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Evaluation Report

Acequinocyl

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Overview

Registration Decision for Acequinocyl

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*[1] and in accordance with the Pest Control Products Regulations, has granted conditional registration Acequinocyl Technical as well as Shuttle 15 SC Miticide and Kanemite 15 SC Miticide. The end-use product Shuttle 15 SC Miticide controls specific mites in commercial greenhouses and shadehouses on container-grown ornamental, floral, foliage and nursery crops. The end-use product Kanemite 15 SC Miticide controls specific mites in field-grown ornamentals and pome fruit.

Current scientific data from the registrant, scientific reports and information from other regulatory agencies were evaluated to determine if, under the proposed conditions of use, the products have value and do not present an unacceptable risk to human health or the environment.

This report summarizes the information evaluated and provides the results of the evaluation as well as the reasons for the registration decision, with an outline of the additional scientific information required from the applicant. It also describes the conditions of registration that applicant must meet to ensure that the health and environmental risks as well as the value of these pest control products are acceptable for their intended use.

This overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of acequinocyl as well as of the end-use products Shuttle 15 SC Miticide and Kanemite 15 SC miticide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks[2] to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 As per subsection 28(1) of the *Pest Control Products Act.*

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

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

What Is Acequinocyl?

Acequinocyl is a contact miticide that is applied to leaves to control specific mites. Acequinocyl can be applied in greenhouses and shadehouses on container-grown ornamental, floral, foliage and nursery crops as well as on field-grown ornamentals and pome fruit using ground application equipment. Acequinocyl inhibits electron transfer at the mitochondrial level in target mites and is effective against all immature life stages. It may have indirect effects on adults of some target pest species.

Health Considerations

Can Approved Uses of Acequinocyl Affect Human Health?

Acequinocyl is unlikely to affect your health when used according to the label directions.

People could be exposed to acequinocyl through diet (food and water) or when handling and applying the product. When assessing health risks, the PMRA considers two key factors: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only the uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

Acequinocyl as well as Kanemite 15 SC Miticide and Shuttle 15 SC Miticide were of low toxicity to animals after a single dose administration, were not irritating to the skin or eyes and did not cause skin sensitization. Acequinocyl did not cause cancer in animals and was not genotoxic[4]. There was also no indication that acequinocyl caused damage to the nervous system, and there were no effects on reproduction. The first sign of toxicity in animals given daily doses of acequinocyl over longer periods of time was disruption of the blood coagulation system, characterized by increased clotting time and internal hemorrhage. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When acequinocyl was given to pregnant animals, effects on the developing fetus were not observed, indicating that the fetus was not more sensitive to acequinocyl than the adult animal. Consequently, no extra protective measures were applied during the risk assessment.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that children in the 1 to 2 year old and 3 to 5 year old subpopulations, which would ingest the most acequinocyl relative to body weight, are expected to be exposed to less than 26% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from acequinocyl is not of concern for all population subgroups.

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Each MRL value determines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using end-use products containing acequinocyl on pome fruit were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Evaluation Report.

[4] Genotoxic chemicals are those capable of causing damage to DNA. Such damage can potentially lead to the formation of a malignant tumour, but DNA damage does not lead inevitably to the creation of cancerous cells.

Workplace Risks From Handling Shuttle 15 SC Miticide and Kanemite 15 SC Miticide

Occupational risks are not of concern when Shuttle 15 SC Miticide and Kanemite 15 SC are used according to the label directions, which include protective measures.

Direct skin contact can occur when farmers and custom applicators mix, load or apply either Shuttle 15 SC Miticide or Kanemite 15 SC Miticide and when workers re-enter freshly treated fields, nurseries, greenhouses and shadehouses. Therefore, the label specifies that anyone mixing/loading Kanemite 15 SC Miticide must wear a long-sleeved shirt, long pants and gloves and that anyone applying Kanemite 15 SC Miticide must wear a long-sleeved shirt and long pants. The label for Shuttle 15 SC Miticide also specifies that anybody mixing/loading/applying the end-use product must wear a long-sleeved shirt, pants and gloves. The labels also require that workers do not enter treated areas for 12 hours after application. Taking into consideration these label statements, the number of applications and that occupational exposure is expected to be of short to medium duration for handlers and workers, risk to these individuals is not a concern.

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

Environmental Considerations

What Happens When Acequinocyl Is Introduced Into the Environment?

Acequinocyl is toxic to freshwater and estuarine/marine invertebrates; therefore, label instructions are required to protect these organisms during pesticide application and handling. Aquatic buffer zones are required during application.

