Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note REG2006-01

Bifenazate

The active ingredient (a.i.) bifenazate and associated end-use products Acramite 50WS for control of European red mite, two-spotted spider mite and McDaniel mite on apple and grape as well as Floramite SC for control of two-spotted spider mite and Lewis mite on indoor ornamentals, including those grown and/or maintained in containers or in the ground in greenhouses, shadehouses and interiorscapes, have been granted temporary registration under the Pest Control Products Regulations. Bifenazate is a reduced-risk chemical according to the criteria outlined in Regulatory Directive DIR2002-02, *The PMRA Initiative for Reduced-Risk Pesticides*.

This Regulatory Note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registration for the technical grade active ingredient bifenazate and the associated end-use products Acramite 50WS for the control of European red mite, two-spotted spider mite and McDaniel mite on apple and grape as well as Floramite SC for the control of two-spotted spider mite and Lewis mite on indoor ornamentals.

Crompton Co. will be submitting the final report of the apple dislodgeable foliar residue (DFR) study, UCC-D2341 50WP on Apples: Dislodgeable Foliar Residue Study, and the final report of the greenhouse ornamental DFR study, FLORAMITE™ 50WP in *Spathiphyllum*: Dislodgeable Foliar Residue Study, as a condition of these temporary registrations. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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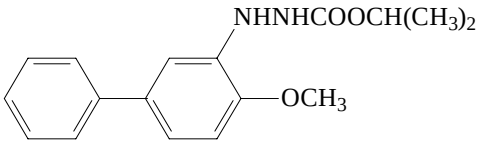
1.0 The Active Substance, its Properties and Uses

1.1 Identity of the Active Substance and Impurities

Active substance		Bifenazate
Function		Insecticide
Chemical name		
1.	International Union of Pure and Applied Chemistry	Isopropyl 3-(4-methoxybiphenyl-3-yl)carbazate
2.	Chemical Abstracts Service (CAS)	hydrazine carboxylic acid, 2-(4-methoxy-[1,1'-biphenyl]-3-yl)-, methylethyl ester
CAS number		149877-41-8
Molecular formula		$C_{17}H_{20}N_2O_3$
Molecular weight		300.36
Structural formula		
Nominal purity of active		96.7%
Identity of relevant impurities of toxicological, environmental or other significance		The technical grade bifenazate does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances

1.2 Physical and Chemical Properties of Active Substances and End-use Product(s)

Technical Product: Bifenazate

Property	Result	Comment
Colour and physical state	Beige solid	

Property	Result	Comment
Odour	Slight odour characteristic of aromatic compounds	
Melting point or range	120–124°C	
Boiling point or range	n/a	
Density	1.31 g/cm^3 at 25°C	
Vapour pressure at 20°C	< 1 × 10^{-7} torr	
Henry's law constant at 20°C	< 1.0 × 10^{-8} atm m^3/mole	Non-volatile from moist soil and water surfaces
Ultraviolet (UV)–visible spectrum	**Media λ_{max} (nm) ϵ (L/mol × cm)** Acidic 206 27 019 232 24 373 264 12 516 Neutral 206 27 686 232 25 058 264 12 413 Alkaline 232 24 736 264 12 698 Not expected to absorb UV at λ > 300 nm	
Solubility in water at 20°C	0.376 mg/100 mL	
Solubility in organic solvents at 20°C	**Solvent** **g/100 mL** methanol 5.07 acetonitrile 11.1 ethyl acetate 11.3 toluene 2.62 hexane 0.0232 n-octanol 0.954	
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 3.4 ± 2.85%	

Property	Result	Comment
Dissociation constant (pK_a)	pK_a = 12.94 ± 0.06 at 23°C	
Stability (temperature, metal)	Stable for 16 weeks when exposed to stainless steel and mild steel. A decomposition of 3.4% was observed after exposure to continuous sunlight (ultraviolet radiation) for a period of seven days.	

End-use Products: Floramite SC and Acramite 50WS

Property	Floramite SC™	Acramite 50WS
Colour	Off-white, beige	Not provided
Odour	Characteristic	Not provided
Physical state	Liquid	Solid
Formulation type	Suspension concentrate	Wettable powder
Nominal guarantee	22.6%	50%
Formulants	The product does not contain any USEPA or PMRA List 1 formulants or formulants known to be TSMP Track 1 substances.	The product does not contain any USEPA or PMRA List 1 formulants or formulants known to be TSMP Track 1 substances. It contains 0.42% crystalline silica, a List 2 formulant.
Container material and description	High density polyethylene (HDPE) bottles	Water soluble bags packaged in 1 pound, 48 gauge polyethylene, foil lined pouches.
Bulk density	1.061 g/cm^3 at 20°C	1.74 g/cm^3
pH of 1% dispersion in water	6.9	4.6
Oxidizing or reducing action	n/a	n/a

Property	Floramite SC™	Acramite 50WS
Storage stability	Stable for 12 months when stored at ambient temperature in commercial packaging.	Stable for 2 years when stored at 20°C in commercial packaging.
Explodability	n/a	n/a

1.3 Details of Uses

Crompton Co. has applied for registration of two commercial class end-use products containing bifenazate. Acramite 50WS, containing 50% bifenazate, is intended for control of European red mite, two-spotted spider mite and McDaniel mite on apple and grape. Floramite SC, containing 22.6% bifenazate, is intended for control of two-spotted spider mite and Lewis mite on indoor ornamentals (including plants that are grown and/or maintained in containers or in the ground in greenhouses, shadehouses and interiorscapes). A maximum of one application per crop per year is proposed for all use sites. Application is by ground application equipment only.

The active ingredient, bifenazate, belongs to the carbazate class of insecticides. The exact mode of action of bifenazate has not been documented, but is believed to be a gamma-aminobutyric acid (GABA) gated chloride channel antagonist, which targets mite pests that come in direct contact with the product or in contact with its residue. Bifenazate does not have systemic activity.

These products have been registered in the United States with the same product names since 2002 (Acramite 50WS) and 2001 (Floramite SC).

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Substance as Manufactured

Two high-performance liquid chromatography (HPLC) methods with UV detection were provided for the determination of the active ingredient and structurally related impurities present in the product at levels above 0.1%. Quantitation of the active ingredient was by internal standard method using acetanilide, and quantitation of all impurities was by external standard method using their respective reference standards. The method for the active ingredient was assessed to be precise as shown by the relative standard deviation (RSD) of 0.31% and specific as demonstrated by the absence of any interference peaks around the response peak of the active ingredient. The requirement of recovery data for the active ingredient to show the method accuracy was waived as no sample cleanup procedure was conducted prior to analysis. The method for the impurities was assessed to be accurate as shown by the recovery data, which ranged from 100.4 to 101.7%; precise as evidenced by the RSD, which ranged from 1.4 to 7.2%; and specific as demonstrated

by the absence of any interference peaks around the response peaks of the analytes of interest in the chromatograms provided.

2.2 Method for Formulation Analysis

Two HPLC methods with UV detection were provided for the determination of the active ingredient in the two formulations. Quantitation of the active ingredient in both formulations was by internal standard using acetanilide. The analytical method for Acramite 50WS gave a wide linearity range at 50–150% of the nominal active ingredient concentration in the product and good precision with RSD of 0.31%. The requirement of method accuracy as shown by the recovery data was waived as no sample cleanup procedure was conducted prior to analysis. The requirement of method specificity as shown by the chromatograms was also waived as all formulants present in the product were not expected to cause any analytical interferences.

No validation data were provided for the analytical method for Floramite SC™. However, no sample cleanup procedure was conducted prior to analysis. In addition, quantitation of the active ingredient was based on the reference analytical standard of the active ingredient prepared at the same concentration of the active ingredient present in the sample, and all formulants in the product were not expected to cause any analytical interferences. Therefore, the requirement of validation data was waived.

Both methods submitted for the analysis of the active ingredient in the two formulations were assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for Residue Analysis

2.3.1 Methods for Environmental Residue Analysis

An HPLC method with UV detection was provided for the determination of bifenazate and transformation products D1989 and D3598 in field soil from three separate sites: North Carolina, California and Washington. The samples were extracted with acetonitrile (ACN), and the extracts cleaned by liquid-liquid partition between 2% aqueous sodium sulfate or 10% sodium chloride and methylene chloride. The validation data provided for all three sites showed that the method is accurate as demonstrated by overall mean recovery range of 89–96%; precise as shown by the RSD range of 3.0–4.0% at 0.01, 0.05 and 0.10 ppm fortification levels; sensitive with a limit of quantitation (LOQ) of 0.01 ppm for all analytes; and specific as demonstrated by the absence of any interference peaks around the retention time of the analytes of interest. The method is, therefore, assessed to be acceptable for the determination of all three analytes in soil.

2.3.2 Multiresidue Methods for Residue Analysis

Bifenazate (D2341) and the metabolite D3598 (diazinecarboxylic acid, 2-(4-methoxy-[1,1',-biphenyl]-3-yl), 1-methylethyl ester) were screened through multiresidue methods A, C, D, E and F, described in the *Pesticide Analytical Manual* (PAM), Volume I, Third

Edition (USFDA 1994). The test substances are not acids, phenols or substituted ureas; therefore, Protocol B and Protocol G were not tested. As bifenazate and D3598 were both naturally fluorescent, they were tested through Protocol A. Bifenazate was unstable in methanol, and D3598 was not well resolved by HPLC; therefore, neither analyte could be accurately quantified. Acceptable relative retention times through Protocol C were obtained with a DB-1 type column using either electron capture detection (ECD) or nitrogen-phosphorus detection (NPD). Apple samples, representing a non-fatty food, were spiked separately with bifenazate and D3598, and tested through Protocol D without Florisil cleanup. Interference from matrix components did not allow quantification of either analyte at the 0.1 ppm spiking level, and neither analyte was adequately recovered at the 2.0 ppm spiking level (recoveries ranged from 24 to 43%). Protocols E and F were not suitable for bifenazate and D3598 as recoveries from Florisil were all less than 30%. Conversion of bifenazate to D3598 and of D3598 to bifenazate was observed during testing of several methods. Therefore, none of the multiresidue methods are acceptable for analysis of bifenazate and D3598 residues. Data on the behaviour of the animal metabolites A1530 (1,1'-biphenyl, 4-ol) and A1530-sulfate through multiresidue method testing were not provided.

2.3.3 Methods for Residue Analysis of Plants and Plant Products

Although parent bifenazate was the predominant residue identified in apple, orange and cotton metabolism studies, the oxidative coulometric electrochemical detector used in the proposed enforcement method requires that bifenazate be maintained in a reduced state by the addition of ascorbic acid. As a result, the metabolite D3598 is converted to bifenazate, and combined residues of bifenazate and D3598 are detected. Therefore, in plant matrices, the residue of concern for enforcement and risk assessment purposes is defined as bifenazate and the metabolite D3598 (expressed as bifenazate).

A method was developed to determine residues of bifenazate (D2341) and the oxidized metabolite D3598 in plant matrices. Briefly, homogenized crop samples are extracted with ACN containing acetic acid; an optional additional hexane extraction step may be performed for orange samples. Samples are partitioned with 2% aqueous sodium sulfate and dichloromethane (DCM). The organic phase is dried and redissolved in HPLC mobile phase (ACN:NaOAc:HOAc) containing ascorbic acid, which reduces D3598 to bifenazate (D2341) and prevents oxidation of bifenazate. Combined residues of bifenazate and D3598 are quantified by reverse-phase HPLC with Oxidative Coulometric Electrochemical Detection (OCECD). The reported method limit of detection (LOD) is 0.005 ppm, and the limit of quantitation (LOQ) is 0.01 ppm.

Method validation was done for bifenazate and D3598 at spiking levels of 0.01 to 1.0 ppm in apples, apple pomace (bifenazate only), apple juice (bifenazate only), grapes, grape juice, raisins, strawberries, peaches, plums, prunes, peppers and cucumbers; as well as at spiking levels of 0.01 to 0.5 ppm in oranges, tomatoes, tomato puree and tomato paste. Mean recoveries for each matrix, analyte and spiking level were within the acceptable range of 70–120%.

Detector linearity was observed in the range of 0.005 to 0.100 ppm, with a coefficient of determination (r^2) of > 0.99. Some control samples contained low but detectable residues (0.006–0.008 ppm), and residues ≥ LOD in the controls were subtracted from the corresponding spiked samples to correct for background. The peaks of interest were well defined and symmetrical. In addition, there appeared to be no carryover to the following chromatograms. Additional peaks outside of the region of interest were observed in some samples.

The enforcement method for determination of bifenazate and D3598 residues in apples was successfully validated by an independent laboratory, indicating good reproducibility and reliability. Radiovalidation data provided to the USEPA were not submitted to the PMRA; according to the USEPA, the analytical method detected 75% and 71% of the residues detected by radioanalysis in the metabolism studies on apples and oranges, respectively.

The method was considered to be adequately validated in all crop matrices tested.

2.3.4 Methods for Residue Analysis of Food of Animal Origin

The residue of concern for enforcement and risk assessment purposes was defined in milk and ruminant tissues (except fat) as bifenazate plus the metabolites D3598 (expressed as bifenazate), A1530 and A1530-sulfate (expressed as A1530). The residue of concern was defined in ruminant fat as bifenazate plus the metabolite D3598 (expressed as bifenazate).

A method was developed to determine residues of bifenazate (D2341) and the metabolites D3598, A1530 and A1530-sulfate in bovine tissues and milk. The same method is to be used for data gathering and enforcement. Residues in homogenized fat are extracted with ACN, and coextracted lipids are precipitated by freezing. The fat extract is evaporated to dryness and redissolved in HPLC mobile phase (ACN:NaOAc:HOAc) containing ascorbic acid, which reduces D3598 to D2341 and prevents oxidation of D2341. Residues in milk and homogenized muscle, liver and kidney are extracted with ACN and ACN:0.1% aqueous acetic acid (HOAc) (1:1, v/v), and an aliquot of each extract is partitioned with 2% aqueous sodium sulfate and DCM. The organic phase is evaporated to dryness and redissolved in HPLC mobile phase containing ascorbic acid. Combined residues of D2341 and D3598 are quantified by reverse-phase HPLC-OCECD. A separate aliquot of each extract is incubated with concentrated HCl at 60°C to hydrolyse A1530-sulfate to A1530, then partitioned with 2% aqueous sodium sulfate and DCM. The organic phase is evaporated and redissolved in HPLC mobile phase containing ascorbic acid. In fat, A1530-sulfate is not a major metabolite, so fat is not analysed for A1530-sulfate and no A1530 hydrolysis step is conducted. Combined residues of A1530 and A1530-sulfate are quantified by reverse phase HPLC followed by fluorescence detection with an excitation wavelength of 270 nm and an emission wavelength of 370 nm. The LODs for the combined residues of bifenazate and D3598 (expressed as bifenazate) as well as for the combined residues of A1530 and A1530-sulfate (expressed as A1530) are each 0.005 ppm. The LOQs for the

combined residues of bifenazate and D3598 (expressed as bifenazate) as well as for the combined residues of A1530 and A1530-sulfate are 0.01 ppm.

The method gave acceptable recoveries (generally between 70% and 120%) and coefficients of variation (<20%) of D2341, D3598, A1530 and A1530-sulfate at spiking levels of 0.01 and 0.1 ppm in milk, muscle, liver, kidney and fat (fat was not spiked with A1530-sulfate, and D3598 spiking in fat was at 0.2 ppm instead of 0.1ppm). Linearity was observed in the range of 0.005 to 0.1 ppm D2341 and A1530, with coefficients of determination (r^2) of > 0.999. No residues were detected in control samples. The peaks of interest were well defined and symmetrical. In addition, there appeared to be no carryover to the following chromatograms, although additional peaks outside of the region of interest were observed in some samples. The enforcement method for determination of bifenazate-equivalent residues in bovine milk, liver, kidney and fat was successfully validated by an independent laboratory, indicating good reproducibility and reliability.

3.0 Impact on Human and Animal Health

3.1 Integrated Toxicological Summary

The toxicological database for bifenazate was complete and consisted of studies performed using rats, mice and dogs.

Technical grade bifenazate was considered to be of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was non-irritating to the skin and minimally irritating to the eyes of rabbits. Results of skin sensitization testing in guinea pigs using the Buehler method were negative; however, in documentation provided to the PMRA by Crompton Co., it was noted that bifenazate was a dermal sensitizer using the Magnusson/Kligman method (USEPA 2003). This study was not submitted to the PMRA for review. In view of the conflicting results from the two dermal sensitization studies, the PMRA choses to err on the side of conservatism and concludes that the label for Bifenazate Technical should reflect the dermal sensitization potential.

Floramite SC was of low acute toxicity by the oral and inhalation routes in rats, and was of low toxicity via the dermal route in rabbits. It was non-irritating to the skin and minimally irritating to the eyes of rabbits. A Buehler skin sensitization study in guinea pigs was negative.

Acramite 50WS was of low acute toxicity by the oral route in rats and mice, and of low acute toxicity via the dermal and inhalation routes in rats. It was minimally irritating to the skin and eyes of rabbits as well as was negative in a skin sensitization study in guinea pigs using the Buehler method.

Bifenazate was rapidly absorbed and eliminated in rats after both single and repeated dosing, with no apparent sex difference. Single low-dose animals absorbed ~85% of the

administered dose, whereas absorption appeared to be saturated at the high dose, as evidenced by 57–64% of the administered dose recovered in the feces in a biliary study. Fecal excretion was the primary route of elimination, with the biliary system contributing a major role in the process. Urinary excretion was a more minor route of excretion, and elimination in expired air was negligible.

In a repeated-dose study, approximately one third of the administered radiolabelled dose was excreted in the urine of both male and female rats, the majority of which was excreted within the first 24 hours after dose administration. Slightly more than half of the administered radiolabel was excreted via the feces. Biliary excretion was not examined.

Residual tissue/carcass radioactivity was < 0.6% of the administered dose after animals received either the single low dose, the single high dose or the repeated low dose. The highest concentrations in tissues were noted in the liver, whole blood and red blood cells after single dosing. High-dose females had higher radioactivity levels (twofold to threefold) in the spleen and red blood cells compared to males at 168 hours postdose. After repeated dosing, the highest concentrations were noted in the liver, kidneys and spleen.

Bifenazate underwent extensive metabolism. Three major urinary metabolites and five fecal metabolites were identified in addition to parent compound. Metabolic profiles were similar for both single- and repeat-dosing studies. A significant amount of parent compound was detectable in the feces of the high-dose group only, indicating saturation of the metabolic pathways.

The effects observed after short- and long-term exposure to bifenazate were consistent throughout the database, with the primary target being the hematopoietic system in all species, following both dietary and dermal exposure. The dog appeared to be the most sensitive species with respect to hematological effects. In rats, the females appeared to be more sensitive, which correlated with the finding in the metabolism study that females had higher radioactivity levels in the spleen and red blood cells compared to males. Evidence of a secondary response by the hematopoietic system was manifest as increased splenic extramedullary hematopoiesis, trace to moderate myeloid hyperplasia in the bone marrow as well as changes in other blood parameters.

Additional possible target organs included the liver (hepatocellular hypertrophy, weight changes, and the presence of pigment), kidney (weight changes and the presence of pigment), adrenals (vacuolization of the adrenal cortex in the rat) and mammary gland (edema and ductal epithelial hyperplasia in the 90-day dog study only). The effect on the adrenals was observed in high-dose male rats from the 90-day study only. Although it appears that male rats were not adequately challenged in the 2-year rat study, no effects on the adrenals were observed at the highest dose tested (10 mg/kg bw/day). Therefore, a no observed adverse effect level (NOAEL) for non-neoplastic adrenal effects after chronic dosing in rats is 10 mg/kg bw/day.

The NOAELs were equivalent in both the 90-day and 1-year dog studies, suggesting no increase in toxicity with increased duration of exposure. However, a number of additional parameters were affected in the 1-year study (moderate myeloid hyperplasia of the bone marrow, leukocytes, segmented neutrophils and plasma bilirubin) that were not affected in the 90-day study. No increase in toxicity with increased duration of exposure was observed in female rats; however, durational effects could not be adequately assessed in the males as the maximum tolerated dose was not attained in these animals in the 2-year study.

