidion in Spiropidion by HPLC, DACO: 2.13.1 CBI
- 3161284 2017, Spiropidion - Validation of Analytical Method SA-134/1, DACO: 2.13.1 CBI
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Human and Animal Health

PMRA References

Document Number

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