Acequinocyl enters the environment when used as a miticide on field-grown ornamentals and pome fruit trees as well as on nursery crops in greenhouses and shadehouses. Acequinocyl is non-persistent to slightly persistent in both soil and water. The major transformation products formed in soil and water are non-persistent to slightly persistent in soil and slightly persistent in water. Acequinocyl and its major transformation products are not expected to leach through the soil profile beyond 30 cm; therefore, they are not expected to enter ground water. Based on its low volatility (vapour pressure and Henry's law constant), acequinocyl residues are not expected in the air.

Acequinocyl presents a negligible risk to wild mammals, birds, earthworms, bees, beneficial arthropods, terrestrial plants, fish, amphibians and algae. However, it is expected to adversely affect aquatic invertebrates living in freshwater and estuarine/marine habitats adjacent to areas of application. Therefore, specific instructions to reduce spray drift to aquatic invertebrates are provided on the end-use product label. Also, buffer zones of 1 to 35 metres (depending on timing of application) are required to protect nearby freshwater and estuarine/marine habitats from the effects of spray drift.

Value Considerations

What Is the Value of Acequinocyl?

Acequinocyl, a miticide, controls two-spotted spider mites and spruce spider mites on greenhouse and field grown ornamentals. When used on pome fruit, acequinocyl controls two-spotted spider mites and European red mites.

A single application of acequinocyl controls specific mites on ornamentals (greenhouse, shadehouse and field grown) and pome fruit. It is also compatible with current management practices and conventional crop production systems. Growers are familiar with the monitoring techniques to determine if and when applications are needed.

There are no miticides from the same class as acequinocyl currently registered for use on the listed crops; therefore, acequinocyl offers a new class of miticide for resistance-management purposes. When applied according to the label directions, acequinocyl is effective at controlling two-spotted spider mite, spruce spider mite and European red mite.

Measures to Minimize Risk

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

Key Risk-Reduction Measures

Human Health

- On the Shuttle 15 SC Miticide and Kanemite 15 SC Miticide labels, the following text will appear: “Wear a long-sleeved shirt and long pants during all product handling activities. In addition, wear chemical-resistant gloves during mixing, loading, clean-up and repair activities.”

Environment

- As Kanemite 15 SC Miticide is toxic to aquatic invertebrates, exposure of these organisms to spray drift should be minimized. Specific instructions to reduce spray drift are provided on the end-use product label.

- Kanemite 15 SC Miticide cannot be sprayed within 1 to 35 metres of sensitive aquatic habitats. The distance allowed depends on the timing of application (early vs. late in the season).

What Additional Scientific Information Is Required?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of these registrations. More details are presented in the Science Evaluation section of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

- **Environment**
    - Identification of the unknown major transformation product in the phototransformation on soil study. Submission of this information to the PMRA must be made no later than 1 December 2008.
    - An acute toxicity study and a chronic toxicity study using the major transformation product acequinocyl-OH (R1) with the freshwater invertebrate *Daphnia magna*. Submission of this information to the PMRA must be made no later than 1 December 2008.
    - An acute toxicity study using the major transformation product, acequinocyl-OH (R1), with two estuarine/marine invertebrates: saltwater mysid and eastern oyster. Submission of this information to the PMRA must be made no later than 1 December 2008.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted[5], the PMRA will publish a consultation document when there is a proposed decision on the applications to convert the conditional registrations to full registrations or on the applications to renew the conditional registrations, whichever occurs first.

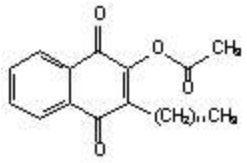
The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra_infoserv@hc-sc.gc.ca).

[5] As per subsection 28(1) of the *Pest Control Products Act.*

Science Evaluation

1.0 The Technical Grade Active Ingredient, Its Properties and Uses

1.1 Identity of the Technical Grade Active Ingredient

Active substance		Acequinocyl
Function		Miticide
Chemical name		
1.	**International Union of Pure and Applied Chemistry (IUPAC)**	3-dodecyl-1,4-dihydro-1,4-dioxo-2-naphthyl acetate
2.	**Chemical Abstracts Service (CAS)**	2-(acetyloxy)-3-dodecyl-1,4-naphthalenedione
CAS number		57960-19-7
Molecular formula		$C_{24}H_{32}O_4$
Molecular weight		384.5
Structural formula		
Purity of the technical grade active ingredient		96.8%