No evidence of carcinogenic potential was observed in mice or in female rats. Although male rats were not adequately challenged in the 2-year study, the dose levels chosen for the study appeared to be reasonable based on the effects observed in the female rats at the mid-dose in the 90-day study. In addition, no hyperplastic indices were observed in these animals, and bifenazate was determined to be non-genotoxic in both in vitro and in vivo mutagenicity studies.

In a two-generation reproductive toxicity study in rats, there were no effects on measured reproductive parameters, nor was there any offspring toxicity. Effects observed in the parental animals of both generations consisted solely of marginal decreases in body weight and body weight gain, although it should be noted that hematological parameters are not measured in this type of study. No evidence of teratogenicity was observed in developmental toxicity studies in both rats and rabbits. In a range-finding developmental toxicity study in rabbits, an increase in abortions as well as increased mortality were observed at dose levels of $\geq$ 200 mg/kg bw/day and $\geq$ 500 mg/kg bw/day, respectively; however, neither were observed in the main study at doses up to and including 200 mg/kg bw/day, which was the highest dose tested. There was no evidence of increased susceptibility of the young in any of the studies.

A functional observation battery (FOB) performed during weeks 8 and 13 of the 90-day rat study did not reveal any neurotoxic effects, and no other evidence of neurotoxic potential was observed throughout the bifenazate toxicology database.

Although effects on leukocytes (increased in dogs and decreased in mice) and lymphocytes (decreased in mice) were observed, these changes were not accompanied by any histopathological alterations in lymphoid tissues; therefore, the toxicologic relevance of these findings is uncertain.

3.2 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for bifenazate is 0.01 mg/kg bw/day. The 12-month dietary study in dogs was considered the most appropriate study to assess chronic dietary exposure. The NOAEL was 1.0 mg/kg bw/day, based on hematological effects, and the standard uncertainty factor (UF) of 100 is applied to account for intraspecies and interspecies variability.

The ADI is calculated according to the following formula:

$$ADI = \frac{NOAEL}{UF} = \frac{1.0 \text{ mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day}$$

3.3 Acute Reference Dose

No acute reference dose (ARfD) was determined as there were no toxicological concerns following acute exposures to bifenazate.

3.4 Toxicological Endpoint Selection: Occupational and Bystander Risk Assessment

Acramite 50WS will be applied as a foliar spray for the control of mites on apples and grapes at a maximum application rate of 421 g a.i./ha using ground application equipment (airblast). Handler exposure is expected to be predominantly by the dermal route, with inhalation exposure accounting for 1.4% of total deposition. Assuming that two days are required per application, the mixer/loader/applicator could potentially be exposed for up to two days per year. Handler exposure is, therefore, expected to be short term and intermittent. Postapplication, re-entry workers could have contact with foliage during scouting, pruning, thinning and harvesting activities. Exposure to re-entry workers is expected to be intermediate term in duration and predominantly via the dermal route.

Floramite SC will be applied indoors as a foliar spray for the control of mites on all types of ornamental plants, including bedding plants, flowering plants, foliage plants, bulb crops, perennial plants and woody plants. Floramite SC can be used in all indoor areas where plants are grown and/or maintained in containers or in the ground including greenhouses, shadehouses and interiorscapes. Floramite SC will be applied at a maximum rate of 0.159 kg a.i./ha (based on a spray rate of 2000 L/ha) using mobile or stationary high-volume hydraulic hand sprayers, or backpack equipment. Handler exposure is expected to be predominantly by the dermal route, with inhalation exposure accounting for a maximum of 4.6% of total deposition. One application may be made per crop cycle. Assuming that 2 days are required per application and that there are 5 crop cycles/year for ornamentals (chrysanthemums and roses), the mixer/loader/applicator could potentially be exposed for a total of 10 days per year per crop. If other crops (e.g., potted plants, bedding plants) are treated on a rotation basis, the frequency of exposure may increase. Handler exposure is, therefore, considered to be short to intermediate term in duration, on an intermittent basis. Postapplication, based on the nature of the re-entry activities associated with greenhouse operations (e.g., scouting, pinching, hand pruning, hand harvesting), there is potential for intermediate- to long-term exposure on an intermittent to continuous basis, predominately via the dermal route.

Given that a repeat-dose study was conducted via the most relevant route of exposure (dermal), the 21-day dermal study in rats was considered the most appropriate for use in the short-term risk assessment. In addition, as there was no pronounced increase in toxicity with increased duration of exposure, this study was also considered the most appropriate for use in the intermediate-term risk assessment. The NOAEL from this study

was 80 mg/kg bw/day, based on hematological effects at the next highest dose level. No additional uncertainty factors or safety factors were considered necessary in addition to the standard 100× uncertainty factor for intraspecies and interspecies variation. Therefore, the target margin of exposure (MOE) is 100.

In the absence of a long-term study conducted via the dermal route of exposure, the NOAEL of 80 mg/kg bw/day from the 21-day dermal toxicity study in the rat was also considered the most appropriate for use in the long-term risk assessment. An additional uncertainty factor was added, in addition to the standard 100×, to account for uncertainty regarding extrapolation to long-term exposure. Therefore, the target MOE is 300.

No repeat-dose toxicology studies were conducted via the inhalation route of exposure. Therefore, the combined results of the dietary studies in dogs (90-day and 12-month), with a NOAEL of 1.0 mg/kg bw/day, were considered the most appropriate for use in the risk assessment for inhalation exposures (all durations). This NOAEL was based on hematological effects and histopathology of the liver and kidney. Effects on hematological parameters were observed as early as the one-month sampling period in the 90-day dog study, thus supporting the use of this NOAEL for short-term exposure scenarios. No additional uncertainty factors or safety factors were considered necessary in addition to the standard 100× uncertainty factor for intraspecies and interspecies variation. Therefore, the target MOE is 100.

Dermal Absorption

Male Sprague Dawley rats were administered nominal doses of 0.0096 or 2.4 mg/cm² of bifenazate and monitored up to 168 hours post-dosing. All animals were exposed for a period of 6 hours. There were three monitoring periods: 6, 24 and 168 hours. Mean dermal absorption values (n=4) at 168 hours post-dosing for the 0.0096 and 2.4 mg/cm² dose levels were 13.20% and 6.54%, respectively. Total absorbed dose was calculated by adding the percentage of administered dose in urine, feces, cage wash, skin from the application site, liver, gastrointestinal tract and carcass. Blood samples were collected, but were not included in the calculation of total absorbed dose. No explanation was provided for this in the study report.

A high proportion of the applied dose was recovered (32.81–48.49%). This is considered a major limitation of the study. It is assumed that this proportion of the applied dose was not available for absorption. As such, the dose absorbed as a percentage of the available dose, as opposed to the percentage of the administered dose, was calculated. This more accurately reflects the degree of absorption. The absorbed dose as a percentage of the available dose for the low dose groups ranged from 26.03% to 32.46%. Given the limitations of this study, it is not considered to be appropriate to use these data quantitatively.

3.5 Impact on Human and Animal Health Arising from Exposure to the Active Substance or to its Impurities

3.5.1 Operator Exposure Assessment

3.5.1.1 Handler Exposure and Risk

Acramite 50WS

Acramite 50WS contains bifenazate at a guaranteed concentration of 0.5 g a.i./g product as a wettable powder formulation in water soluble pouches for the control of mites on apples and grapes. The most typical equipment used for application of insecticides to apples and grapes is an airblast sprayer pulled behind an open or closed cab tractor. Boom sprayers pulled behind tractors may also be used for broadcast applications over grape vines. The product is packaged in 227 g water soluble pouches. The product will be applied at a maximum rate of 3 pouches/0.8 ha (0.421 kg a.i./ha). The product may be applied once per season. The proposed label specifies that "Applicators and other handlers MUST WEAR: chemical resistant gloves, long-sleeved shirt and long pants, shoes plus socks."

Exposure to Acramite 50WS during mixing, loading and applying by airblast equipment was 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 that facilitate the generation of scenario-specific exposure estimates. To estimate exposure for each use scenario, appropriate subsets were created from the mixer/loader and applicator database files of the PHED. As PHED data are not available for mixers/loaders using soluble concentrate powder formulations in water soluble packaging, the PHED was subset to represent the following two exposure scenarios (based on workers wearing a single layer of clothing and gloves):

- mixer/loader—wettable powder open mixing/loading using a 90% protection factor to estimate exposure from water soluble packets; and
- applicator—open cab airblast.

All data were normalized for kilogram of active ingredient handled. Unit exposures are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. Unit exposures for mixer/loader and applicator are summarized in Appendix II, Table 1. The primary route of exposure was dermal, with inhalation accounting for a maximum of 1.4% of total deposition.

The exposure estimates and MOEs for farmers mixing, loading and applying Acramite 50WS using airblast equipment are summarized Appendix II, Table 2.

The dermal and inhalation MOEs for farmers mixing, loading and applying Acramite 50WS to apples and grapes for short-term duration while wearing single layer (long-sleeved shirt and long pants) plus gloves are acceptable. The combined MOE (dermal + inhalation) of 760 is acceptable.

Floramite SC

Floramite SC contains bifenazate at a guaranteed concentration of 22.6% (240 g a.i./L) as a liquid soluble concentrate formulation for the control of mites on all types of ornamental plants including bedding plants, flowering plants, foliage plants, bulb crops, perennial plants and woody plants grown indoor in greenhouses, shadehouses and interior plantscapes (interiorscapes). Typical equipment used to apply Floramite SC in greenhouses are hydraulic/compressed air high-volume sprayers with a single-nozzle that applies product as a foliar-directed spray. This would include a hand held spray gun/mobile hydraulic sprayer, high- or low-pressure spray line, or backpack sprayer. Automated, overhead high-volume boom sprayers may also be used in greenhouse settings. The product can be applied once/crop cycle. The product will be diluted at a rate of 133 mL/400 L water, and applied to foliage at up to 2000 L/ha. Assuming a spray rate of 2000 L/ha, the equivalent application rate is 0.159 kg a.i./ha. The proposed label specifies that "Applicators and other handlers MUST WEAR: chemical resistant gloves, long-sleeved shirt and long pants, shoes plus socks." A restricted entry interval (REI) for greenhouse ornamentals is not specified on the proposed label.

Exposure for mixing, loading and applying Floramite SC to greenhouse ornamentals was estimated using the PHED Version 1.1. To estimate exposure for workers wearing single layer and gloves, appropriate subsets of A, B and C were created from the following PHED database files:

- liquid, open pour, low-pressure handwand;
- liquid, open pour, high-pressure handwand; and
- liquid, open pour, backpack sprayer.

All data were normalized for kilogram of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. Unit exposures for mixer/loader/applicator are summarized in Appendix II, Table 3. The primary route of exposure was dermal, with inhalation accounting for a maximum of 4.6% of total deposition. Exposures are expected to be similar, or less, for shadehouses and interior plantscapes.

The exposure estimates and MOEs for greenhouse workers mixing/loading/applying Floramite SC using high-pressure or low-pressure handwand or backpack equipment are summarized in Appendix II, Table 4.

The dermal and inhalation MOEs for greenhouse workers mixer/loader/applicators applying Floramite SC to greenhouse ornamentals for short- to intermediate-term exposure are acceptable. The combined MOEs (dermal + inhalation) for low-pressure handwand, high-pressure handwand and backpack sprayer are 3850, 994 and 44 924, respectively. These combined MOEs are considered acceptable.

3.5.1.2 Postapplication Exposure and Risk

Bifenazate has a very low vapour pressure ($<1.33 \times 10^{-7}$ kPa) and is, therefore, considered non-volatile in both indoor and outdoor settings. Due to bifenazate's low

vapour pressure, postapplication inhalation exposure is expected to be insignificant relative to dermal exposure. Therefore, only postapplication dermal exposures will be quantified.

Acramite 50WS will be applied once per season using airblast application equipment. The product will be applied at a maximum rate of 3 pouches/0.8 ha (0.421 kg a.i./ha). For grapes, a range of re-entry activities take place at different stages of cultivation. Girdling, cane turning, leaf pulling, hand harvesting and tying were identified as frequent activities involving high levels of foliar contact. Cane turning is the cutting of the green canes hanging down by the grape bunches. Cane turning is not considered a major re-entry activity for grape production in Canada. Girdling is the removal of a ring of bark from the trunk, arm or cane below the fruit that it is intended to affect. Re-entry workers are assumed to work an eight-hour day. Exposures are expected to be short- to intermediate-term in duration and occur on a daily basis.

For apples, a range of re-entry activities take place at difference stages of cultivation. Thinning, pruning and harvesting were identified as frequent activities which involved high levels of foliar contact. Other re-entry activities such as scouting, weeding and irrigation occur less frequently and involve lower levels of foliar contact. Re-entry workers are assumed to work an eight-hour day. Exposures are expected to be short- to intermediate-term in duration and occur on a daily basis.

To estimate exposure to bifenazate residues during postapplication activities, dislodgeable foliar residue (DFR) data were used. A DFR study was submitted to estimate dislodgeable foliar residues and their dissipation on grapes at two test sites in California and New York. A single application of Acramite 50WS was applied at a rate of 0.56 kg a.i./ha (5.6 µg/cm²; the proposed Canadian rate is 4.21 µg/cm²). DFR levels were measured prior to application, 4–12 hours after application and then 1, 2, 3, 5, 10, 14, 21 and 28 days after application. The application method, application rates, frequency and monitoring times were relevant to the proposed use pattern.

At both test sites, DFR levels peaked on the day of application and decreased gradually until 28 days after application. By 28 days after application, measurable residues still remained on the foliage. Residues on the day of application at the New York site (mean = 0.894 µg/cm²) were higher than those at the California site (mean = 0.623 µg/cm²). Geographical and climatic conditions at the New York site are considered to be more relevant to Canadian growing regions given the growing season, average temperature and average precipitation. Based on an application rate of 5.6 µg/cm² and a mean DFR value on the day of application of 0.894 µg/cm², the percentage of the applied dose retained on the foliage at the New York site was determined to be 15.9%. The actual mean DFR data are summarized in Appendix II, Table 5. The R^2 value of the New York DFR data were less than 0.85; as such, the grape DFR data were not considered adequate for interpolation. Actual study data were used in determination of postapplication exposure and risk.

A DFR study was reported to be in progress for apples in California and New York using the same formulation and rate as the grape DFR study. However, the apple DFR study was not submitted to PMRA for review; therefore, the grape DFR study was used as surrogate data for apples. Submission of the apple DFR study will be required to confirm the evaluation of postapplication exposure of re-entry workers to bifenazate residues on apples.

The following equation was used to calculate risks for workers performing postapplication activities:

Dermal exposure (µg/kg bw/day) = (DFR × TC × ET) / (bw)

Where:

DFR	=	Dislodgeable foliar residue: Day zero values; sampled immediately after spray had dried (1–2 hours after application). The DFR values used were taken from the actual New York data (refer to Appendix II, Table 5)
TC	=	Transfer coefficient: refer to Appendix II, Table 6.
ET	=	Exposure time: 8 hours/day
bw	=	Body weight: 70 kg for adults (male and female)

To determine the potential exposure of re-entry workers, the DFR values were coupled with activity-specific transfer coefficients. Daily exposures and MOEs for workers conducting re-entry activities on apples and grapes are summarized in Appendix II, Table 6. MOEs approached the acceptable target MOE of 100. For grapes, an REI of 12 hours is considered acceptable for all activities except girdling and cane turning, which require a 5-day REI, as well as hand harvesting, tying, pruning, training, leaf pulling and thinning, which require a 2-day REI. For apples, an REI of 12-hours is considered adequate for all re-entry activities.

Floramite SC will be applied once per crop cycle to all types of indoor ornamental plants in greenhouses, shadehouses and interiorscapes. Floramite SC will be diluted at a rate of 133 mL/400 L water and applied as a foliar spray at up to 2000 L/ha. Cultivation of ornamentals in general, and cut flowers in particular, involves a number of re-entry activities with high postapplication exposure potential. These tasks include pruning, pinching, thinning and hand harvesting. Cultivation of cut flowers also involves bunching and bundling. It is assumed that workers conduct re-entry activities for 8 hours/day for 6 to 7 days per week; the range of re-entry activities and the types of plants handled vary throughout the day and from day to day, and re-entry activities are highly dependent on crop stage. Duration of exposures ranges from intermediate- to long-term (i.e., 5 months to 12 months per year). Exposures would be intermittent to continuous (i.e., every day) and are predominantly dermal.

There are no data to determine the transfer coefficients for all activities related to ornamentals other than cut flowers. Consequently, the transfer coefficients for cut flowers were used to conduct a quantitative exposure and risk assessment.

A summary of a DFR study for greenhouse ornamentals was submitted, which suggested that the mean DFR value on the day of application was 0.096 µg/cm². As only the summary was submitted, the PMRA cannot use the data quantitatively. As such, greenhouse DFR default assumption of 20% of the application rate was used for the fraction that is retained on foliage. Submission of the final report of the greenhouse DFR study will be required to support this evaluation.

The following equations were used to calculate exposure for workers performing postapplication activities:

Dermal exposure (µg/kg bw/day) = (AR × FR × TC × ET) / (bw)

Where:

AR	=	Application rate: the maximum application rate is 1.59 µg a.i./cm²
FR	=	Fraction retained on foliage: default of 20%
DFR	=	Dislodgeable foliar residue: DFR = (AR × FR) = (1.59 × 0.2) = 0.318 µg a.i./cm²
TC	=	Transfer coefficient: based on a generic transfer coefficient (refer to Appendix II, Table 7)
ET	=	Exposure time: 8 hours/day
bw	=	Body weight: 70 kg for adults (male and female)

To determine the potential exposure of greenhouse workers conducting re-entry activities, DFR values were coupled with generic transfer coefficients for ornamentals/cut flowers. Daily exposure and MOEs of greenhouse workers to bifenazate residues are summarized in Appendix II, Table 7.

The MOEs for greenhouse workers conducting re-entry activities on greenhouse ornamentals approach the target MOE of 300. Consequently, submission of the final report of the greenhouse DFR study will be required to confirm the PMRA's evaluation of the postapplication exposure of re-entry workers in greenhouses and shadehouses on ornamentals.

The MOEs for workers conducting re-entry activities on interior plantscapes were not quantified. However, given that re-entry activities with interior plantscapes are expected to involve less foliar contact and duration of exposure than greenhouses, the daily exposure to workers handling treated interior plantscapes is expected to be less than exposures in a greenhouse setting.

3.5.2 Bystanders

Acramite 50WS

There is limited potential for dermal exposure to adults and youth to Acramite 50WS during harvesting apples at pick-your-own operations. Harvesting apples at a pick-your-own operation is expected to occur only once per year. As no endpoints of acute toxicological concern were identified, a quantitative exposure assessment was not required for the pick-your-own scenario.

Floramite SC
For the proposed greenhouse-use scenario, bystander exposure and risk during and after application was considered minimal compared to mixer/loader/applicator scenarios and, therefore, not quantified.

3.5.3 Workers

Refer to Section 3.5.1.2.

3.5.4 Consumers

No residential uses are requested and no toxicological endpoints of concern were identified for bystander exposure. Therefore, an aggregate residential and dietary risk assessment is not required.

4.0 Residues

4.1 Residue Summary

4.1.1 Nature of the Residue in Plants

Apple Metabolism
Bifenazate was radiolabelled uniformly in the phenyl ring ([^{14}C]-D2341). It was formulated as a 50% wettable powder and applied once as a foliar spray to apple trees under field conditions. The total radioactive residues (TRRs) in apples harvested 101 days after treatment at 0.42 kg a.i./ha or 2.24 kg a.i./ha were 0.088 ppm and 0.373 ppm, respectively. Detailed residue characterization was performed only on fruit treated at the higher rate. A surface wash with ACN removed 65.5% of the TRRs (0.244 ppm). In total, identified residues accounted for 52.8% of the TRRs (0.197 ppm) in the mature apples. The predominant residue was parent bifenazate (46.9% of the TRRs; 0.175 ppm). Other minor residues identified were D3598 (diazinecarboxylic acid, 2-(4-methoxy-[1,1',-biphenyl]-3-yl), 1-methylethyl ester), D4642 (diazinecarboxylic acid, 2-(4-methoxy-[1,1',-biphenyl]-3-yl), 1-methylethyl ester 2-oxide), D1989 (1,1'-biphenyl, 4-methoxy), and D6887 (carbamic acid, (4-methoxy-[1,1'biphenyl]-3-yl)-, 1-methylethyl ester), each at ≤4.5% of the TRRs (≤0.017 ppm). Unidentified polar components were characterized at 22.0% of the TRRs (0.082 ppm); no single component exceeded 7.4% of the TRRs (<0.028 ppm).

Orange Metabolism
Bifenazate was radiolabelled uniformly in the phenyl ring ([^{14}C]-D2341). It was formulated as a 50% wettable powder and applied once as a foliar spray to orange trees grown in containers under a polyethylene roof and exposed to ambient environmental conditions. The TRRs in oranges harvested at 43 days after treatment, following treatment at 0.42 kg a.i./ha or 2.24 kg a.i./ha were 0.353 ppm and 1.466 ppm, respectively. Detailed residue characterization was performed only on mature fruit

treated at the higher rate. Surface washing with ACN removed 80.6% of the TRRs (1.182 ppm). In total, identified residues in the mature oranges accounted for 86.5% of the TRRs (1.268 ppm). The predominant residue was parent bifenazate (79.2% of the TRRs; 1.121 ppm). Minor metabolites identified were D3598, D4642, D1989 and D9963 [(1,1'-biphenyl)-4-methoxy-3-ol], each at ≤6% of the TRRs (≤0.088 ppm). Unidentified polar components were characterized at 5.9% of the TRRs (0.086 ppm); no single component exceeded 1% of the TRRs (<0.015 ppm).

Cotton Metabolism

Bifenazate was radiolabelled uniformly in the phenyl ring ([^{14}C]-D2341). It was formulated as a 50% wettable powder and applied once as a foliar spray to cotton plants grown outdoors in pots, at the late bloom to early boll stage (beginning of the cotton boll formation). The application rate was 0.56 or 2.24 kg a.i./ha, but detailed residue characterization was performed only on samples from the high rate treatment group. The TRRs in gin trash (leaves, petioles, calyx and unopened immature bolls) and cotton seed harvested 112 days after treatment were 0.838 ppm and 0.125 ppm, respectively. Identified residues accounted for 50.6% of the TRRs in gin trash (0.424 ppm). The predominant residue identified was parent bifenazate (40.3% of the TRRs; 0.338 ppm). Minor metabolites identified were D3598, D4642, D1989, A1530 (1,1'-biphenyl, 4-ol) and D9963, each at ≤6.1% of the TRRs (≤0.051 ppm). Less than 0.3% of the TRRs in cotton seed were identified. Unidentified polar components accounted for 11.4% of the TRRs (0.014 ppm) in cotton seed and 22.6% of the TRRs (0.189 ppm) in gin trash; no single component exceeded 2% of the TRRs (<0.02 ppm). Bound residues were characterized as protein (24.1% of the TRRs, 0.030 ppm in seed), carbohydrate (11.8% of the TRRs, 0.099 ppm in gin trash; 12.2% of the TRRs, 0.015 ppm in seed) and lignin (19.2% of the TRRs, 0.160 ppm in gin trash; 30.7% of the TRRs, 0.039 ppm in seed). In cotton seed, radioactivity was reincorporated into fatty acids of triglycerides (22.7% of the TRRs; 0.028 ppm).

4.1.2 Bifenazate Metabolism in Plants

The metabolic profiles for bifenazate were similar in apples, oranges and cotton. After foliar application of bifenazate, there was little translocation of residues from the leaves to the fruit or seed. Radioactivity was present primarily as surface residues, with little penetration into the edible portions of the fruit or seed. The parent compound bifenazate was the predominant metabolite identified in the three crops, and no other metabolites were identified at > 10% of the TRRs. The metabolism of bifenazate proceeded via oxidation, loss of the hydrazine carboxylic acid group, demethylation and hydroxylation. In addition, bound residues were formed by reaction with natural matrix components.

As only fruit and oilseed metabolism studies have been submitted, the nature of the residue of bifenazate in all plants is not understood. However, the metabolic profile for apples, orange and cotton can be extended to all proposed crops in the current submission (apple, grape, peach and strawberry). For future use expansions, additional metabolism studies conducted in dissimilar crops (i.e., root/tuber vegetable, small grain, *Brassica* vegetable or leafy vegetable) may be required.

Although parent bifenazate was the predominant residue identified in apple, orange and cotton metabolism studies, the oxidative coulometric electrochemical detector used in the proposed enforcement method requires that bifenazate be maintained in a reduced state by adding ascorbic acid. As a result, the metabolite D3598 is converted to bifenazate, and combined residues of bifenazate and D3598 are detected. Therefore, in plant matrices, the residue of concern for enforcement and risk assessment purposes is defined as bifenazate and the metabolite D3598 (expressed as bifenazate).

4.1.3 Confined Accumulation in Rotational Crops

Bifenazate formulated as a 50% wettable powder, radiolabelled uniformly in phenyl ring ([^{14}C]-D2341), was applied to loamy sand soil in pots inside a greenhouse, at a rate of 0.56 kg a.i./ha or 5.6 kg a.i./ha. Lettuce, carrots and wheat were planted at 30- and 125-day plantback intervals (PBIs); wheat was also planted at a 360-day PBI (low rate only). Following soil treatment at 0.56 kg a.i./ha, TRRs accumulated at ≥ 0.010 ppm in mature lettuce at the 30-day PBI (0.014 ppm) and in all wheat commodities (forage, straw, chaff and grain) at the 30-, 125- and 360-day PBIs (0.011–0.117 ppm). Following the soil treatment at 5.6 kg a.i./ha, TRRs accumulated at ≥ 0.010 ppm in all crop matrices at all plantback intervals tested. The highest residues were found in wheat straw. Radioactivity in all crops generally decreased with longer plantback intervals. No metabolites were identified in any rotational crop matrix. The majority of the radioactivity in the rotational crop matrices was present as minor unidentified polar metabolites or bound to the plant matrix.

4.1.4 Field Accumulation in Rotational Crops

No field rotational crop study is required at this time as no residues were identified in rotational crops under confined conditions and none of the crops in the proposed use pattern are rotated. Therefore, no plantback restrictions are necessary at this time.

4.1.5 Nature of the Residue in Animals

Metabolism in Lactating Goat

Bifenazate was radiolabelled uniformly in the phenyl ring ([^{14}C]-D2341). It was administered orally by capsule to a lactating goat at a dose level of 10 mg/kg wet feed on a daily basis for 4 consecutive days. In total, 68.2% of the administered dose (% AD) was recovered in excreta (feces 46.5%; urine 19.5%), milk (0.22%), and tissues (1.98%). In tissues, the highest residue levels were in liver (1.773 ppm) and kidney (0.263 ppm). The predominant residues identified were A1530-sulfate in milk (40.7% of the TRRs; 0.019 ppm), A1530 in kidney and muscle (11.6–13.6% of the TRRs; 0.002–0.036 ppm) and bifenazate in fat (53.1–58.5% of the TRRs; 0.061–0.066 ppm). Minor residues identified, each at < 9% of the TRRs (<0.03 ppm) were bifenazate (milk, loin muscle, kidney, liver), D3598 (milk, muscle, fat, kidney, liver), A1530 (milk, fat, kidney, liver), D1989 (milk, muscle, fat, kidney, liver) and D9569 ([1,1'-biphenyl]-4,4'-diol in liver, kidney). Conjugates of A1530 (sulfate and glucuronide) and bifenazate (glucuronide) were characterized in muscle, fat, kidney and liver at 1.5–21.9% of the TRRs

(0.002–0.038 ppm). Residues in liver and kidney were covalently bound to protein (42.2–78.3% of the TRRs; 0.111–1.388 ppm). The metabolism of bifenazate in lactating goat proceeds via oxidation, loss of the hydrazine carboxylic acid group, demethylation and hydroxylation. Conjugation with glucuronic acid or sulfate groups and covalent binding to amino acids or peptides also occurs.

The oxidative coulometric electrochemical detector used in the proposed enforcement method requires that bifenazate be maintained in a reduced state by the addition of ascorbic acid. As a result, the metabolite D3598 is converted to bifenazate, and combined residues of bifenazate and D3598 are detected. Therefore, the residue of concern for enforcement and risk assessment purposes in ruminant fat is defined as bifenazate and the metabolite D3598 (expressed as bifenazate), and the residue of concern for enforcement and risk assessment purposes in milk and ruminant tissues (except fat) is defined as bifenazate as well as the metabolites D3598 (expressed as bifenazate), A1530 and A1530-sulfate (expressed as A1530).

As there are no poultry feed items in the proposed use pattern, a hen metabolism study is not required at this time. However, should the petitioner requests registration for use of bifenazate on poultry feed items, a metabolism study in laying hen will be required.

Methods for Residue Analysis of Plants and Plant Products

A method (HPLC-OCECD; Jablonski 1998) was proposed for data gathering and enforcement purposes. The method LOQ for combined residues of bifenazate and the metabolite D3598 was reported as 0.01 ppm. This method was found to give acceptable recoveries (generally 70–120%; coefficient of variation [CV] < 20%) for the analysis of apples, apple pomace, apple juice, grapes, grape juice, raisins, strawberries, peaches, plums, prunes, oranges, peppers, cucumbers, tomatoes, tomato puree and tomato paste. The independent laboratory validation supported the reliability and reproducibility of the method for the determination of bifenazate and D3598 in plant matrices. Radiovalidation data were provided to the USEPA; according to their review, the analytical method detected 75% and 71% of the residues detected by radioanalysis in the metabolism studies on apples and oranges, respectively. Bifenazate and the metabolite D3598 were screened through the multiresidue methods A, C, D, E, and F, as described in the PAM, Volume I, Third Edition (1994). None of the multiresidue methods are acceptable for analysis of bifenazate and D3598 residues.

Methods for Residue Analysis of Food of Animal Origin

A method (HPLC-OCECD, HPLC-fluorescent detection; Jablonski 1999) was proposed for data gathering and enforcement purposes. The LOQ for combined residues of bifenazate and D3598 (expressed as bifenazate) was stated as 0.01 ppm (milk and all tissues), and the LOQ for combined residues of A1530 and A1530-sulfate (expressed as A1530) was stated as 0.01 ppm (milk and tissues except fat). This method was found to give acceptable recoveries (generally 70–120%; CV < 20%) for the analysis of livestock matrices. The independent laboratory validation supported the reliability and reproducibility of the method for the determination of combined residues of bifenazate, D3598 (expressed as bifenazate), A1530 and A1530-sulfate (expressed as A1530) in

milk, liver and kidney as well as for combined residues of bifenazate and D3598 (expressed as bifenazate) in fat.

Bifenazate and the metabolite D3598 were screened through the multiresidue methods A, C, D, E and F, as described in the PAM, Volume I, Third Edition (1994). None of the multiresidue methods are acceptable for analysis of bifenazate and D3598 residues. Data on the behaviour of the animal metabolites A1530 and A1530-sulfate through multiresidue method testing were not provided.

4.1.6 Storage Stability Data

Plant Matrices

In the freezer storage stability study, samples were spiked separately with bifenazate and the metabolite D3598 at 0.1 ppm, and stored at ≤-8°C. The data indicated that residues of bifenazate and D3598 were stable for 224 days on the surface of apple, grape and peach. In homogenized crops, bifenazate residues were stable for 7 days in grape and peach, 42 days in apple, 75 days in orange, and 180 days in pepper, strawberry and prune; residues of D3598 were stable for 7 days in grape, 42 days in peach and apple, 182 days in prune, and 186 days in pepper. Residues of bifenazate were stable in apple juice for 295 days, in apple pomace for 181 days, and in grape juice for 186 days. Residues of D3598 were stable in grape juice for 186 days.

Due to the apparent instability of residues in some crop homogenates, samples in the supervised residue trials and processing studies were stored as whole fruit as long as possible to minimize the storage of homogenates. The storage intervals of whole and homogenized crop samples in apple, grape, strawberry and peach supervised residue trials as well as in apple and grape processing studies have been validated by the storage stability data provided.

Animal Matrices

In the freezer storage stability study, samples of milk and homogenized muscle, liver, kidney and fat were spiked separately with bifenazate, D3598 or A1530 at a level of 0.2 ppm, and stored at ≤-20°C. The data indicated that residues of bifenazate and D3598 were stable in milk for 202 days and in fat for 95 days, but were rapidly degraded in muscle, kidney and liver (losses of 28 to 91% after 2 days of storage). Residues of A1530 were stable in milk for 202 days, muscle for 28 days, liver for 76 days, kidney for 14 days and fat for 95 days.

Due to the apparent instability of residues in some tissues, samples in the livestock feeding study were analysed within one day of animal sacrifice. Therefore, the storage intervals of animal matrices have been validated by the storage stability data provided.

4.1.7 Crop Field Trials

Apple

Supervised crop field trials in apples were conducted in growing regions representative of Canada, in zones 1 (four trials), 1A (one trial), 5 (four trials), 5B (three trials) and 11 (five trials). Apples were treated once at 0.56 kg a.i./ha (1.3-fold the Canadian label rate). The maximum residues in apples collected at a preharvest interval (PHI) of 7 days were 0.575 ppm. Residues in apples decreased with increasing PHIs. A maximum residue limit (MRL) of 0.6 ppm should be established to cover residues of bifenazate and the metabolite D3598 in/on apple resulting from treatment at the maximum label rate (0.42 kg a.i./ha) and harvested at the label PHI (7 days).

Grape

Supervised crop field trials in grapes were conducted with bifenazate in growing regions representative of Canada, in zones 5 (four trials) and 11 (two trials). Grapes were treated once at 0.56 kg a.i./ha (1.3-fold the Canadian label rate). The maximum residues in grapes collected at a PHI of 14 days were 0.97 ppm. Residues in grapes did not increase with increasing PHIs. An MRL of 1.0 ppm should be established to cover residues of bifenazate in/on grape resulting from treatment at the maximum label rate (0.42 kg a.i./ha) and harvested at the label PHI (14 days).

4.1.8 Processed Food/feed

Apple

Bifenazate was applied to apples at 2.8 kg a.i./ha, and the apples were processed into wet pomace and juice. A comparison of the residues in the raw agricultural commodity (RAC) with those in each processed fraction resulted in a concentration factor of 1.8-fold for wet apple pomace and a reduction factor of 0.2-fold for apple juice. MRLs will not need to be established to cover residues of bifenazate in apple processed fractions. The MRL for the RAC will cover residues in apple juice, and it is not necessary to consider the processing factor for wet apple pomace as this is not a human food commodity.

Grape

Bifenazate was applied to grapes at 2.8 kg a.i./ha, and the grapes were processed into raisins and juice. A comparison of the residues in the RAC with those in each processed fraction resulted in a concentration factor of 1.2-fold for raisins and a reduction factor of 0.1-fold for grape juice. The maximum residue expected on raisins, based on the highest average field trial (HAFT) for grape (0.97 ppm) and the average concentration factor for raisins (1.2-fold), would be 1.16 ppm. Consequently, an MRL of 1.2 ppm should be established to cover residues of bifenazate in/on raisins. An MRL will not need to be established to cover residues of bifenazate in grape juice, as these residues will be covered by the MRL for the RAC.

4.1.9 Meat/Milk/Poultry/Eggs

Dairy cows were administered 1, 3 or 10 ppm bifenazate daily in the diet for 28 days. Based on the proposed Canadian use pattern (apple pomace is the only livestock feed item), the maximum theoretical dietary burden (MTDB) for cattle is 1.0 ppm. The expected residues in milk and meat (except fat) resulting from feeding at 10× the MTDB are < LOQ (<0.02 ppm), and the expected residues in fat resulting from feeding at 1× the MTDB are < LOQ (<0.01 ppm). Consequently, MRLs to cover bifenazate residues in animal commodities should be established at 0.02 ppm for milk and ruminant tissues (except fat), and at 0.01 ppm for ruminant fat.

As there are no poultry feed items in the proposed use pattern, a feeding study in poultry is not required. However, if the petitioner requests registration for use of bifenazate on poultry feed items, a poultry feeding study may be required in the future.

4.1.10 Dietary Risk Assessment

The proposed Canadian use of bifenazate on apples and grapes does not pose an unacceptable chronic dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and Behaviour in the Environment

5.1 Physical and Chemical Properties Relevant to the Environment

Bifenazate has a low solubility in water (3.76 mg/L) under environmentally relevant pH conditions. The low values of vapour pressure (< $1.33 \times l0^{-5}$ Pa at 20°C) and Henry's law constant (< $1. 0 \times 10^{-8}$ atm m^3/mole) indicate that bifenazate is non-volatile under field conditions and from moist soil and water surfaces. Bifenazate has a potential for bioaccumulation in organisms (log K_{ow}: 3.4). The dissociation constant value (pK_a: 12.94 ± 0.06 at 23°C) indicates that bifenazate exists mostly as an undissociated molecule in environmentally relevant pH conditions. The UV/visible absorption spectrum (maximum at 264 nm) suggests that bifenazate has a low potential for phototransformation in the environment (Appendix IV, Table 1).

5.2 Abiotic Transformation

Phenyl-ring labelled [^{14}C]bifenazate hydrolysed rapidly and completely with half-lives of 9.0 days, 6.0 days, 16.8 hours and 1.45 hours at pH 4, pH 5, pH 7 and pH 9, respectively (Appendix IV, Table 2). The rate of hydrolysis was pH dependent, the most rapid at pH 9 (DT_{50}: 1.45 hours) and the slowest at pH 4 (DT_{50}: 9.0 days). No residues of the parent compound were detected in any of the pH solutions at the end of the 30-day study period. Three major hydrolysis products, D3598, D9472 and D1989, and one unidentified major product (molecular weight of 384, $H_{20}C_{25}O_4$ or $H_{20}C_{24}N_2O_3$), were detected in all the pH buffer solutions. One minor transformation product, D9963, was detected with a

maximum of 6.6% applied radioactivity (AR) in pH 9. These results indicate that hydrolysis is an important route of transformation in the environment.

Phenyl-ring labelled [^{14}C]bifenazate transformed completely on soil with half-lives of 0.28 and 0.17 hours in the dark and light-exposed samples, respectively. Due to the rapidity of the transformation in both the irradiated and dark controls soils, possibly due to hydrolysis, net photolysis half-life could not be calculated. Two major transformation products, D3598 and D1989, were detected in both the dark control and light-exposed samples. The half-lives of 22 and 64 hours in the dark and light-exposed samples, respectively, indicate that D3598 is rapidly transformed in soils.

In the aquatic environment, the half-lives of 1.9 to 16.2 hours indicate that phototransformation of bifenazate in water would be an important route of transformation in the environment. No residues of parent compound were detected in both the irradiated and dark samples at the end of the 3-day study period. There were four major transformation products, D3598, D9472, D1989 and D9963, detected in the irradiated samples. Total CO_2 evolved amounted to a maximum of 4% AR, and no volatiles were formed.

The low vapour pressure ($< 1.33 \times l0^{-5}$ Pa at 20°C) and Henry's law constant ($<1.0 \times 10^{-8}$ Pa.m^3/mole) indicate that bifenazate is essentially non-volatile and volatilization would not be an important route of transformation in the environment.

5.3 Biotransformation

Phenyl ring-labelled [^{14}C]bifenazate transformed rapidly in a sandy loam soil under aerobic conditions with a half-life of less than 0.5 hour. The parent compound decreased to 2.8% by 0.5 hour post-treatment and was 0.6% at day 28 post-treatment. These values indicate that bifenazate is non-persistent in the terrestrial environment under aerobic conditions. Two major transformation products, D3598 (92% AR) and D1989 (26.8% AR), were detected. The half-life (10.2 hours) and the concentration at the end of the study period (2.8%) indicate that D3598 is also non-persistent in soils under aerobic conditions. For D1989, maximum concentration of 26.8% AR was observed at day 3 post-treatment, which declined to 21.9% AR by the end of the 28-day study period. Non-extractable [^{14}C] residues were 73.8% AR at day 28 post-treatment. The evolved $^{14}CO_2$ accounted for 1.1% AR and no other organic volatile compounds were detected.