1.2 Physical and Chemical Properties of the Active Substance and End-use Products

Technical Product—Acequinocyl Technical

Property	Result
Colour and physical state	Munsell 2.5Y 6.9/6.0 (Light brown), solid flakes
Odour	Faint earthy odour
Melting range	59.6°C (Capillary method)
Boiling point or range	Not determined due to decomposition above 200°C. (Siwoloboff method)
Density	1.13 (Pycnometer method)
Vapour pressure at 25°C	1.69×10^{-6} Pa (By extrapolation of the vapour pressure curve from 70°C to 140°C)
Henry's law constant at 20°C	9.63×10^{-7} atm m^3/mol
Ultraviolet (UV)—visible spectrum	λ_{MAX} (nm) / ϵ (L/mol•cm) (pH 1) / (unbuffered) / (pH 14) 242 / 16524 / 16582 / 19055 245 / / / 13149 248 / 16989 / 16873 / 255 / / / 10473 262 / / 12916 / 265 / 13615 / / 270 / 13905 / 13207 / 275 / / / 2172 330 / 2836 / / 335 / / 2851 / 362 / / / 8999 (Solvent: 90% aqueous methanol)
Solubility in water at 20°C	6.69 µg/L (Column elution method using HPLC analysis with unbuffered water, purified by ion exchange and distillation).

Property	Result	
Solubility in organic solvents at 20°C (g/100 mL)	**Solvent** n-Heptane Methanol n-Octanol Acetone Xylene 1,2-Dichloroethane Ethyl Acetate	**Solubility** 36.0 6.1 29.2 >250 >250 >250 >250
n-octanol–water partition coefficient (K_{ow})	log K_{ow} > 6.2 (HPLC method using 75/25 methanol/purified water as the eluent).	
Dissociation constant (pK_a)	Could not be measured due to very low water solubility. (By conductometric and spectrophotometric methods) The proposed product does not have any dissociable moieties.	
Stability (temperature, metal)	Stable with aluminum powder, aluminum (II) ions, and iron powder. Incompatible with iron (III) ions; test material blackens and gives off acetic acid odour.	

End-use Products—Shuttle 15 SC Miticide and Kanemite 15 SC Miticide

Property	Result
Colour	Pale yellow
Odour	Detergent-like odour
Physical state	Suspension
Formulation type	SU (suspension)
Guarantee	Acequinocyl.....15.8%, nominal (Limits: 15.0–16.6%)
Container material and description	HDPE, 500 mL
Density at 20°C	1.04
pH of 1% dispersion in water	7.1
Oxidizing or reducing action	The test substance showed no significant temperature changes or chemical incompatibilities with monoammonium phosphate, potassium permanganate, zinc dust or water over a 24-hour period.

Property	Result
Storage stability	No significant change in the active ingredient concentration was observed over a one year period under ambient conditions.
Explodability	The product is not explosive.

1.3 Directions for Use

Shuttle 15 SC Miticide is for use in greenhouse and shadehouses on container grown ornamentals to control two spotted spider mites and spruce spider mites. Kanemite 15 SC Miticide is for use on field grown ornamentals and pome fruit to control two spotted spider mites, spruce spider mites and European red mites. These products are applied as foliar treatments using ground application equipment. The application rate or concentration and maximum number of applications varies depending on the crop (Table 1.3.1).

Table 1.3.1 Pest Control Claims for Acequinocyl

Crop	Pest	Rate	Maximum Number of Applications per Year
Greenhouse and field grown ornamentals* (except roses)	Two-spotted spider mite	0.21 - 0.46 L product/500 L water (0.07-0.15 g a.i./L)	2
	Spruce spider mite		
Greenhouse and field grown roses**	Two spotted spider mite	0.21 L product/500 L water (0.07 g a.i./L)	2
Pome fruit (Crop Group 11)	Two spotted spider mite	2.07 L product/ha (0.34 kg a.i./ha)	2
	European red mite		

* Do not apply to impatiens.

** Do not apply to miniature-roses.

1.4 Mode of Action

Acequinocyl is classified as Group 20B Miticide (Insecticide Resistance Action Committee, 2005), which function by inhibiting electron transfer at Complex III in the mitochondria. Acequinocyl is active against all motile life stages, as well as eggs. It is primarily effective after contact with the target pest, though ingestion will contribute to efficacy.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Technical Grade of Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

Plant and Animal
High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantification. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. A waiver rationale for extraction efficiencies of acequinocyl residues in plant and animal matrices was submitted. Since the enforcement analytical method employs the same extraction strategies as the one used in the metabolism studies, the waiver rationale was accepted. Methods for residue analysis in plant or animal matrix are summarized in Table 1, Appendix I.