In aerobic river and pond sediment/water systems, phenyl-ring labelled [^{14}C]bifenazate transformed rapidly with DT_{50} values of less than 6 hours. No residues of parent compound were detected after seven days of incubation. Two major transformation products, D3598 (DT_{50} 1.0–5.0 days) and D9472 (DT_{50} 2.0–4.5 days), were detected in both systems. Both products decreased to less than 1.3% AR at the end of the study period. These values indicate that the parent compound and the transformation products are non-persistent in the aquatic environment under aerobic conditions. The DT_{90} values of 19–23 and 4.8–5.0 days for D3598 and D9472, respectively, indicate that both transformation products have a low potential for a residue carryover. Nine additional

minor transformation products were detected, none of which individually exceeded 7% of the AR. Two of these products were identified as D9963 and A1530. The formation of $^{14}CO_2$ was significant, (22.6–33.7% AR) in both pond and river systems.

Under anaerobic sediment/water systems, phenyl-ring labelled [^{14}C]bifenazate transformed slowly, with a half-life of 77.9 days. This value indicates that bifenazate is moderately persistent in the aquatic environment under anaerobic conditions. The parent compound was present at 4.8% AR at the end of the 356-day study period. Upon application to the water surface, most of the parent compound immediately partitioned to the sediment phase. Two major transformation products, desmethyl D3598 (14.7% AR) and A1530 (24.8%) were identified. Desmethyl D3598 was extremely unstable during isolation and converted almost immediately to A1530. At the end of the 12-month study period, desmethyl D3598 and A1530 were present at 11.4 and 21.6 % AR. Minor transformation product D3598 was detected with a maximum concentration of 3.7% AR at day 0, which transformed with a DT_{50} of 5.5 days. Non-extractable ^{14}C was 51.5% AR at the end of the study period. No organic volatiles ^{14}C were detected, and the total $^{14}CO_2$ released was < 0.2%.

As hydrolysis is also an important route of transformation, especially under alkaline pH conditions, the rapid transformation observed in aerobic conditions is due to both biotransformation and hydrolysis.

5.4 Mobility

Unaged soil column leaching study with two sandy loams, a silt clay and a silt loam indicated that the parent compound and major transformation products D3598 and D1989 have a low potential to leach in soils. The total amount of applied radioactivity leached was < 2.2% AR in all the soils and less than 0.2% AR was detected in soil depths greater than 24 cm. Over 93% of the AR was detected in the top 6 cm of the silt loam, sandy loam and silt clay loam soil columns, and 76.3% in the another sandy loam column. The concentrations of the parent compound in 0–6 and 6–12 cm soil depths were 1.7–9.3 and ≤ 0.1% AR, respectively. No residues were detected beyond the 12 cm soil depth. D3598 and D1989 reached maximum concentrations of 10.4 and 26.1% AR in a silty clay loam, respectively. In the soil, extractable and bound residues ranged from 39.2 to 65.3 and from 35.2% to 61.9% AR, respectively.

Bifenazate is essentially non-volatile; therefore, data on its mobility in air are not required.

The adsorption K_d values for the major transformation product, D1989, were 84, 5, 77, 38 and 246 for silt loam, sandy loam 1, silt clay loam, sandy loam 2 and loam sediment, respectively. The corresponding K_{oc} values were 3905, 3011, 3962, 3725 and 6185. Based on K_{oc} values, D1989 was slightly mobile in four agricultural soils and immobile in a sediment.

5.5 Dissipation and Accumulation Under Field Conditions

Under Canadian and comparable American field conditions, bifenazate and major transformation product D3598 transformed rapidly in loam, silt loam and sandy loam soils, with half-lives (bifenazate + D3598) ranging from 4 to 6 days. In other American field studies, the half-lives were 4 to 5 days. These values indicate that bifenazate and major transformation product D3598 were non-persistent under Canadian use conditions. These results are in agreement with those of the laboratory, which indicated rapid transformation by hydrolysis, phototransformation and biotransformation. Another major transformation product, D1989, was also detected, but no residues were detected after 60 days post-treatment. The DT_{90} values for bifenazate + D3598 under Canadian field conditions were less than 22 days, and neither the residues of parent compound nor the transformation products were detected in soils after 90 days post-treatment. The parent compound and transformation products, therefore, have no potential for residue carryover to the following crop season. No residues were detected below 30 cm soil depth; therefore, the parent compound and transformation products have a low potential to leach and contaminate the groundwater under field conditions. As no leaching or volatilization is expected, transformation appears to be the major route of dissipation under field conditions.

5.6 Bioaccumulation

The applicant requested a waiver for a fish bioaccumulation, in response to a data gap based on a log K_{ow} of 3.4. The waiver was based on rapid transformation of bifenazate in aquatic systems, which makes the measurement of fish bioaccumulation experimentally difficult. Bifenazate degrades rapidly in natural water and sediments (aerobic DT_{50}: < 6h) and is also unstable under photolytic conditions ($t_{½}$:1.9 hours). The applicant also reported a bioconcentration factor (BCF) of 155 [log BCF = 0.85(log K_{ow})–0.70, Veith, DeFoe and Bergstedt 1979, based on experimentally determined log K_{ow} of 3.4] and of 83, calculated from the USEPA bioaccumulation predictor model BCFWINNT. These values indicate that Bifenazate has a low potential for bioaccumulation in fish and other organisms. Therefore, the reviewer accepted the waiver request.

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Bifenazate transforms rapidly in soils and is non-persistent (laboratory aerobic soil $t_{1/2}$ < 0.5 hour and field DT_{50} of parent + D3598: 4 to 6 days). Important routes of transformation are hydrolysis, especially in neutral and alkaline conditions ($t_{½}$: 6.0 days at pH 5, 16.8 hours at pH 7 and 1.45 hours at pH 9), phototransformation ($t_{1/2}$: 0.17 hour) and biotransformation (aerobic soil $t_{1/2}$ < 0.5 hour) (Appendix IV, Table 2). Three major transformation products were detected in soils under laboratory conditions: D3598 and D1989 in the hydrolysis, phototransformation and aerobic biotransformation studies; and D9472 in the hydrolysis studies (Appendix IV, Table 3). One minor transformation product, D9963, was also detected in the hydrolysis studies. Under field conditions, major transformation products D3598 and D1989 were detected; however, they were non-persistent as no residues were detected after 60–90 days postapplication.

A laboratory soil column leaching study indicated that the parent compound has a low potential to leach in soils. Under field conditions, the parent compound and transformation products did not leach beyond 30 cm soil depth; therefore, they have a low potential to leach and contaminate groundwater. The field DT_{90} values (<22 days) and the absence of residues at 90 days postapplication indicate that the parent compound and transformation products do not accumulate in soils; therefore, the parent compound and transformation products have no residue carryover to the following crop period. As leaching was minimal and no volatilization expected, transformation appears to be the principal route of dissipation under field conditions.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

Bifenazate transforms rapidly in the aquatic environment by hydrolysis, especially in neutral and alkaline conditions ($t_{½}$: 6.0 days at pH 5, 16.8 hours at pH 7 and 1.45 hours at pH 9), by phototransformation ($t_{1/2}$: 1.9–16.2 hours), and by biotransformation under aerobic conditions ($t_{½}$ < 6 hours) (Appendix IV, Table 4). Parent compound is, therefore, non-persistent in the aquatic environment under aerobic conditions. A sediment/water study, however, indicated that it is moderately persistent under anaerobic conditions ($t_{½}$: 77.9 days). Five major transformation products were detected in aquatic systems: D3598, D1989, D9963, D9472 and A1350 (Appendix IV, Table 6). Bifenazate has a low potential for bioaccumulation in fish and other organisms.

5.9 Expected Environmental Concentrations

Floramite SC
According to the Floramite SC label, the proposed maximum application rate is 125 mL (30 g a.i.)/400 L water for indoor ornamental use. Ornamental outdoor use and greenhouse vegetable use are not supported by the PMRA. As environmental exposure of bifenazate through treated vegetation, soil and water is limited with the proposed indoor use, the expected environmental concentrations (EECs) were not calculated.

Acramite 50WS
The EECs in soil, water and diets of birds and mammals are presented in Appendix IV, Table 8. These EECs were estimated assuming a conservative scenario in which the proposed maximum application rates of Acramite 50WS is over sprayed on soil, water and vegetation.

6.0 Effects on Non-target Species

6.1 Effects on Terrestrial Organisms

Bifenazate is toxic to earthworms, with 14-day no observed effect concentration (NOEC) and lethal concentration 50% (LC_{50}) values of 76 and > 1083 mg a.i./kg, respectively (Appendix V, Table 1). Bifenazate would, therefore, adversely affect them at concentrations greater than 76 mg a.i./kg soil. Bifenazate is moderately toxic to bees,

with a no observed effect level (NOEL) and lethal dose 50% (LD_{50}) of 2.7 and 7.8 µg/bee, respectively. Bifenazate would have adverse effects on predatory and parasitic arthropods if the application rates exceed 5 g a.i./ha.

Bifenazate is slightly toxic to wild birds on an acute basis. The acute LD_{50} and NOEL for the bobwhite quail were 1032 and 276 mg a.i./kg bw, respectively. The dietary LC_{50} and NOEC for the bobwhite quail were 2077 and 292 mg a.i./kg diet, respectively. The corresponding values for the mallard were 656 and 292 mg a.i./kg diet. These values indicate that bifenazate is slightly toxic to moderately toxic to birds on a short-term dietary basis. Bifenazate has no adverse effects on the reproductive performance of bobwhite quail and mallard up to 262.5 and 115 mg a.i./kg diet, respectively. Bifenazate is practically non-toxic to the rat on an acute basis (LD_{50} > 5000 mg a.i./kg bw). The 90-day and 2-year dietary NOECs for rat were 40 and 80 mg a.i./kg diet, respectively. For the mouse, 2-year NOEC was 10 mg a.i./kg diet. Reproductive performance of wild mammals would be adversely affected at concentrations greater than 200 mg a.i./kg diet.

Bifenazate has no adverse effects on non-target plants, as the application of 1.10 kg a.i./ha did not affect the seedling emergence and vegetative vigour of several crop plants.

6.2 Effects on Aquatic Organisms

Bifenazate is highly toxic to daphnids (LC_{50}: 0.50 mg a.i./L), cold water (NOEC and LC_{50}: 0.16 and 0.76 mg a.i./L, respectively) and warm water fish (NOEC and LC_{50}: 0.30 and 0.58 mg a.i./L, respectively) on an acute basis (Appendix V, Table 2). It would adversely affect algae at concentrations greater than 0.252 mg a.i./L water. Bifenazate had no significant negative effect on the growth of duckweed up to 3.82 mg a.i./L, the highest concentration tested. Bifenazate is very highly toxic to marine invertebrates (mysid NOEC and LC_{50}: 0.04 and 0.058 mg a.i./L, respectively) and highly toxic to fish (sheepshead NOEC and LC_{50}: 0.136 and 0.416 mg a.i./L, respectively).

6.3 Effects on Biological Methods of Sewage Treatment

These data are not required for the PMRA.

6.4 Risk Characterization

6.4.1 Environmental Behaviour

Bifenazate rapidly transforms in soils by hydrolysis and biotransformation. It is non-persistent in soils and has a low potential for accumulation and residue carryover. Three major transformation products (D3598, D9472 and D1989) were detected in soils under laboratory conditions. The transformation products D3598 and D1989, which were identified under field conditions, did not accumulate in soils; therefore, these transformation products have no residue carryover to the following crop period. The

parent compound and transformation products have a low potential to leach and contaminate groundwater.

In the aquatic environment, Bifenazate transforms rapidly by hydrolysis, phototransformation and by biotransformation under aerobic conditions. Parent compound is, therefore, non-persistent in the aquatic environment under aerobic conditions. However, it is moderately persistent under anaerobic conditions. Five major transformation products were detected in aquatic systems under laboratory conditions: D3598, D1989, D9963, D9472 and A1350.

6.4.2 Terrestrial Organisms

Floramite SC
Bifenazate is non-toxic to birds and mammals. Further, terrestrial organisms are not directly exposed to the proposed indoor use; therefore, the risk to these organisms is limited with the proposed use of Floramite.

Acramite 50WS
Risk to terrestrial organisms was assessed by the NOEL or NOEC values of the most sensitive species (Appendix V, Table 3). The proposed use of Acramite 50WS suggests that exposure is likely to occur through the consumption of treated foliage and food sources, with the greatest risk arising from oral ingestion of treated foliage or diet. Dietary intake (DI) was estimated from the information on the food consumption (FC) and the EEC of bifenazate in the diet (DI = FC × EEC). Assessment of acute risk to wild birds and mammals was based on the number of days of intake of treated foliage that will result in observable effects. Dietary and reproductive risk to birds and mammals as well as acute risk to bees and soil organisms were assessed using risk quotient (RQ: EEC/ NOEC) values.

Assessment of risk to terrestrial organisms (Appendix V, Table 3) indicated that the proposed use of Acramite 50WS will pose a negligible to low risk to earthworms, bees, non-target vascular plants and wild birds on an acute, dietary and reproductive basis. The proposed use of Acramite 50WS, however, poses a high risk to beneficial predatory and parasitic arthropods, and moderate to high risk to mammals on a dietary and reproductive basis.

6.4.3 Aquatic Organisms

Floramite SC
Bifenazate is highly toxic to aquatic organisms. With the proposed indoor use, aquatic organisms are not directly exposed to Floramite SC; therefore, the risk to these organisms with the proposed use is limited. However, a label statement is required stating not to contaminate aquatic systems by effluents, drainage or waste water from the treated greenhouses.

Acramite 50WS

Risk to aquatic organisms was assessed by the risk quotient values using the most sensitive fish and invertebrate species (Appendix V, Table 4) and the EECs in water in a conservative scenario of direct overspray (100% deposition) at the maximum application rate, i.e., 0.14 mg a.i./L. The risk quotient values indicated that the proposed use of Acramite 50WS will pose a risk to freshwater invertebrates as well as marine fish and invertebrates on an acute and chronic basis, if exposed directly to the proposed maximum application rate. Acramite 50WS, however, will not adversely affect algae and non-target aquatic plants with the proposed maximum application rate.

6.4.3.1 Environmental Concerns

An assessment of the environmental safety with the proposed use of Floramite SC and Acramite 50WS has identified the following concerns.

Floramite SC

- Floramite SC will pose a risk to aquatic organisms if greenhouse effluents are discharged into aquatic systems.

Acramite 50WS

- The proposed use of Acramite 50WS may pose a risk to beneficial predatory and parasitic arthropods.

- The proposed use of Acramite 50WS may pose a dietary and reproductive risk to wild mammals.

- Bifenazate is highly toxic to fish and other aquatic organisms; the proposed use of Acramite 50WS may pose a risk to freshwater invertebrates and marine organisms.

6.5 Risk Mitigation

The risk assessment indicated that the proposed uses pose a risk to beneficial predators and parasites, mammals and aquatic organisms. The parent compound and transformation products are rapidly transformed in the environment and, therefore, have a low potential for residue carryover. They also have a low potential to leach and contaminate the groundwater and to be transported by the surface water to aquatic systems. The risk associated with the proposed use of Acramite is, therefore, limited. Nevertheless, mitigatory label statements are required to minimize the potential risk to terrestrial and aquatic organisms with the proposed uses of Floramite SC and Acramite 50WS.

Floramite SC

The following label statement is required to protect the fish and other aquatic organisms from the contamination of aquatic systems with greenhouse effluents and drainage water.

- This product is highly toxic to aquatic organisms. Do not discharge effluent, waste and drainage water containing this product into water bodies, such as lakes, streams, ponds, rivers and estuaries.

Acramite 50WS

The proposed use of Acramite 50WS may pose a risk to beneficial predators and parasites, freshwater invertebrates and marine organisms. To protect these organisms from the use of Acramite 50WS, the following mitigatory and precautionary label statements are required.

- This product may be harmful to beneficial predatory or parasitic arthropods. The best available application technique, which minimizes off-target drift, should be used to reduce effects on beneficial arthropods in the adjacent field.

- This product is toxic to fish and other aquatic organisms.

- Do not over spray aquatic systems including sloughs, coulees, ponds, prairie potholes, lakes, rivers, streams and wetlands.

- Do not contaminate these habitats when cleaning and rinsing spray equipment or containers.

The following statements are required under the DIRECTIONS FOR USE section of the Acramite 50WS label.

DO NOT apply during periods of dead calm or when winds are gusty.

DO NOT apply by air.

Airblast application: **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands), and estuarine/marine habitats.

Buffer zones

Method of application	Buffer zone (metres) required for the protection of:	
	Freshwater habitat	Estuarine/marine habitat
Airblast (early growth stage)	2	3
Airblast (late growth stage)	2	2

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended Use

Crompton Co. has applied for registration of two commercial class end-use products, containing bifenazate. Acramite 50WS, containing 50% bifenazate, is intended for control of European red mite, two-spotted spider mite and McDaniel mite on apple and grape. Floramite SC, containing 22.6% bifenazate, is intended for control of two-spotted spider mite and Lewis mite on indoor ornamental plants (including plants that are grown and/or maintained in containers or in the ground in greenhouses, shadehouses and interiorscapes).

For Acramite 50WS, the efficacy data support an application rate of 3 × 227 g water soluble pouches/800 L/0.8 ha (421 g a.i./ha) for control of European red mite and 2 × 227 water soluble pouches/800 L/0.8 ha (281 g a.i./ha) for control of two-spotted spider mite and McDaniel mite on apple and grape. Application timing is as soon as mites appear. There is a maximum of one application per year with PHIs of 7 days (apple) and 14 days (grape).

For Floramite SC, the efficacy data support an application rate 0.133 L product/400 L (30 g a.i./400 L) for control of two-spotted spider mite and Lewis mite on indoor ornamentals (including plants grown and/or maintained in greenhouses, shadehouses and interiorscapes). Application timing is as soon as mites appear. These is a maximum of one application per year.

7.1.2 Mode of Action

The active ingredient of Acramite 50WS and Floramite SC, bifenazate, belongs to the carbazate class of insecticides. The exact mode of action of bifenazate has not been documented, but is believed to be a GABA-gated chloride channel antagonist, which

targets pests that come in direct contact with it or in contact with its residue. After the target pest contacts or ingests bifenazate, this compound interferes with the GABA receptors, resulting in repetitive nervous discharges from the mite's neurons. Bifenazate does not have systemic activity.

7.1.3 Crops

Acramite 50WS will be used on apple and grape. Floramite SC will be used on ornamental plants (including plants grown and/or maintained in containers or in the ground in greenhouses, shadehouses and interiorscapes).

7.1.4 Effectiveness Against Pest

7.1.4.1 Effectiveness of Acramite 50WS

European Red Mite on Apple
Thirteen small-plot field trials assessed the efficacy of Acramite 50WS for control of European red mite on apple. Efficacy data indicated that Acramite 50WS reduces the number of European red mite (i.e., 94–98% control) on apple compared to untreated controls at an application rate of 420 g a.i./ha. Therefore, efficacy data support the application rate of 421 g a.i./ha (i.e., 3 pouches/800 L/0.8 ha) for control of European red mite on apple to provide quick knockdown and longer residual control of mite populations on treated foliage.

Two-spotted Spider Mite on Apple
Eight small-plot field trials assessed the efficacy of Acramite 50WS for control of two-spotted spider mite on apple. Acramite 50WS reduced the number of two-spotted spider mite (i.e., 91–100% control for up to 28 days after treatment). Submitted efficacy data indicate that the tested lowest effective rate for two-spotted spider mite on apple is 280 g a.i./ha (i.e., 2 pouches/800 L/0.8 ha).

McDaniel Mite on Apple
Only two small-plot field trials assessed the efficacy of Acramite WS for control of McDaniel mite on apple. Efficacy data were inconsistent in these two trials. However, as McDaniel mites have a similar biology to two-spotted spider mites and pest management practices are similar, it is believed that the lowest effective rate will also be similar. The application rate of 281 g a.i./ha (i.e., 2 pouches/800 L/0.8 ha) can be supported for two-spotted spider mite and McDaniel mite.

European Red Mite and Two-spotted Spider Mite on Grape
Two small scale efficacy trials on grape support the label claims approved for these mite pests on apple. Therefore, the rates of 421 g a.i./ha (i.e., 3 pouches/800 L/0.8 ha) and 281 g a.i./ha (i.e., 2 pouches/800 L/0.8 ha) for European red mite and two-spotted spider mite, respectively, should be adequate to control these pests on grape.

McDaniel Mite on Grape
McDaniel mite is not a pest of grape in Canada.

7.1.4.2 Effectiveness of Floramite SC

Two-spotted Spider Mites on Greenhouse Ornamentals
Results from 10 greenhouse trials assessed the efficacy of Floramite SC for control of two-spotted spider mite on greenhouse ornamentals (i.e., marigolds, zinnia, brugmansia and ornamental roses). Efficacy data showed that bifenazate reduced the number of two-spotted spider mite by 84–100% at the application rate of 30 g a.i./400 L.

Lewis mites on Greenhouse Ornamentals
One greenhouse trial assessed the efficacy of Floramite SC for control of Lewis mite on greenhouse ornamentals (i.e., poinsettia). Efficacy data indicated that bifenazate reduced the number of Lewis mite by 94–100% at the application rate of 28.3 g a.i./378 L. As well, Lewis mites have a similar biology to the two-spotted spider mite and pest management practices are similar; it is assumed that the lowest effective rate will also be similar. The application rate of 30 g a.i./400 L can be supported for Lewis mite.

7.1.5 Total Spray Volume

Due to the mode of action of the active ingredient bifenazate, Acramite 50WS and Floramite SC are effective mainly after contact or ingestion by mites. Therefore, thorough, uniform coverage of all foliage and fruit is essential for good control. The approved spray volume for Acramite 50WS for the control of the approved mite pests on apple and grape is 1000 L/ha (i.e., 800 L/0.8 ha). The approved application rate for Floramite SC (i.e., 0.133 L) must be diluted in a spray volume of 400 L and plants should be sprayed to run off.

7.2 Phytotoxicity to Target Plants or Target Plant Products

No adverse effects, such as phytotoxicity to target plants, were reported in trials conducted with Acramite 50WS or Floramite SC.

7.3 Observations on Undesirable or Unintended Side Effects

Data regarding the effect of Acramite 50WS and Floramite SC on beneficial/predacious insects and mites were unclear. Additional data are needed to assess the proposed label claims that these products are safe in biological control programs.

7.3.1 Impact on Succeeding Crops

Undesirable or unintended side effects on succeeding crops were not reported and are not expected.

7.3.2 Impact on Adjacent Crops

Undesirable or unintended side effects on adjacent crops were not reported and are not expected.

7.3.3 Impact on Seed Viability

Not applicable.

7.3.4 Tank-mixing Recommendations

Tank-mixes were not proposed.

7.4 Economics

The applicant provided no data on the projected economic value of the use of Acramite 50WS to the apple or grape industry in Canada or Floramite SC to the indoor ornamental industry. As such, economic values were obtained from published literature and other sources.

Approximately 25 825 ha were planted for commercial apple production in Canada in 2001, with the largest percentage in Ontario (38%), followed by Quebec (26%) and British Columbia (23%). Acramite 50WS has potential for use in all apple-growing areas of Canada, for major pests (i.e., European red mite and two-spotted spider mite) and minor pests (e.g., McDaniel mite).

In 2001, 10 589 ha of grapes were in commercial production in Canada, with the largest percentages in Ontario (70%) and British Columbia (27%). Acramite 50WS has potential for use in all grape growing areas of Canada, for minor mite pests such as European red mite, two-spotted spider mite and McDaniel mite.

In 2001, 846 ha of ornamentals were planted in commercial greenhouses in Canada, with the largest percentage in Ontario (48%), followed by British Columbia (21%) and Quebec (17%). Floramite SC has potential for use in all greenhouse ornamental growing areas of Canada, for major pests (i.e., two-spotted spider mite). Lewis mite is considered a minor pest and is mainly a pest of poinsettia grown in British Columbia.

7.5 Sustainability

7.5.1 Survey of Alternatives

7.5.1.1 Chemical Control Practices

The major alternative miticide active ingredients currently registered for control of the pests on the proposed Acramite 50WS label include, but are not necessarily limited to, the following.

Crop	Pest	Available Alternative Active Ingredients
Apple	European red mite	Carbamate (formetanate hydrochloride), fumigant (methyl bromide), mineral oil, organochlorine (dicofol), organophosphate (diazinon, malathion, phosalone, phosmet—suppresses), pyridazinones (pyridaben)
	Two-spotted spider mite	Avermectin (abamectin), carbamate (formetanate hydrochloride), dinitrophenol (dinocap plus related active compounds), fumigant (methyl bromide), mite growth regulator (clofentezine) organochlorine (dicofol), organophosphate (diazinon, dimethoate, malathion, phosalone, phosmet—supresses), pyridazinones (pyridaben)
	McDaniel mite	Fumigant (methyl bromide), organochlorine (dicofol), organophosphate (malathion), pyridazinones (pyridaben)
Grape	European red mite	Fumigant (methyl bromide), organochlorine (dicofol), pyridazinones (pyridaben)
	Two-spotted spider mite	Fumigant (methyl bromide), organochlorine (dicofol), organophosphate (malathion), pyridazinones (pyridaben)

The major alternative miticide active ingredients currently registered for control of the pests on the proposed Floramite SC label include, but are not necessarily limited to, the following.

Crop	Pest	Available Alternative Active Ingredients
Indoor ornamental (greenhouse, interior plantings)	Two-spotted spider mite	Botanical (pyrethrin)
	Lewis mite	Greenhouse ornamentals: avermectin (abamectin), organophosphate (acephate, chlorpyrifos, malathion, naled), fenbutatin oxide (organotin), pyridazinones (pyridaben), soap Interior plantings: botanical (pyrethrin), soap

7.5.1.2 Non-chemical Control Practices

Apple
Use a superior oil for prebloom applications. Pesticide rotation is very important, especially in hot weather when mite outbreaks are likely to occur. Pesticides can be detrimental to biological control agents. Biological control of mites on apple may be achieved if populations of predacious mites (i.e., *Amblyesius fallacis, Typhlodromus pyri, Zetzellia mali* and *Balaustium spp*.) are not harmed.

Grape
Regular assessments of mite abundance must be performed. Sprays are usually applied after there is 10% defoliation. Pesticides can be detrimental to biological control agents. Whenever possible, pesticides that are harmful to beneficial insects and mites should be avoided.

Greenhouse Flowers
Biological methods for the control of mites on greenhouse flowers include the release of predacious mites (i.e., *Phytoseiulus persimilis,* which is the main biological control agent used against two-spotted spider mite, *Amblyesius californicus* and *Metaseiulus occidentalis*) and beneficial insects (i.e., *Stethorus punctillum* and *Feltiella acarisuga*). In addition, cultural methods such as proper clean up between crops, removing heavily infested leaves, turning off circulation fans in heavily infested areas, misting plants and maintaining high relative humidities will help to reduce the number of mites on greenhouse crops.

7.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Acramite 50WS and Floramite SC are compatible with current management practices. These products can be applied with conventional application equipment used in orchards, vineyards and greenhouses. Growers are familiar with the monitoring techniques used to determine if and when applications are needed. The unique mode of action of these end-use products offer growers another alternative to rotate with currently registered chemicals.

The effect of the proposed end-use products on beneficial/predacious insects and mites is unclear. Additional data are needed to determine if the proposed products are safe in biological control programs.

7.5.3 Contribution to Risk Reduction

Acramite 50WS and Floramite SC are potential alternatives to the older classes of insecticides/miticides (e.g., organophosphates) listed in Section 7.5.1. The PMRA and the USEPA are currently re-evaluating organophosphate insecticides. Bifenazate is believed to be a GABA-gated chloride channel antagonist, somewhat similar to endosulfan.

Bifenazate represents an alternative class of miticides for pest management on apple, grape, and indoor ornamentals. Currently, there are no reports of resistance. However, the potential for resistance or the development of future cross resistance for control of the proposed pests is possible and should be monitored.

Bifenazate is a reduced-risk chemical according to the criteria outlined in Regulatory Directive DIR2002-02, *The PMRA Initiative for Reduced Risk Pesticides*.

7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Development of resistance to bifenazate has not been reported. However, any mite population may contain individuals naturally resistant to this product and other pesticides with similar modes of action. The resistant biotypes may dominate the insect population if these insecticides are used repeatedly in the same field. Other resistance mechanisms that are not linked to site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay insecticide resistance:

- Where possible, rotate the use of this product with different groups that control the same pests.
- Insecticide use should be based on an integrated pest management (IPM) program that includes scouting and record keeping and considers cultural, biological and other chemical control practices.
- Monitor treated pest populations for resistance development.
- Contact the local extension specialist or certified crop advisors for any additional pesticide resistance management and IPM recommendations for the specific site and pest problems in the area.
- For further information or to report suspected resistance, contact (company representatives) at (toll free number) or at (Internet site).

Resistance management statements have been incorporated into the proposed labels for Acramite 50 WS and Floramite SC as outlined in Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

7.6 Conclusions

On apple, the lowest effective rate of Acramite 50WS is 421 g a.i./ha (3 pouches/0.8 ha) for control of European red mite and 281 g a.i./ha (2 pouches/0.8 ha) for control of McDaniel mite and two-spotted spider mite. On grape, the lowest effective rate of Acramite 50WS for control of European red mite is 421 g a.i./ha (3 pouches/0.8 ha) and for control of two-spotted spider mite is 281 g a.i./ha (2 pouches/0.8ha). A minimum

spray volume of 1000 L water/ha is recommended for apple and grape. McDaniel mite is not a pest of grape in Canada.

On greenhouse ornamentals, efficacy data demonstrated that the lowest effective rate of Floramite SC for control of two-spotted spider mite and Lewis mite is 30 g a.i./400 L (28.4 g a.i./378 L; 0.133 L product/400 L). Greenhouse efficacy data are adequate to support the registration of the proposed product for the control of two-spotted spider mite and Lewis mite in shadehouses and interiorscapes (indoor public, commercial, institutional and industrial settings). One application at the application rate of 30 g a.i./400 L will provide protection of treated foliage for up to 28 days after treatment.

7.6.1 Summary

Acramite 50WS is acceptable for use on apple and grape to control European red mite, two-spotted spider mite and McDaniel mite. Acceptable application rates and a summary of application timings are provided in Table 7.6.1. Only one application per crop per year is supported.

Adequate efficacy data have been submitted to support use of Floramite SC against two-spotted spider mite and Lewis mite on greenhouse ornamentals. Greenhouse efficacy data are adequate to support the registration of Floramite SC for the control of two-spotted spider mite and Lewis mite in shadehouses and interiorscapes (indoor public, commercial, institutional and industrial settings). Acceptable application rates and a summary of application timings are provided in Table 7.6.2. Only one application per crop cycle is supported.

No phytotoxic effects to foliage or fruit were reported in submitted efficacy trials when Acramite 50WS or Floramite SC was applied.

Table 7.6.1 Summary of Supported Label Statements for Acramite 50WS

Pest/Crop	Number of Pouches/ 0.8 ha (2 acres)/Water Volume	Application Rate (g a.i./ha)	Minimum Spray Volume (L/ha)	Summary of Application Timing
European red mite on apple and grape	3 pouches / 0.8 ha (2 acres) / 800 L This rate is equivalent to 15 pouches / 4 ha / 4000 L	421	1000	Apply 1 application per year, as soon as mites appear.
Two-spotted spider mite on apple and grape	2 pouches / 0.8 ha (2 acres) / 800 L This rate is equivalent to 10 pouches / 4 ha / 4000 L	281		
McDaniel mite on apple				

Table 7.6.2 Summary of Supported Label Statements for Floramite SC

Pest/Crop	Application Rate (L product/ 400 L)	Application Rate (g a.i./400 L)	Summary of Application Timing
Two-spotted spider mite and Lewis mite on indoor ornamentals grown in greenhouses, shadehouses and interiorscapes	0.133	30	Apply 1 application per crop cycle, as soon as mites appear.

8.0 Toxic Substances Management Policy Considerations

During the review of bifenazate, PMRA has taken into account the federal Toxic Substances Management Policy and has followed its Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. It has been determined that this product does not meet TSMP Track 1 criteria for the following reasons.

- Bifenazate does not meet the criteria for persistence. Its values for half-life in aerobic soil (<0.5 hour) and water (<6 and 77.9 days under aerobic and anaerobic conditions, respectively), are below the TSMP Track 1 cut-off criteria for water and soil (≥182 days).

- Bifenazate is not bioaccumulative. The *n*-octanol–water partition coefficient (log K_{ow}) is 3.4, which is below the TSMP Track 1 cut-off criterion of ≥ 5.0.

- Toxicity of the product is described in sections 3.6, 4.7 and 6.4.

- Bifenazate does not form any major transformation products that meet the TSMP Track 1 criteria.

- **By-products or microcontaminants:** Bifenazate (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- **Formulants:** The formulated products do not contain any formulants that are known to contain TSMP Track 1 substances. The formulated product Floramite SC does not contain any List 1 or 2 (USEPA and PMRA) formulants. Acramite 50WS, however, contains "Dixie Clay" (32.8%), which contains 1.28% crystalline silica. Crystalline silica is classified as a List 2 formulant.

9.0 Regulatory Decision with Additional Data Requirements

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of bifenazate and associated end-use products, Acramite 50WS, for control of European red mite, two-spotted spider mite and McDaniel mite on apple and grape, and Floramite SC, for control of two-spotted spider mite and Lewis mite on greenhouse ornamentals. The Agency has concluded that the use of bifenazate and the associated end-use products in accordance with the enclosed annotated labels has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. The Agency has determined that these products are eligible for temporary registration, subject to the Terms and Conditions outlined in the registration letter and summarized below:

- The final report of the apple DFR study UCC-D2341 50WP on Apples:Dislodgeable Foliar Residue Study must be submitted.

- The final report of the greenhouse ornamental DFR study FLORAMITE™ 50WP in Spathiphyllum: Dislodgeable Foliar Residue Study must be submitted.

List of Abbreviations

a.i.	active ingredient
ACN	acetonitrile
AD	administered dose
ADI	acceptable daily intake
AR	applied radioactivity
cm	centimetre(s)
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
bwg	body-weight gain
C_{max}	maximum concentration
CV	coefficient of variation
DAT	day(s) after treatment
DCM	dichloromethane
DER	Data Evaluation Report
DI	dietary intake
DFR	dislodgeable foliar residue
ECD	electron capture detection
EEC	expected environmental concentration
F_1	first filial generation
F_2	second filial generation
FC	food consumption
FOB	functional observation battery
g	gram(s)
GABA	gamma-aminobutyric acid
GD	gestation day
ha	hectare(s)
HAFT	highest average field trial
HCl	hydrochloric acid
Hct	hematocrit
Hgb	hemoglobin
HDPE	high density polyethylene
HOAc	acetic acid
HPLC	high-performance liquid chromatography
K^+	potassium
K_d	adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon adsorption coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection

LOQ	limit of quantitation
LPM	litres per minute
MAS	maximum average score
max.	maximum
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
mg	milligram(s)
MIS	maximum irritation score
min.	minimum
MOE	margin of exposure
MRL	maximum residue limit
MTDB	maximum theoretical dietary burden
n/a	not applicable/not available
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen-phosphorus detection
OCECD	Oxidative Coulometric Electrochemical Detection
P	parental generation
PBI	plantback interval
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
r^2	coefficient of determination
RAC	raw agricultural commodity
RBC	red blood cell
REI	restricted entry interval
ROC	residue of concern
RSD	relative standard deviation
SDEV	standard deviation
$t_{1/2}$	half-life
TC	transfer coefficient
TSMP	Toxic Substances Management Policy
TRR	total radioactive residues
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume

Appendix I Toxicology

Table 1 Toxicology Summary Table

METABOLISM

Rate and extent of absorption and excretion:
Rapidly absorbed and eliminated in rats after single low dose (10 mg/kg), single high dose (1000 mg/kg) or repeated low dose (10 mg/kg), with no apparent sex difference.

Single dose studies
Single low-dose animals absorbed ~85% of the administered dose. Absorption appeared to be saturated at the high dose, as evidenced by 57–64% of the administered dose recovered in the feces in the biliary study. Greater than 93% of the administered dose was recovered within 72 hours for both single low- and high-dose groups. The C_{max} was reached at 5–6 hours and 18–24 hours for the low- and high-dose groups, respectively. The $t_{1/2}$ was 12–13 hours and 12–16 hours for the low- and high-dose groups, respectively. Fecal excretion was the primary route of elimination, with the biliary system contributing a major role in the process. Urinary excretion was a more minor route of elimination, and elimination in expired air was negligible (<1%).

Single low dose ♂ (10 mg/kg at 168 hours): feces 66.1%, urine 24.3%, carcass/tissues 0.6%
Single low dose ♀ (10 mg/kg at 168 hours): feces 66.4%, urine 24.7%, carcass/tissue 0.6%
Single high dose ♂ (1000 mg/kg at 168 hours): feces 82%, urine 7.9%, carcass/tissue 0.4%
Single high dose ♀ (1000 mg/kg at 168 hours): feces 82.8%, urine 9.4%, carcass/tissue 0.5%
Biliary single low dose ♂ (10 mg/kg at 72 hours): feces 7.4%, urine 11.3%, bile 73.6%, carcass 1.4%
Biliary single low dose ♀ (10 mg/kg at 72 hours): feces 7.9%, urine 10.6%, bile 68.6%, carcass 1.4%
Biliary single high dose ♂ (1000 mg/kg at 72 hours): feces 56.7%, urine 3.4%, bile 25.7%, carcass 1.0%
Biliary single high dose ♀ (1000 mg/kg at 72 hours): feces 64.2%, urine 1.4%, bile 20.7%, carcass 1.1%

Repeat dose study
Approximately one third of the administered radiolabelled dose was excreted in the urine of both male (33.94%) and female (29.78%) rats, the majority of which (75%) was excreted within the first 24 hours after dose administration. Slightly more than half of the administered radiolabel was excreted via the feces (approximately 54 and 57% in males and females, respectively). Biliary excretion was not examined. About 90% of the administered radiolabel was excreted within 7 days postdose.

Distribution / target organ(s):
Single dose
Residual tissue/carcass radioactivity was < 0.6% of the administered dose at 168 hours after both single low and high doses. The highest concentrations in tissues were noted in the liver, whole blood and RBCs in the low- and high-dose groups. At 1000 mg/kg increased radioactivity in the spleen was observed, and the detected radioactivity in RBCs had a slower rate of elimination. High-dose females had higher radioactivity levels (twofold to threefold) in the spleen and RBCs compared to males at 168 hours postdose.

Repeated dose
< 0.5% of administered dose was present in the tissues/carcass. Highest concentrations were noted in the liver, kidneys and spleen.