Soil, Sediment and Ground Water
High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (68.4%–102% with the LOQ of 0.01 ppm and 91.0%–120% at 10× LOQ) were obtained in environmental media. Methods for residue analysis in soil, sediment and ground water are summarized in Table 2, Appendix I.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The PMRA conducted a detailed review of the toxicological database for acequinocyl. The database is complete, consisting of the full array of laboratory animal (in vivo) and cell culture (in vitro) toxicity studies currently required for health hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the toxicity of this pest control product.

Acequinocyl belongs to the quinoline class of miticides and the mode of action is binding to the Q_o centre of Complex III in the mitochondria of the mite cells and inhibiting electron transfer. Acequinocyl is a known Vitamin K antagonist and thereby is thought to disrupt blood coagulation.

Acequinocyl was of low acute toxicity by the oral route in Sprague-Dawley rats and CD-1 mice, of low toxicity via the dermal route in Sprague-Dawley rats, and of slight acute toxicity via the inhalation route in Sprague-Dawley rats. It was minimally irritating when applied to the skin and non-irritating to the eyes of Japanese White rabbits. Results of skin sensitization testing in Dunkin-Hartley guinea pigs using the Buehler method were negative.

Shuttle 15 SC Miticide and Kanemite 15 SC Miticide formulations were of low acute toxicity by the oral route in Sprague-Dawley rats and CD-1 mice and of low acute toxicity via the dermal and inhalation routes in Sprague-Dawley rats. The products were non- irritating when applied to the skin and eyes of Japanese White rabbits. Results of skin sensitization testing in Dunkin-Hartley guinea pigs using the Buehler method were negative.

Absorption of acequinocyl was rapid and low (8–13% of the administered dose [AD]). Whole body and time-course plasma studies revealed that distribution of the administered radioactivity was rapid and extensive, regardless of dosing regimen or gender, with the highest concentrations observed in the gastrointestinal tract and the liver. There was no evidence of sequestration in any tissues. Peak plasma time was 2–6 hours for the low-dose and 24 hours for the high-dose regardless of radiolabel position or sex. There was no evidence of binding to red blood cells. Excretion occurred primarily via the fecal route of elimination (81–91% of the AD), with the urinary route accounting for 12–15% of the AD. Biliary excretion studies determined that 20% (low-dose) and 3–5% (high-dose) of the administered radioactivity in the feces was attributed to the bile. Excretion via respiration was considered negligible. Metabolic profiles were similar for all excretion routes, regardless of label position or dose regimen, with only slight quantitative variation. The parent compound was extensively metabolized and accounted for minor amounts of administered radioactivity (<1%–8.3%). In addition to the parent compound, eleven metabolites were detected. The major metabolite in plasma was 2-hydroxy-3-dodecyl-1,4-naphthalenedione. Hexanoic, butanoic, and benzoic acid derivatives were present in lesser amounts in the plasma, with the benzoic acid derivative being the major metabolite in the feces. In urine, the hexanoic acid, butanoic acid, and the naphthalenedione derivatives represented the major metabolites. The metabolite profile in the bile was similar except for the presence of a glucuronide conjugate product which represented the majority of radioactivity.

The effects observed after short- and long-term dosing with acequinocyl were consistent throughout the database, regardless of study duration, dosing route, and species, with the primary target being the coagulation system. Disruption of the blood coagulation system was characterized by increased prothrombin time, increased activated partial thromboplastin time, and internal hemorrhage. A secondary response was also observed as evidenced by elevated numbers of platelets and reticulocytes, increased fibrinogen, and congestion of the spleen. Findings such as increased liver weight, elevated hepatic enzymes, altered liver function (reduced total protein, globulin, albumin, cholesterol, phospholipids), the presence of liver periportal fat, hepatocyte vacuolation, and the incidence of non-neoplastic lesions provided

evidence that supported the liver as a possible target organ. Effects on reproductive organs were also evidenced by decreased prostatic weights, arrested prostate development, and immature reproductive organs (testes, vesicles, uterus, vagina, ovaries).

There was evidence in mice and rats suggestive of increased toxicity with increased duration of dosing. Effects observed in the chronic studies in both species occurred at dose levels that were approximately 10-fold lower than the doses at which they occurred in studies of subchronic duration. Additionally, it appears that male animals are affected by exposure to the chemical at a lower dose as compared to females even though metabolism studies did not reveal any gender differences.

No evidence of carcinogenic potential of acequinocyl was observed in the oncogenicity studies conducted in the rat or the mouse. The dose levels chosen for these studies were deemed adequate based on the observed clinical effects. In addition, acequinocyl was determined to be non-genotoxic in both in vitro and in vivo mutagenicity studies.