Toxicologically significant compound(s):
Bifenazate underwent extensive metabolism. Metabolites identified were the result of metabolic reactions including hydrazine oxidation, demethylation, ring hydroxylation, and molecular scission with loss of the hydrazinecarboxylic acid portion with subsequent glucuronide or sulfate conjugation with glucuronic acid or sulfate. Metabolic profiles were similar for both single and repeat dosing studies. A significant amount of parent compound was detectable in the feces of the high-dose group only, indicating saturation of the metabolic pathways.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES—Bifenazate Technical			
Oral	Rat, Sprague-Dawley 5/sex 5000 mg/kg	$LD_{50} \geq$ 5000 mg/kg	Low toxicity No clinical signs of toxicity observed.
Oral	Mouse, CD-1 5/sex 5000 mg/kg	$LD_{50} \geq$ 5000 mg/kg	Low toxicity One ♀ found dead on day 8 postdosing and exhibited lacrimation, lethargy, irregular gait, laboured breathing on day 7, and ↓ feces on days 2–5 and 7. One surviving ♀ lost weight during the study.
Dermal	Rat, Sprague-Dawley 5/sex 5000 mg/kg moistened with 0.9% saline/g test material	$LD_{50} \geq$ 5000 mg/kg	Low toxicity No clinical signs of toxicity observed.
Inhalation	Rat, Sprague-Dawley 5/sex 4.4 mg/L, nose-only for 4 hours	$LC_{50} \geq$ 4.4 mg/L	Low toxicity Clinical signs of toxicity included moist rales, chromodacryorrhea, and/or red/brown nasal discharge on all rats. One ♂ and one ♀ lost weight during the first week.
Skin irritation	Rabbit, New Zealand White 3/sex 0.5 g moistened with 0.5 ml of 0.9% physiological saline for 4 hours	MIS = 0.3 (1 hour) MAS = 0	Non-irritating
Eye irritation	Rabbit, New Zealand White 3/sex 0.1 ml (54 mg)	MIS = 5.0 (1 hour) MAS = 0.44	Minimally irritating
Skin sensitization (Buehler)	Guinea Pig, Dunkin Hartley 20/sex 0.3 ml of undiluted test material moistened with either 0.3 ml of 0.9% saline (1st and 2nd inductions) or 4 drops of saline (3rd induction and challenge)	Negative	Not a sensitizer

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Skin sensitization (Magnusson/ Kligman)	*Study not submitted to the PMRA, but referenced in an USEPA document provided by the Company.	Positive	Skin sensitizer
ACUTE STUDIES—Floramite SC (22.6 % a.i.) [studies performed with test substance containing 43.4% a.i.]			
Oral	Rat, Wistar 5/sex 2000 mg/kg (♀) or 5000 mg/kg (♀/♂)	$LD_{50} \geq$ 5000 mg/kg (♂) LD_{50}: between 2000 and 5000 mg/kg	Low toxicity Clinical signs of toxicity included emaciation, diarrhea, soiled anogenital area, few feces, chromorhinorrhea, lethargy, dyspnea, flaccid appearance, diarrhea, wet anogenital and oronasal area, which generally appeared between days 4–12.
Dermal	Rabbit, New Zealand White 5/sex 5000 mg/kg undiluted for 24 hours	$LD_{50} \geq$ 5000 mg/kg	Low toxicity Clinical signs included few feces and soiling of the anogenital area between days 2–4.
Inhalation	Rat, CD 5/sex 1.9 mg/L, nose-only for 4 hours	LC_{50} > 1.9 m/L	Low toxicity Clinical signs of toxicity included laboured breathing, slow respiration, and material around the eyes and nose in several animals during the exposure period and up to 4 hours afterward.
Skin irritation	Rabbit, New Zealand White 2♂ and 1♀ 0.5 ml of undiluted test substance	MIS = 0 MAS = 0	Non-irritating
Eye irritation	Rabbit, New Zealand White 3 ♀ 0.1 ml of undiluted test substance	MIS = 6 (1 hour) MAS = 0	Minimally irritating
Skin sensitization (Buehler)	Guinea Pig, Hartley 10/sex (5/sex for naive control) 0.4 ml of undiluted test substance for both induction and challenge	Negative	Not a sensitizer

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES—Acramite 50WS (50% a.i.) [studies performed with test substance containing 51.9% a.i.]			
Oral	Rat, Sprague-Dawley 5/sex 5000 mg/kg	$LD_{50} \geq 5000$ mg/kg	Low toxicity Clinical signs of toxicity included moist rales and moderate alopecia on extremities/snout, excessive salivation, anogenital staining and decreased activity. Slight bw loss in 2 ♂ and 3 ♀ during first week.
Oral	Mouse, CD-1 5/sex 5000 mg/kg	$LD_{50} \geq 5000$ mg/kg	Low toxicity One ♂ developed moderate alopecia on extremities/snout on day 8 until end of study. One ♀ lost weight.
Dermal	Rat, Sprague-Dawley 5/sex 5000 mg/kg	$LD_{50} \geq 5000$ mg/kg	Low toxicity No clinical signs of toxicity observed.
Inhalation	Rat, Sprague-Dawley 5/sex 5.2 mg/L, nose-only for 4 hours	$LC_{50} > 5.2$ mg/L	Low toxicity Clinical signs of toxicity included laboured breathing, moist rales, chromodacryorrhea, red nasal discharge and/or lacrimation. Loss of bw in one ♂ and 2 ♀ during first week.
Skin irritation	Rabbit, New Zealand White 3/sex 0.5 g test substance moistened with 0.5 ml saline	MIS = 0.8 (0.5 hour) MAS = 0.2	Minimally irritating
Eye irritation	Rabbit, New Zealand White 3/sex 30 mg of test substance	MIS = 4.0 (1 hour) MAS = 0.67	Minimally irritating
Skin sensitization (Buehler)	Guinea Pig, Dunkin Hartley 40/sex 0.3 ml of undiluted test substance moistened with saline	Negative	Not a sensitizer

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
SHORT-TERM TOXICITY			
21-day dermal	Rat, Sprague-Dawley [Crl:CD(BR)]VAX/Plus 10/sex/dose 0, 80, 400 and 1000 mg/kg bw/day	NOAEL = 80 mg/kg bw/day LOAEL = 400 mg/kg bw/day	**400 mg/kg bw/day**: ♀: ↓ bw (9%), mild hyperchromasia 2/10 vs 0/10 control, anisocytosis 2/10 vs 0/10 control, polychromasia 1/10 vs 0/10 control ♂/♀: ↓ food consumption (8%/12%), ↑ spleen extramedullary hematopoiesis **1000 mg/kg bw/day**: ♂: ↓ urine volume, ↑ absolute spleen weight ♀: ↓ RBC, ↓ Hct, ↑ total bilirubin, mild hyperchromasia 2/10 vs 0/10 control, anisocytosis 2/10 vs 0/10 control, polychromasia 3/10 vs 0/10 control ♂/♀: ↓ bw (11% /10%), ↓ food consumption (14% /17%), ↓ Hgb, ↑ relative spleen weight, ↑ spleen extramedullary hematopoiesis * Reticulocytes not measured

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day dietary	Rat, Sprague-Dawley 10/sex/dose 0, 40, 200, or 400 ppm in the diet Equal to 0/0, 2.7/3.2, 13.8/16.3 or 27.7/32.6 mg/kg bw/day in ♂/♀ FOB performed on all animals during weeks 8 and 13	NOAEL: ♂: 13.8 mg/kg bw/day ♀: 3.2 mg/kg bw/day LOAEL: ♂: 27.7 mg/kg bw/day ♀: 16.3 mg/kg bw/day	**13.8/16.3 mg/kg bw/day:** ♀: – ↓ bw (10%) and bwg (19%) – ↓ food efficiency and food consumption – marginal ↓ in Hgb, RBC – ↑ relative spleen weight (26%) – ↑ hepatocellular hypertrophy (5/10) **27.7/32.6 mg/kg bw/day:** – ↓ bw in ♂ (16%) and in ♀ (8–14%) – ↓ bwg in ♂ (26%) and ♀(28%) – ↓ food consumption and food efficiency in ♂/♀ – marginal ↓ in Hgb (♂/♀), RBC (♂/♀), Hct (♀) – ↑ relative spleen weight in ♀ (36% relative to bw; 20% relative to brain weight) – ↓ liver weight in ♂ (14% absolute and relative to brain weight) – hepatocellular hypertrophy in ♂ (8/10) and ♀ (5/10); minimal cell necrosis in ♂ (5/10) – vacuolization of the zona fasciculata of adrenal cortex in ♂ (10/10 vs 3/10 controls) – ↑ splenic extramedullary hematopoiesis in ♂ (minimal to slight) (6/10) and splenic red pulp pigment in ♂ (slight to moderate) (10/10) * No signs of neurotoxicity were observed in the FOB at weeks 8 or 13.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day dietary	Dogs, Beagle 4/sex/dose 0, 40, 400 or 1000 ppm in the diet Equal to 0/0, 0.9/1.3, 10.4/10.7 and 25.0/28.2 mg/kg bw/day in ♂/♀	NOAEL: ♂:0.9 mg/kg bw/day ♀: 1.3 mg/kg bw/day LOAEL: ♂: 10.4 mg/kg bw/day ♀: 10.7 mg/kg bw/day	**10.4/10.7 mg/kg bw/day:** ♂: ↓ protein beta-globulins, ↑ bilirubin in urine, kidney basophilic tubules (2/4 vs 0/4 in controls), liver vacuolation (3/4 vs 0/4 in controls) ♀: ↑ K^+, ↑ absolute liver weight (27%), hepatocellular hypertrophy ♀ (1/4), mammary gland edema 2/4 vs 0/4 control, mammary gland ductal epithelial hyperplasia 4/4 vs 0/4 control ♂/♀: ↓ RBC, ↓ Hgb, ↓ Hct, ↑ MCV, ↑ MCH, ↑ platelets, anisocytosis (3/4 both sexes), ↑ relative liver weight (18%/25%), brown pigment in Kupffer cells (2/4 in ♂ and 3/4 in ♀ vs 0/4 in controls) **25.0/28.2 mg/kg bw/day:** ♂: ↑ MCH, ↑ alkaline phosphatase, ↑ cholesterol, ↓ protein beta-globulins, ↑ bilirubin in urine, brown colouration in urine, kidney basophilic tubules (2/4 vs 0/4 in controls), liver vacuolation (3/4 vs 0/4 in controls) ♀: mammary gland edema 2/4 vs 0/4 control, mammary gland ductal epithelial hyperplasia 3/4 vs 0/4 control ♂/♀: ↓ bwg (69%/64%), ↓ food efficiency (61%/57%), ↓ RBC, ↓ Hgb, ↓ Hct, ↑ MCV, ↑ platelets, ↑ reticulocytes, anisocytosis (4/4 both sexes), ↑ K^+, ↑ absolute liver weight (22%/30%), ↑ liver weight relative to bw (34%/33%), ↑ liver weight relative to brain weight (27%/28%), hepatocellular hypertrophy (1/4 in ♂ and 3/4 in ♀ vs 0/4 in controls), brown pigment in Kupffer cells (4/4 in ♂ and 4/4 in ♀ vs 0/4 in controls) * Effects on blood parameters were observed at 1 month in both the mid- and high-dose groups.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
12-month dietary	Dogs, Beagle 5/sex/dose 0, 40, 400 or 1000 ppm in the diet Equal to 0/0, 1.01/1.05, 8.95/10.42 and 23.94/29.19 mg/kg bw/day in ♂/♀	NOAEL: ♂: 1.01 mg/kg bw/day ♀: 1.05 mg/kg bw/day LOAEL: ♂: 8.95 mg/kg bw/day ♀: 10.42 mg/kg bw/day	**8.95/10.42 mg/kg bw/day:** ♂: ↑ leukocytes, ↑ segmented neutrophils, ↓ protein beta-globulins ♀: ↑ total bilirubin ♂/♀: ↓ RBC, ↓ Hgb, ↓ Hct, ↑ platelets, ↑ MCV, ↑ reticulocytes, trace to moderate myeloid hyperplasia of bone marrow, trace brown pigment in liver (hemosiderin), trace to mild pigment in kidney tubular epithelium (hemosiderin) **23.94/29.19 mg/kg bw/day:** ♂: ↑ leukocytes, ↑ segmented neutrophils, ↓ protein beta-globulins, ↑ total bilirubin in urine ♀: ↑ total bilirubin ♂/♀: ↓ RBC, ↓ Hgb, ↓ Hct, ↑ platelets, ↑ MCV, ↑ reticulocytes, trace to moderate myeloid hyperplasia of bone marrow, trace brown pigment in liver (hemosiderin), trace to mild pigment in kidney tubular epithelium (hemosiderin)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
CHRONIC TOXICITY AND ONCOGENICITY			
78-week dietary	Mouse, Crl:CD-1 (ICR)BR 50/sex/dose 0, 10, 100 or 225 (♂) / 175 (♀) ppm in the diet Equal to 0/0, 1.5/1.9, 15.4/19.7 and 35.1/35.7 mg/kg bw/day in ♂/♀	NOAEL: ♂: 1.5 mg/kg bw/day ♀: 19.7 mg/kg bw/day LOAEL: ♂: 15.4 mg/kg bw/day ♀: 35.7 mg/kg bw/day	**15.4/19.7 mg/kg bw/day:** – ↓ leukocytes in ♂ at week 52 (36%) and week 79 (22%. not significant); and ↓ lymphocytes in ♂ at week 52 (34%) **35.1/35.7 mg/kg bw/day:** – ↓ bw in ♀ throughout the study (↓ 5–9%) – ↓ bwg in ♂ weeks 1–25 (↓ 18%) and in ♀ weeks 1–78 (↓ 16%) – ↓ leukocytes in ♂ at week 52 (39%) and week 79 (38%, not significant) – ↓ lymphocytes in ♂ at week 52 (36%) and week 79 (29%, not significant) – ↑ absolute (↑ 12%) and relative (↑ 12%) liver weight in ♂; ↑ relative liver weight (↑ 13%) in ♀ – ↓ absolute (12%), relative to bw (12%), relative to brain (10%) and kidney weights in ♂ * Increased incidence of liver masses (benign hepatocellular adenomas) in high dose males (21% vs 10% in controls); above historical control range (3.3–14.9%), but not statistically significant; hepatocellular carcinoma not identified in these animals, no hyperplastic foci observed. No evidence of carcinogenic potential **Range-finding studies (mg//kg bw/day not available):** 28-day study (200, 1000, 2500, 5000 ppm) ↓ bwg at all doses; mortality at ≥ 1000 ppm; histopathological lesions in the spleen (hemosiderin) and thymus (Lymphoid necrosis) in ♀ at 200 ppm only. 90-day study (50, 100, 150 ppm) hemosiderin in spleens of both sexes at ≥ 100 ppm

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
2-year dietary	Rat, Sprague-Dawley Crl:CD BR 50/sex/dose 0, 20, 80 or 200 (♂) / 160 (♀) ppm in the diet Equal to 0/0, 1.0/1.2, 3.9/4.8 and 9.7/9.7 mg/kg bw/day in ♂/♀ An additional 10 rats/sex/dose were sacrificed at 53 weeks	NOAEL: ♂: 9.7 mg/kg bw/day ♀: 4.8 mg/kg bw/day LOAEL: ♀: 9.7 mg/kg bw/day	**3.9/4.8 mg/kg bw/day:** – ↑ severity of spleen pigment in ♀ **9.7 mg/kg bw/day:** – ↓ bw in ♀ (↓ 4–9%) weeks 2–50; ↓ bwg in ♀ over weeks 1–49 (↓ 9–17%) and weeks 1–104 (↓ 9%; not statistically significant) – ↓ RBC, Hgb, and Hct at week 13, 26, and 52 (♀) (but not at study termination) – ↑ severity of spleen pigment in ♂/♀ No evidence of carcinogenic potential. * Maximum tolerated dose not attained in ♂
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
Multigeneration reproduction	Rat, Crl:CD®(SD)BR (30/sex/dose) 0, 20, 80 and 200 ppm in the diet Equal to 0/0, 1.5/1.7, 6.1/6.9 and 15.3/17.2 mg/kg bw/day in the P animals, and 0/0, 1.7/1.9, 6.9/7.8 and 17.4/19.4 mg/kg bw/day in F_1 animals [♂/♀], respectively	**Parental (P/F_1) toxicity** * effect levels stated are an average between the doses received by the P and F_1 generation parents NOAEL: ♂: 1.6 mg/kg bw/day ♀: 1.8 mg/kg bw/day LOAEL: ♂: 6.5 mg/kg bw/day ♀: 7.4 mg/kg bw/day **Offspring (F_1/F_2) toxicity** NOAEL: ♂: ≥ 16.4 mg/kg bw/day ♀: ≥ 18.3 mg/kg bw/day LOAEL not established **Reproductive toxicity** NOAEL: ♂: ≥16.4 mg/kg bw/day ♀: ≥ 18.3 mg/kg bw/day LOAEL not established	**<u>Parental (P) toxicity</u>** **15.3/17.2 mg/kg bw/day:** ♀: ↓ bw during gestation (4%), ↓ bw during lactation (6%) ♂/♀: ↓ bw during premating (7%/8%), ↓ bwg during premating (9%/6%) **<u>Parental (F_1) toxicity</u>** **6.9/7.8 mg/kg bw/day:** ♂/♀: ↓ bw during premating (8%/6%), ↓ bwg during premating (8%/7%) **17.4/19.4 mg/kg bw/day:** ♀: ↓ bw during gestation (9%), ↓ bw during lactation (14%), ♂/♀: ↓ bw during premating (10%/15%), ↓ bwg during premating (12%/17%) ↓ food consumption during premating (7–9% week 19–24; 6–16% week 18–29) **Offspring toxicity** No treatment-related effects * bw, bwg and food consumption effects had p values < 0.01 and were consistently observed throughout the various reporting intervals.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity	Rat, Sprague-Dawley Crl:CD®BR 25/dose 0, 10, 100 and 500 mg/kg bw/day by gavage on GD 6–15	**Maternal toxicity** NOAEL: 10 mg/kg bw/day LOAEL: 100 mg/kg bw/day **Developmental toxicity** NOAEL ≥ 500 mg/kg bw/day	**Maternal toxicity** **100 mg/kg bw/day:** ↓ bw (8%), ↓ bwg (23%), ↓ food consumption (12.5%), red material on nose (10/25) **500 mg/kg bw/day:** ↓ bw (11%), ↓ bwg (29%), ↓ food consumption (21%), pale extremities (22/25), red material on forelimbs (8/25), red material on nose (25/25), dried brown vaginal discharge (3/25), decreased defecation (9/25) No treatment-related effects on developmental parameters
Developmental toxicity (range-finding)	Rabbit, New Zealand White (5/dose) 0, 125, 250, 500, 750 or 1000 mg/kg bw/day by gavage on GD 7–20	Not established because this is a range-finding study.	**Maternal toxicity** **≥125 mg/kg bw/day:** – Discoloured urine **≥250 mg/kg bw/day:** – ↓ defecation, body surface staining – ↑ abortions (occurring between GD 17–22) **≥500 mg/kg bw/day:** – ↓ bwg – One animal euthanized *in extremis* on GD 21 with clinical signs of toxicity and necropsy observations of foci on lungs and liver **750 mg/kg bw/day:** – Soft/no stool – One treatment-related death on GD 17 **1000 mg/kg bw/day:** – Soft/no stool – Two treatment-related deaths on GD 11 and 21 Fetal evaluation not performed
Developmental toxicity	Rabbit, New Zealand White (20/dose) 0, 10, 50 or 200 mg/kg bw/day on GD 7–19	Maternal and developmental NOAEL ≥ 200 mg/kg bw/day LOAEL not established	**No adverse effects observed**

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES	RESULTS
GENOTOXICITY		
Gene mutations in bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. Coli* WP2uvrA 10-5000 µg/plate; with and without activation	Negative * The actual study was not available for review by PMRA. Reported results are based on review of the USEPA DER.
Gene mutations in mammalian cells in vitro	L5178Y Mouse lymphoma cells 15, 20, 25, 30, 40 or 50 µg/mL without activation 100, 150, 200, 250, 350 or 500 µg/mL with activation	Negative
Chromosome aberrations in vitro	Chinese hamster ovary cells 12, 24, 36, 47, 71, or 94 µg/mL without activation 20, 40, 79, 119, 157, or 236 µg/mL with activation	Negative
Micronucleus assay (in vivo)	Male and female CD-1 (ICR) mice ♂: 96, 192, or 384 mg/kg ♀: 50, 100, or 200 mg/kg (single intraperitoneal dose; bone marrow harvested 24, 48 and 72 hours postdosing)	Negative **Range-finding study:** 3/20 ♂ died at 384 mg/kg 3/5 ♀ died at 390 mg/kg

Compound-induced mortality: An increase in abortions was observed in the range-finding developmental toxicity study in the rabbit at doses ≥ 250 mg/kg bw/day. Treatment-related deaths occurred at 500 mg/kg bw/day (animal sacrificed *in extremis*), 750 mg/kg bw/day (one animal) and at 1000 mg/kg bw/day (2 animals) in the range-finding developmental toxicity study in rabbits. Mortality occurred at ≥ 1000 ppm in the 28-day range-finding toxicity study in mice (further information not provided).

Recommended ARfD: Not required.

Recommended ADI: 0.01 mg/kg bw/day based on the NOAEL of 1.0 mg/kg bw/day from the 12-month dietary study in dogs and an uncertainty factor of 100× (10× for interspecies variation and 10× for intraspecies variation).

Appendix II Occupational Exposure

Table 1 PHED Exposure Estimates Based on Best Fit[1] Statistical Measure

PHED scenario	Unit exposure (µg a.i./kg a.i. handled)					
	Dermal body	Dermal hands	Dermal total	Inhalation[2]	Total deposition (D+I)	Total absorbed (D+I)
Mixer/loader (wettable powder using 90% protection factor)						
Single layer + gloves	48.72	4.43	53.15	5.6	58.75	24.2
Applicator (airblast)						
Single layer, gloves, open cab	556.36	5.36	561.72	5.8	619.7	202.4

1 Best fit estimate based on adding arithmetic means for normal distributions, geometric means for lognormal distributions, medians for other distributions

2 Inhalation exposure adjusted for respiration rate for light work (17 LPM)

Table 2 Scenario-specific Exposure Estimates and MOEs for Farmers Mixing, Loading and Applying Acramite 50WS to Grapes and Apples

Exposure scenario	PHED total unit exposure [1] (µg a.i/.kg a.i. handled)		Exposure pattern (kg a.i. handled/day)	Daily exposure [2] (mg a.i./kg bw/day)		MOE	
	Dermal deposition	Inhalation		Dermal deposition	Inhalation	Dermal deposition	Inhalation
Farmer mixer/loader/applicator: Wettable powder in water soluble pouches, airblast open cab							
Single layer + gloves	614.87	5.98	16 ha/day at 0.421 kg a.i./ha = 6.74 kg a.i./day	5.92×10^{-2}	5.75×10^{-4}	1352	1738

1 Sum of mixer + loader + applicator dermal and inhalation exposures (deposited)

2 Calculated as [µg a.i./kg a.i. handled/day × application rate × area treated/day] / body weight (70 kg)

Table 3 PHED Exposure Estimates Based on Best Fit[1] Statistical Measure

PHED scenario	Unit exposure (µg a.i./kg a.i. handled)					
	Dermal body	Dermal hands	Dermal total	Inhalation [2]	Total deposition (D+I)	Total absorbed (D+I)
Liquid/open pour low-pressure handwand						
Single layer + gloves	938.8	4.59	943.37	45.2	998.6	375.4
Liquid/open pour high-pressure handwand						
Single layer + gloves	5335.8	249.69	5585.49	151	5736.5	2105.9
Liquid/open pour backpack						
Single layer + gloves	5435.66	10.19	5445.85	62.1	5508	1968.2

[1] Best fit estimate based on adding arithmetic means for normal distributions, geometric means for lognormal distributions, medians for other distributions

[2] Inhalation exposure for handwand adjusted for respiration rate for light work (17 LPM); inhalation for backpack adjusted for moderate work (27 LPM)

Table 4 Scenario-specific Exposure Estimates and MOEs for Workers Mixing, Loading and Applying Floramite SC to Ornamentals and Cut Flowers in Greenhouses and Shadehouses

Exposure scenario	PHED total unit exposure[1] (µg a.i./kg a.i. handled)		Exposure pattern (kg a.i. handled/day)	Daily exposure [2] (mg a.i./kg bw/day)		MOE	
	Total dermal deposition	Inhalation		Dermal deposition	Inhalation	Dermal deposition	Inhalation
Liquid/open pour/low-pressure handwand							
Single layer + gloves	943.4	45.2	2 ha/day at 0.159 kg a.i./ha = 0.319 kg a.i./day	4.3×10^{-3}	2.06×10^{-4}	18608	4855
Liquid/open pour/high-pressure handwand							
Single layer + gloves	5585.5	151		2.55×10^{-2}	6.88×10^{-4}	3143	1453
Liquid/backpack							
Single layer + gloves	5445.9	62.1	150 L/day at 0.0798 g a.i./L water = 0.012 kg a.i./day	9.31×10^{-4}	1.06×10^{-5}	85906	94170

[1] Sum of mixer + loader + applicator dermal and inhalation exposures (deposited)

[2] Calculated as [µg a.i./kg a.i. handled/day × application rate × area treated/day] / body weight (70 kg)

Table 5 Grape Dislodgeable Foliar Residue Data for New York Site

Sampling interval (days)	Study arithmetic mean (µg/cm²)
0	0.894
1	0.762
2	0.698
3	0.479
5	0.284

Table 6 Exposure and MOEs for Workers Conducting Re-entry Activities on Grapes and Apples

Re-entry activity	Transfer coefficient[1] (cm²/hr)	DFR (µg/cm²)	Days postapplication	Exposure[2] (mg/kg/day)	MOE
Grapes (juice, wine, table)					
Girdling and cane turning	18700	0.284	5	0.6069	132
Hand harvesting, tying, pruning, training, leaf pulling, thinning	10000	0.698	2	0.7977	100
Hand line irrigation	1000	0.894	0	0.1124	712
Scouting, hand weeding	700	0.894	0	0.0715	1119
Apples					
Thinning	3000	0.894	0	0.3065	261
Hand harvesting	1500	0.894	0	0.1533	522
Irrigation, hand-line	1100	0.894	0	0.1124	712
Hand pruning, scouting, pinching, tying, training	500	0.894	0	0.0511	1566
Hand weeding, propping, animal control	100	0.894	0	0.0102	7830

[1] Agricultural Re-entry Task Force transfer coefficients

[2] Calculated as (DFR [µg/cm²] × TC [cm²/hr] × duration [hr/day]) / (body weight [kg] × 1000 [µg/mg])

Table 7 Re-entry Exposure Estimates and MOEs for Greenhouse Workers

Re-entry activity	Transfer coefficient[1] (cm^2/hr)	Daily dose[2] (mg/kg bw/day)	MOE
Ornamentals and cut flowers			
Hand harvesting pruning, pinching, thinning, (full foliage development)	7000	0.2544	314
Scouting	4000	0.1157	550
Hand weeding, irrigation, scouting, thinning (minimum foliage development)	2500	0.0723	881

[1] Agricultural Re-entry Task Force transfer coefficients

[2] Calculated as (DFR [µg/cm²] × TC [cm²/hr] × duration [hr/day]) / (body weight [kg] × 1000 [µg/mg])

Appendix III Residues

Table 1 Integrated Food Residue Chemistry Summary

ANALYTICAL METHODOLOGY			
Parameters	**Plant Matrices**	**Animal Matrices**	
Method ID	Jablonski, J.E. (1998) Analytical Method for the Analysis of D2341 and D3598 in Apples and Citrus. Document Number 6998-97-0237-CR-001. Ricerca Inc.	Jablonski, J.E. (1999) Validation of the Residue Method for D2341, D3598 and A1530 in Bovine Tissues and Milk. Document Number 7473-98-01150-CR-001. Ricerca Inc.	
Type	Data gathering and enforcement	Data gathering and enforcement	
Analytes	Bifenazate + D3598 (expressed as bifenazate)	Bifenazate + D3598 (expressed as bifenazate)	A1530 + A1530-sulfate (expressed as A1530)
Instrumentation	HPLC-OCECD	HPLC-OCECD	HPLC-fluorescent detection
LOQ	0.01 ppm	0.01 ppm	0.01 ppm
Standard	External standards of bifenazate were run with each sample set.	External standards of bifenazate were run with each sample set.	External standards of A1530 were run with each sample set.
ILV	The enforcement method for determination of bifenazate and D3598 in apples was successfully validated by an independent laboratory.	The enforcement method for determination of bifenazate and D3598 in bovine milk, liver, kidney, and fat was adequately validated by an independent laboratory.	The enforcement method for determination of A1530 and A1530-sulfate in bovine milk, liver, and kidney was adequately validated by an independent laboratory.
Extraction/ cleanup	Extraction in ACN + 0.1% acetic acid and partitioning with 2% aqueous sodium sulfate and DCM. Ascorbic acid added to maintain bifenazate in reduced state (D3598 reduced to bifenazate).	Muscle, liver, kidney, milk— extraction in ACN and 1:1 ACN:0.1% aqueous acetic acid, partitioning with 2% aqueous sodium sulfate and DCM. Fat—extraction in ACN and precipitation of coextracted lipids by freezing. Ascorbic acid added to maintain bifenazate in reduced state (D3598 reduced to bifenazate).	Muscle, liver, kidney, milk—extraction in ACN and 1:1 ACN:0.1% aqueous acetic acid, partitioning with 2% aqueous sodium sulfate and DCM. Hydrolysis of A1530-sulfate to A1530 in concentrated HCl.

Radio-validation	75% of radioactivity extracted in apples 71% of radioactivity extracted in oranges (Reviewed by USEPA)	No data	No data
Multiresidue method	Bifenazate and D3598 were tested through the United States Food and Drug Administration Multiresidue Protocols (PAM Volume 1). No methods are suitable for analysis of bifenazate and D3598.		No data

NATURE OF THE RESIDUE IN PLANTS—APPLES		
Radiolabel position	^{14}C-substituted phenyl (uniform ring label)	
Test site	Orchard	
Treatment	Foliar; immature fruit present at approximately 6 cm in diameter	
Rate (1 application)	0.42 or 2.24 kg a.i./ha	
Seasonal rate	0.42 or 2.24 kg a.i./ha	
PHI	101 days	
Most of the applied radioactivity remained on the foliage. Most of the radioactivity on the fruit was removed with a surface wash of acetonitrile. Very little radioactivity was found in pomace and juice.		
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**	**Minor Metabolites (<10% of the TRRs)**
Apple (wash, pomace, juice)	Bifenazate	D3598, D1989, D6887, D4642

NATURE OF THE RESIDUE IN PLANTS—ORANGES		
Radiolabel position	^{14}C- substituted phenyl (uniform ring label)	
Test site	Pots in an outdoor enclosure	
Treatment	Foliar; fruit present of variable size and maturity	
Rate (1 application)	0.42 or 2.24 kg a.i./ha	
Seasonal rate	0.42 or 2.24 kg a.i./ha	
PHI	43, 184, 274, 442 days	
Most of the applied radioactivity remained on the foliage. Most of the radioactivity on the fruit was removed with a surface wash of acetonitrile. Peel also contained a significant amount of radioactivity; very little was in pulp and juice.		
Metabolites Identified (43 DAT)	**Major Metabolites (> 10% of the TRRs)**	**Minor Metabolites (< 10% of the TRRs)**
Orange (wash, peel, pulp, juice)	Bifenazate	D3598, D1989, D9963, D4642

NATURE OF THE RESIDUE—COTTON	
Radiolabel position	^{14}C- substituted phenyl (uniform ring label)
Test site	Pots outdoors
Treatment	Foliar; late bloom to early boll set

Rate (1 application)	0.56 or 2.24 kg a.i./ha	
Seasonal rate	0.56 or 2.24 kg a.i./ha	
PHI	112 days	
Most of the applied radioactivity remained on the foliage; within the plant, most of the radioactivity was in the gin trash with only a small proportion penetrating into the seed.		
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**	**Minor Metabolites (<10% of the TRRs)**
Cotton seed	None	Bifenazate, D3598, D1989, D4642
Cotton gin trash	Bifenazate	D3598, D1989, D4642, D9963, A1530
CONFINED ROTATIONAL CROP STUDY—Lettuce, Carrot, Wheat		
Radiolabel position	^{14}C- substituted phenyl (uniform ring label)	
Test Site	Pots in greenhouse	
Formulation used for trial	50% wettable powder	
Application rate and timing	0.56 kg a.i./ha or 5.6 kg a.i./ha to bare soil 30, 125 or 360 days before seeding rotational crops	
Metabolites Identified	**Major Metabolites (> 10% of the TRRs)**	**Minor Metabolites (< 10% of the TRRs)**
Lettuce 30-day PBI 125-day PBI	None	None
Carrot 30-day PBI 125-day PBI	None	None
Wheat 30-day PBI 125-day PBI 360-day PBI	None	None

NATURE OF THE RESIDUE—RUMINANT			
Species	Dose level	Length of dosing	Sacrifice
Lactating goat (*Capra hircus*)	9.95 ppm in the diet	4 consecutive days	9 hours after final dose
66.0% of the administered dose (AD) excreted in urine and feces; 1.98% AD in tissues and organs; 0.22% AD in milk. 31.6% AD unaccounted for (intestinal contents not analyzed).			
Metabolites Identified	**Major Metabolites (>10% TRRs)**	**Minor Metabolites (<10% TRRs)**	
Fat	Bifenazate	D3598; D1989; A1530;	
Muscle	A1530	Bifenazate; D3598; D1989	
Liver	None	Bifenazate; D3598; D1989; A1530; D9569; A1530-sulfate; A1530-glucuronide; bifenazate-glucuronide	
Kidney	A1530	Bifenazate; D3598; D1989; D9569	

Milk	A1530-sulfate	Bifenazate; D3598; D1989; A1530

CROP FIELD TRIALS—Apples

A total of 17 trials were conducted in growing regions representative of Canada, in zones 1 (4 trials), 1A (1 trial), 5 (4 trials), 5B (3 trials), and 11 (5 trials). Trials were conducted with one application at 0.56 kg a.i./ha, equivalent to 1.3-fold the maximum label rate.

Commodity	Total Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Mean	Median	SDEV
Apple	0.56	7	Bifenazate + D3598	40	0.024	0.575	0.574	0.152	0.110	0.140

RESIDUE DECLINE—Apples

Residue decline trials were conducted in zones 1 (1 trial; PHIs of 3, 7, 14, 21 and 28 days), 5 (1 trial; PHIs of 1, 3, 7, 14, and 21 days) and 11 (1 trial; PHIs of 3, 7, 14, 21, and 28 days). Trials were conducted with one application at 0.56 kg a.i./ha, equivalent to 1.3-fold the maximum label rate. Residues generally decreased as the PHI increased from 3 to 21 days.

Commodity	Total Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Mean	Median	SDEV
Apple	0.56	1	Bifenazate + D3598	2	0.202	0.237	0.220	0.220	N/A	N/A
		3		6	0.101	0.496	0.473	0.305	0.338	0.168
		7		6	0.131	0.380	0.379	0.235	0.185	0.113
		14		6	0.070	0.359	0.359	0.186	0.126	0.136
		21		6	0.063	0.247	0.245	0.150	0.127	0.078
		28		4	0.138	0.215	0.212	0.178	0.179	0.04

MAXIMUM RESIDUE LIMITS

The maximum residue level found on apples in growing regions representative of Canada following bifenazate treatment at 1.3-fold the maximum label rate and harvested at the label PHI of 7 days was 0.575 ppm. Therefore, an MRL of 0.6 ppm is recommended for apple.

CROP FIELD TRIALS—Grapes

A total of 6 trials were conducted in growing regions representative of Canada, in zones 5 (4 trials) and 11 (2 trials). All trials were conducted with one application at 0.56 kg a.i./ha, equivalent to 1.3-fold the maximum label rate.

Commodity	Total Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Mean	Median	SDEV
Grape	0.56	14	Bifenazate + D3598	14	0.14	0.97	0.97	0.50	0.49	0.30

RESIDUE DECLINE—Grapes

One decline trial was conducted in Zone 5 with one application at 0.56 kg a.i./ha, equivalent to 1.3-fold the maximum label rate. No trend of residue increase or decrease was observed as the PHI increased from 3 days to 28 days.

Commodity	Total Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Mean	Median	SDEV
Grape	0.56	3	Bifenazate + D3598	2	0.42	0.73	0.58	0.58	N/A	N/A
		7		2	0.42	0.49	0.46	0.46	N/A	N/A
		14		2	0.59	0.79	0.69	0.69	N/A	N/A
		21		2	0.39	0.58	0.49	0.49	N/A	N/A
		28		2	0.54	0.64	0.59	0.59	N/A	N/A

Two decline trials were conducted in zone 10 at 2.8 kg a.i./ha, equivalent to 6.7-fold the maximum label rate. Residues decreased as the PHI increased from 3 to 28 days.

Commodity	Total Rate (kg a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Mean	Median	SDEV
Grape	2.8	3	Bifenazate + D3598	4	0.83	1.31	1.07	1.06	1.05	0.20
		7		4	0.30	1.13	0.72	0.66	0.61	0.35
		14		4	0.15	0.30	0.30	0.24	0.26	0.07
		21		4	0.07	0.31	0.30	0.19	0.19	0.13
		28		4	0.12	0.26	0.23	0.18	0.16	0.07

MAXIMUM RESIDUE LIMITS

The maximum residue level found on grapes in growing regions representative of Canada following bifenazate treatment at 1.3× the maximum label rate and harvested at the label PHI of 14 days was 0.97 ppm. Residues in grapes do not increase with increased PHI. Therefore, an MRL of 1.0 ppm is recommended for grape.

FIELD ACCUMULATION IN ROTATIONAL CROPS

Not submitted or required.

PROCESSED FOOD AND FEED

Fraction (RAC treatment rate)	Mean Residue Levels (ppm)	Mean Processing Factor
Apple—RAC (2.8 kg a.i./ha)	1.45	N/A
Apple—wet pomace (2.8 kg a.i./ha)	2.59	1.8
Apple juice (2.8 kg a.i./ha)	0.21	0.17
Grape—RAC (2.8 kg a.i./ha)	0.22	N/A
Grape juice (2.8 kg a.i./ha)	0.02	0.11
Raisins (2.8 kg a.i./ha)	0.24	1.17

MAXIMUM RESIDUE LIMITS

The maximum residue expected on raisins, based on the HAFT for grape (0.97 ppm) and the average concentration factor for raisins (1.2×), would be 1.16 ppm. Consequently, an MRL of 1.2 ppm is recommended to cover residues of bifenazate in/on raisins. MRLs do not need to be established on apple juice or grape juice, as residues will be covered by the MRLs for the RACs. An MRL does not need to be established on wet apple pomace as it is not a human food commodity.

LIVESTOCK FEEDING					
Wet apple pomace is the only cattle feed commodity on the Canadian label. There are no poultry feed items on the Canadian label. The estimated MTDB is 0.52 ppm for dairy cattle and 1.04 ppm for beef cattle.					
Tissues/Matrices	Feeding Level (ppm)	Mean Residue Levels (ppm)		Anticipated Residues (ppm)	
		Bifenazate + D3598	A1530 + A1530-sulfate	Bifenazate + D3598	A1530 + A1530-sulfate
Muscle	10	< 0.01	< 0.01	< 0.01 (< LOQ)	< 0.01 (< LOQ)
Liver	10	< 0.01	< 0.01	< 0.01 (< LOQ)	< 0.01 (< LOQ)
Kidney	10	≤ 0.01	< 0.01	< 0.01 (< LOQ)	< 0.01 (< LOQ)
Milk (whole and skim)	10	< 0.01	< 0.01	< 0.01 (< LOQ)	< 0.01 (< LOQ)
Butterfat—day 20 (43% milk sample weight)	10	0.01	< 0.01		
Butterfat—day 28 (13% milk sample weight)	10	0.03	< 0.01		
Butterfat—day 20 or 28 (19% milk sample weight)	3	< 0.01	< 0.01		
Fat	10	0.07	< 0.01	< 0.01 (< LOQ)	< 0.01 (< LOQ)
	3	0.02	< 0.01		
	1	< 0.01	< 0.01		

Table 2 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
ROC FOR ENFORCEMENT **Primary crops** **Rotational crops**	 Bifenazate (D2341) + D3598 N/A
ROC FOR RISK ASSESSMENT **Primary Crops** **Rotational Crops**	 Bifenazate (D2341) + D3598 N/A
METABOLIC PROFILE IN DIVERSE CROPS	The metabolic pathway is similar in apples, oranges and cotton, and can be extended to cover all crops on the current proposed label (apple, grape, peach/nectarine and strawberry), but not all crops.

ANIMAL STUDIES		
ANIMALS	**Poultry**	**Ruminant**
ROC FOR ENFORCEMENT	N/A	**Milk and tissues except fat:** bifenazate + D3598 (expressed as bifenazate) + A1530 + A1530-sulfate (expressed as A1530) **Fat:** bifenazate + D3598 (expressed as bifenazate)
ROC FOR RISK ASSESSMENT	N/A	**Milk and tissues except fat:** bifenazate + D3598 (expressed as bifenazate) + A1530 + A1530-sulfate (expressed as A1530) **Fat:** bifenazate + D3598 (expressed as bifenazate)
METABOLIC PROFILE IN ANIMALS	N/A	Similar in goat and rat
FAT SOLUBLE RESIDUE	N/A	Yes

DIETARY RISK from food and water					
Chronic non-cancer dietary risk **ADI = 0.01 mg/kg bw** **EEC = 3.37 µg/L** **Basic risk assessment conducted using MRLs. Refined risk assessment conducted using median values, experimental processing factors and blended residue values.**	**POPULATION**	**ESTIMATED RISK (% of ADI)**			
		Food (basic)	**Food (refined)**	**Food + EEC (basic)**	**Food + EEC (refined)**
	All infants < 1 yr old	106.2	13.8	108.5	16.2
	Children 1 to 2 yrs	215.1	34.1	216.2	35.2
	Children 3 to 5 yrs	161.5	29.8	162.5	30.8
	Children 6 to 12 yrs	88.7	18.3	89.4	19
	Youth 13 to 19 yrs	51.9	11.2	52.4	11.7
	Adults 20 to 49 yrs	45.4	12.5	46.1	13.2
	Adults 50+ yrs	41.1	12.9	41.8	13.6
	Females 13 to 49 yrs	44.1	12	44.8	12.7
	Total population	61.1	14.6	61.8	15.3

Appendix IV Environmental Assessment

Table 1 Physical and Chemical Properties of the Active Ingredient Relevant to the Environment

Property	Value	Comments
Water solubility	3.76 mg/L	Low solubility
Vapour pressure	< 1.33 × $l0^{-5}$ Pa at 20°C	Non-volatile under field conditions
Henry's law constant	< 1. 0 × 10^{-8} atm m^3/mole	Non-volatile from moist soil and water surfaces
log K_{ow}	3.4 ± 2.85%	Potential for bioaccumulation
pK_a	12.94 ± 0.06 at 23°C	Mostly exists as undissociated molecule in the environmentally relevant pH conditions
UV–visible absorption (λmax, nm)	264 in acid, neutral and alkaline pH	Indicates a low potential for phototransformation

Table 2 Fate and Behaviour in the Terrestrial Environment

Property	Test Substance	Value	Comments
Abiotic transformation			
Hydrolysis	[^{14}C]bifenazate	$t_{½}$ at pH 4: 9.0 days	Important route under acid, neutral and alkaline conditions
		$t_{½}$ at pH 5: 6.0 days	
		$t_{½}$ at pH 7: 16.8 hours	
		$t_{½}$ at pH 9: 1.45 hours	
Phototransformation on soil	[^{14}C]bifenazate	$t_{½}$: 0.17 hours (irradiated) $t_{½}$: 0.28 hours (dark)	Importance could not be determined
Biotransformation			
Biotransformation in aerobic soil	[^{14}C]bifenazate	< 0.5 hours	Non-persistent; together with hydrolysis, a principal route of transformation
Biotransformation in anaerobic soil	No data submitted		

Property	Test Substance	Value	Comments
Mobility			
Adsorption / desorption in soil	No data submitted, soil column leaching data were submitted		
Soil leaching	[^{14}C]bifenazate	Leachates < 2.2 % AR; no residues below 12 cm soil depth	Low potential for leaching
Volatilization	VP: < 1.33 × l0^{-5} Pa at 20°C HLC: < 1.0 × 10^{-8} Pa.m^3/mole		Non-volatile and not an important route of transformation
Field studies			
Field dissipation	Acramite: Ontario and Nova Scotia	DT_{50}: 4, 4 and 6 days*	Non-persistent
		DT_{90}: 22, 20 and 22 days*	No residue carryover
	Acramite: Washington	DT_{50}: 5 days*	Non-persistent
		No residues after 60 days	No residue carryover
	Acramite: North Carolina and California	DT_{50}: 4–5 days*	Non-persistent
Field leaching	Acramite: Ontario and Nova Scotia	No residues below 30 cm soil depth	Low potential for leaching
	Acramite: Washington	No residues below 15 cm soil depth	Low potential for leaching
	Acramite: North Carolina and California	No residues below 15 cm depth	Low potential for leaching

*Bifenazate and D3598 combined

Table 3 Transformation Products in the Terrestrial Environment

Property	Test Substance	Transformation Products	
		Major	Minor
Abiotic transformation			
Hydrolysis	[^{14}C]bifenazate	D3598 (58.5%) D9472 (83.5%) D1989 (9.9%) Unidentified (24%)	D9963 (6.6%)
Phototransformation on soil	[^{14}C]bifenazate	D3598 (84.3%) D1989 (11.2%)	None
Biotransformation			
Biotransformation in aerobic soil	[^{14}C]bifenazate	D3598 (92%) D1989 (26.8%)	None
Field studies			
Field dissipation	Acramite 50WS: Ontario and Nova Scotia	D3598 (76% of Bifenazate + D3598)	None
	Acramite 50WS: Washington	D3598 and D1989	None

( ) Maximum concentration of applied radioactivity

Table 4 Fate and Behaviour in the Aquatic Environment

Property	Test Material	Value	Comments
Abiotic transformation			
Hydrolysis	[^{14}C]bifenazate	$t_{½}$ at pH 4: 9 days	Important route under acid, neutral and alkaline conditions
		$t_{½}$ at pH 5: 6.0 days	
		$t_{½}$ at pH 7: 16.8 hours	
		$t_{½}$ at pH 9: 1.45 hours	
Phototransformation in water	[^{14}C]bifenazate	t½: 16.20 hours	Important route of transformation
Phototransformation in natural water	[^{14}C]bifenazate	t½: 1.9 hours	
Biotransformation			
Biotransformation in aerobic water systems	[^{14}C]bifenazate	DT_{50} < 6 hours DT_{50} < 4 days	Important route of transformation
Biotransformation in anaerobic water systems	[^{14}C]bifenazate	DT_{50}: 77.9 days	Moderately persistent
Field studies			
Field dissipation	No data submitted		

Table 5 Identification of Transformation Products

Applicant's Code Name	Chemical Name	CAS Number	Molecular Weight
D3598	diazenecarboxylic acid, 2-(4-methoxy- [1,1' biphenyl]-3-yl)-, 1-methylethyl ester	149878-40-0	298
D1989	1,1'-biphenyl, 4-methoxy	613-37-6	184
D9472	(1,1'-biphenyl)-3,4-diol	92-05-7	186
D9963	(1,1'-biphenyl)-4-methoxy-3-ol	Unavailable	200
D4111	(1,1'-biphenyl)-3-amino-4-methoxy	39811-17-1	199
D5863	(1,1'-biphenyl)-4-methoxy-3-hydrazine-N,N'-dicarboxylic acid, bis-(1-methylethyl ester)	Unavailable	386
D6887	carbamic acid, (4-methoxy-[1,1'biphenyl]-3-yl)-, 1-methylethyl ester	Unavailable	285
D4642	diazinecarboxylic acid, 2-(4-methoxy-[1,1',-biphenyl]-3-yl), 1-methylethyl ester 2-oxide	Unavailable	314

Table 6 Transformation Products in the Aquatic Environment

Property	Test Substance	Transformation Products	
		Major	Minor
Abiotic transformation			
Hydrolysis	[^{14}C]bifenazate	D3598 (58.5%) D9472 (83.5%) D1989 (9.9%) Unidentified (24%)	D9963 (6.6%)
Phototransformation in water	[^{14}C]bifenazate	D3598 (74.4%) D9472 (15.6%) D1989 (13.8%) D9963 (20.7%)	None
Phototransformation in natural water	[^{14}C]bifenazate	D3598 (58.4%) D1989 (12.8%) D9963 (17.2%) D9472 (11.7%)	None
Biotransformation			
Biotransformation in aerobic sediment/ water	[^{14}C]bifenazate	D3598 (33.6%) D9472 (21.6%)	D9963 A1530

Property	Test Substance	Transformation Products	
		Major	Minor
Biotransformation in anaerobic soil/water	[^{14}C]bifenazate	D3598 (14.7%) A1530 (24.8%)	D9472 (2.7%)

( ) Maximum concentration of applied radioactivity

Table 7 Fate of Major Transformation Products in the Environment

Transformation product	$t_{½}$ or DT_{50}	Interpretation
D3598	Soil phototransformation DT_{50}: 64 hours	Important route of transformation
	Aerobic soil biotransformation $t_{½}$: 10.2 hours	Important route of transformation non-persistent in soil under aerobic conditions
	Aerobic aquatic biotransformation $t_{½}$: 1–5 days DT_{90}: 19–23 days	Non-persistent and no carryover in water under aerobic conditions
	Field DT_{50} (bifenazate + D3598): 4–6 days Field DT_{90} (bifenazate + D3598): < 22 days No residues below 30 cm soil depth	Non-persistent; no carryover and no leaching
D1989	Soil K_{oc}: 3011–3962	Slightly mobile
	Sediment K_{oc}: 6189	Immobile
	No residues after 60 days under field conditions No residues below 30 cm soil depth	Non-persistent; no carryover and no leaching
D9472	Aerobic aquatic biotransformation $t_{½}$: 2–4.5 days DT_{90}: 5 days	Non-persistent and no carryover in water under aerobic conditions
	No residues detected under field conditions	
D9963	No residues detected under field conditions	

Table 8 Maximum EEC in Soil, Water and Diets of Birds and Mammals

Organism	EEC
Soil (mg a.i./kg soil)	0.19
Water (mg a.i./L water)	0.14
Bobwhite quail diet (mg a.i./kg dw diet)	73.71
Mallard duck diet (mg a.i./kg dw diet)	14.34
Rat diet (mg a.i./kg dw diet)	212.39
Mouse (mg a.i./kg dw diet)	211.12
Rabbit (mg a.i./kg dw diet)	317.59

Table 9 Level 1 Estimated Environmental Concentrations of Bifenazate and Transformation Product D3598 in Potential Drinking Water Sources

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Acute[1]	Chronic[2]	Acute[3]	Chronic[4]	Acute[3]	Chronic[4]
Bifenazate	0	0	1.2	0.0025	0.5	0.001
D3598[5]	1.65	3.37	1.88	0.1	0.6	0.05

Notes:

1 90^{th} percentile of daily average concentrations

2 90^{th} percentile of yearly average concentrations

3 90^{th} percentile of yearly peak concentrations

4 90^{th} percentile of yearly average concentrations

5 Transformation product—application rate equivalent to maximum allowable parent rate = 0.418 kg a.i./ha

Appendix V Environmental Toxicology and Risk Assessment

Table 1 Summary of Toxicity to Non-target Terrestrial Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity
Invertebrates				
Earthworm	Acute	Bifenazate Technical	LC_{50} > 1083 mg a.i./kg dry soil NOEC (mortality/body weight): 76 mg a.i./kg dry soil	Adverse effects at > 76 mg a.i./kg
Bees	Contact	Bifenazate Technical	NOEL: 2.7 µg a.i./bee LD_{50}: 7.8 µg a.i./bee	Moderately toxic
Arthropods	Contact: *Orius laevigatus*	480 g/L SC formulation	NOEL (mortality/fecundity): 300 g a.i./ha (the highest tested application rate) LD_{50} not reached in this study	
	Contact: *Chrysoperla carnea*	480 g/L SC formulation	NOEL (mortality/fecundity): 300 g a.i./ha (the highest tested application rate) LD_{50} not reached in this study	
	Contact *Poecilus cupreus*	480 g/L SC formulation 42.9% purity	NOEL (mortality/prey consumption): 300 g a.i./ha LD_{50} not reached in this study.	
	Contact: *Thyphlodromus pyri* (Tier 1)	480 g/L SC formulation	LD_{50}: 27.8 g a.i./ha NOEL (mortality): 10 g a.i./ha NOEL (fecundity): 5 g a.i./ha	
	Contact: *Thyphlodromus pyri* (Tier 2)	480 g/L SC formulation	NOEL (mortality): 600 g a.i./ha (the highest tested application rate) NOEL (fecundity): 25 g a.i./ha LD_{50} not reached in this study	
	Contact: *Aphidius rhopalosiphi*	480 g/L SC formulation	LD_{50}: 752 g a.i./ha NOEL (fecundity): 100 g a.i./ha	
	Contact: *Encarsia formosa*	480 g/L SC formulation	NOEL (mortality/fecundity): 300 g a.i./ha (the highest tested application rate) LD_{50} not reached in this study	

Birds				
Bobwhite quail	Acute oral	Bifenazate Technical	LD_{50}: 1032 mg a.i./kg bw NOEL (mortality/body weight): 276 mg a.i./kg bw	Slightly toxic
	Acute dietary	Bifenazate Technical	LC_{50}: 2077 mg a.i./kg diet NOEC (mortality): 529 mg a.i./kg diet NOEC (sublethal effects): 292 mg a.i./kg diet	Slightly toxic
	Reproduction	Bifenazate Technical	NOEC: 262.5 mg a.i./kg diet	
Mallard duck	Acute dietary	Bifenazate Technical	LC_{50}: 656 mg a.i./kg diet NOEC (mortality/body weight): 292 mg a.i./kg diet	Moderately toxic
	Reproduction	Bifenazate Technical	NOEC:115 mg a.i./kg diet	
Mammals				
Rat	Acute	Bifenazate	LD_{50} (effect) > 5000 mg a.i./kg bw	Non-toxic
	90-day dietary	Bifenazate	NOEC (effect): 40 mg a.i./kg bw	
	2-year dietary	Bifenazate	NOEC (effect): 80 mg a.i./kg bw	
	Reproduction	Bifenazate	NOEC (parental toxicity): 20 mg a.i./kg bw NOEC (reproductive toxicity): 200 mg a.i./kg bw	
Mouse	Dietary	Bifenazate	2-year NOEC (effect): 10 mg a.i./kg bw	
Vascular Plants				
Vascular plant	Seedling emergence	UCC-D2341-50W	NOEC: 1.10 kg a.i./ha	No adverse effects up to 1.10 kg a.i/.ha
	Vegetative vigour	UCC-D2341-50W	NOEC: 1.10 kg a.i./ha	

Table 2 Summary of Toxicity to Non-target Aquatic Organisms

Test Organism	Test Substance	Endpoint Values (mg a.i./L)	Degree of Toxicity
Freshwater species			
Waterflea *Daphnia magna*	Bifenazate Technical	48-hour EC_{50}: 0.50	Highly toxic
		21-day $NOEC_{(reproduction\ and\ growth)}$: 0.15	Adverse effects at > 0.15 mg a.i./L
Rainbow trout *Oncorhynchus mykiss*	Bifenazate Technical	96-hour LC_{50}: 0.76 96-hour $NOEC_{mobility}$: 0.16	Highly toxic
Bluegill sunfish *Lepomis macrochirus*	Bifenazate Technical	96-hour LC_{50}: 0.58 96-hour $NOEC_{sublethal}$: 0.30	Highly toxic
Green alga *Selenastrum capricornutum*	Bifenazate Technical + transformation products	96-hour $EC_{50(cell\ density)}$: 0.89 96-hour $EC_{50(area\ under\ growth\ curve)}$: 0.90 96-hour $EC_{50(growth\ rate)} \geq 2.02$ 96-hour $NOEC_{sublethal}$: 0.252	Effects observed at > 0.252 mg a.i./L
Blue-green alga *Anabaena flosaquae*	Bifenazate Technical + transformation products	96-hour $EC_{50(cell\ density)}$: 2.0 96-hour $EC_{50(area\ under\ growth\ curve)}$: 1.8 96-hour $EC_{50(growth\ rate)} \geq 4.48$ 96-hour $NOEC_{(cell\ density)} > 1.13$ 96-hour $NOEC_{(area\ under\ growth\ curve)} > 0.53$ 96-hour $NOEC_{50(growth\ rate)} > 1.13$	Effects observed at > 0.53 mg a.i./L
Freshwater diatom *Navicula pelliculosa*	Bifenazate Technical + transformation products	96-hour $EC_{50(cell\ density)} > 0.81$ 96-hour NOEC > 0.517	Effects observed at > 0.517 mg a.i./L
Duckweed *Lemna gibba*	Bifenazate Technical	7-day NOEC: 3.82	No effect up to 3.82 mg a.i./L
Marine species			
Mysid shrimp *Mysidopsis bahia*	Bifenazate Technical	96-hour LC_{50}: 0.058 96-hour $NOEC_{(mobility)}$: 0.04	Very highly toxic
Eastern oyster *Crassostrea viginica*	Bifenazate Technical	96-hour $EC_{50(shell\ deposition)}$: 0.28 96-hour $NOEC_{(shell\ deposition)}$: 0.078	Highly toxic
Sheepshead minnow *Cyprinodon variegatus*	Bifenazate Technical	96-hour LC_{50}: 0.416 96-hour $NOEC_{(mobility)}$: 0.136	Highly toxic

Table 3 Risk to Terrestrial Organisms

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Invertebrates					
Earthworm	Acute	NOEC: 76 mg a.i./kg soil	0.19 mg a.i./kg soil	< 0.003	Negligible risk
Bee	Contact	NOEC: 3020 g a.i./ha	421 g a.i./ha	0.14	No risk
Predatory arthropod	Contact	NOEC: 5 g a.i./ha	421 g a.i./ha	84.2	High risk
Parasitic arthropod	Contact	NOEC: 100 g a.i./ha	421 g a.i./ha	4.21	Moderate risk
Birds					
Bobwhite quail	Acute	NOEL: 276 mg a.i./kg bw	DI:1.12 mg a.i./ind/day	42 days	Negligible risk
	Dietary	NOEC: 292 mg a.i./kg diet	73.71 mg a.i./kg diet	0.25	Low risk
	Reproduction	NOEC: 262.5 mg a.i./kg diet	73.71 mg a.i./kg diet	0.28	Low risk
Mallard duck	Dietary	NOEC: 292 mg a.i./kg diet	14.24 mg a.i./kg diet	0.05	Negligible risk
	Reproduction	NOEC: 115 mg a.i./kg diet	14.24 mg a.i./kg diet	0.12	Low risk
Mammals					
Rat	Acute	NOEL > 500 mg a.i./kg bw*	12.7 mg a.i./ind/day	13.7 days	Low risk
	Dietary	NOEC: 40 mg a.i./kg diet	212.39 mg a.i./kg diet	5.31	Moderate risk
	2-year dietary	NOEC: 80 mg a.i./kg diet	212.39 mg a.i./kg diet	2.65	Moderate risk
	Reproduction	NOEC: 200 mg a.i./kg diet	212.39 mg a.i./kg diet	1.06	Moderate risk
Mouse	2-year dietary	NOEC: 10 mg a.i./kg diet	212.12 mg a.i./kg diet	21.2	High risk

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Vascular Plants					
Vascular plant	Seedling emergence	NOEC: 1.10 kg a.i./ha	0.421 kg a.i./ha	0.38	No risk
	Vegetative vigour	NOEC: 1.10 kg a.i./ha	0.421 kg a.i./ha	0.38	No risk

* NOEL=1/10th of LD_{50} of 5000 mg a.i./kg bw

Table 4 Risk to Aquatic Organisms

Organism	Exposure	Endpoint Value* (mg a.i./L)	EEC (mg a.i./L)	RQ	Risk
Freshwater Species					
Waterflea	Acute	NOEC: 0.05**	0.14	2.88	Moderate risk
	Chronic (reproduction)	NOEC: 0.15	0.14	0.93	Low risk
Rainbow trout	Acute	NOEC: 0.16	0.14	0.88	Low risk
Alga	Acute	NOEC: 0.252	0.14	0.56	Low risk
Vascular plant	Acute effects	NOEC: 3.82	0.14	0.37	Low risk
Marine Species					
Mysid shrimp	Acute	NOEC: 0.04	0.14	3.5	Moderate risk
Eastern oyster	Acute	NOEC: 0.078	0.14	1.75	Moderate risk
Sheepshead minnow	Acute	NOEC: 0.136	0.14	1.03	Moderate risk

* Most susceptible species

** 1/10th of LC_{50}

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