There was no evidence of increased susceptibility of the young from the rat or rabbit developmental studies. An increase in early resorptions was observed at the same dose (rabbit) or at a greater dose (rat) than that which caused maternal toxicity. In both species, maternal toxicity led to premature sacrifice and was characterized by clinical signs and necropsy findings consistent with internal hemorrhage.

In a two-generation reproductive toxicity study, no effects on measured reproduction parameters were observed and there was no evidence of increased sensitivity in the young. The effects observed in both the offspring and the parental animals were similar in nature and consisted primarily of hemorrhaging which led to an increase in pup death. The effects in pups were noted only after they were weaned and were eating the diet exclusively, and most likely were attributed to the increased dose levels on a mg/kg bw basis achieved during this period.

Limited neurotoxicity tests conducted on pups post-partum in the two-generation reproduction study (functional development tests such as pupillary reflex test, an open field exploration test, and a water maze test with learning and memory phases) and in the 28-day dermal study (fore- and hindlimb grip strength measurements) did not reveal any evidence that acequinocyl poses a neurotoxicity concern. In the subchronic rat oral toxicity study, clinical signs of neurotoxicity such as piloerection and decreased spontaneous motor activity were only observed at the highest dose.

Additional safety factors for the protection of children and pregnant females from relevant endpoints of concern, or any database uncertainty regarding a potential for increased sensitivity in these population subgroups, were not warranted.

Results of the acute and chronic tests conducted on laboratory animals with acequinocyl and its associated end-use products are summarized in Tables 3 and 4, Appendix I.

3.2 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) is 0.023 mg/kg bw/day, calculated using the NOAEL in males of 2.3 mg/kg bw/day from the 2-year dietary study in the rat. Treatment-related effects at the LOAEL (9 mg/kg bw/day in males) included hypertrophy of the eyeball and corneal abnormalities. This study is of an appropriate route and duration, with the lowest NOAEL in the database. The standard uncertainty factor (UF) of 100 is applied to account for interspecies extrapolation and intraspecies variability.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF/SF}} = \frac{2.3 \text{ mg/kg bw/day}}{100} = 0.023 \text{ mg/kg bw/day}$$

3.3 Determination of Acute Reference Dose

An acute reference dose (ARfD) was not determined because an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

The ADI = 0.023 mg/kg bw/day based on the NOAEL of 2.3 mg/kg bw/day from the 2-year dietary study in the rat, coupled with an uncertainty factor of 100× (10× for interspecies variation and 10× for intraspecies variation).

There is no ARfD for acequinocyl (see section 3.3).

Short-term dermal: The most appropriate toxicology endpoint for this exposure scenario with respect to duration and route is the NOAEL of 200 mg/kg bw/day from the rat dermal 28-day study. The target margin of exposure (MOE) is 100 (10× for interspecies variation and 10× for intraspecies variation).

Intermediate-term dermal: The NOAEL of 200 mg/kg bw/day from the rat dermal 28-day study was considered to be the most appropriate for use in the intermediate-term dermal exposure scenario. This study is of the appropriate route (dermal) of exposure. Furthermore, evidence in the toxicology database does not suggest an increase in toxicity over the short to intermediate duration of exposure. The target MOE is 100 (10× for interspecies variation, and 10× for intraspecies variation).

Long-term dermal: The most appropriate toxicological endpoint for a long-term exposure scenario is the NOAEL of 2.3 mg/kg bw/day from the 2-year dietary study in the rat. Taking into account the gastrointestinal tract absorption value of 15% for acequinocyl, the NOAEL of 2.3 mg/kg bw/day translates to a NOAEL of 0.35 mg/kg bw/day for risk assessment purposes. The target MOE is 100 (10× for interspecies variation, and 10× for intraspecies variation).

Given limited potential for exposure via the inhalation route, together with absence of repeat dose inhalation studies, toxicology endpoints for this route were not established.

3.4.1.2 Dermal Absorption

In an in vivo rat study, the absorption, distribution and excretion (via urine and feces) of radioactivity was studied in male rats following a single dermal dose of ^{14}C-acequinocyl. Dose preparations resulted in nominal levels of 0.001, 0.01, 0.1 or 1.0 mg/cm^2. For each dose level, groups of 4 animals were sacrificed at the following times following administration: 0.5, 1, 2, 4, 10, 24, and 168 hours (there was not a 168 hours sacrifice at the 1.0 mg/kg dose level)

Mean recoveries of radioactivity from all dose groups were found to be acceptable in the range of 94.08–101.5% of the total radioactivity administered. The largest proportion of radioactivity was recovered from skin wash (surface of the skin) and dose site covering. The mean relative amount of radioactivity absorbed (including urine, feces, cage wash, tissues/organs and carcass) generally decreased with increasing dose. Monitoring of animals for 168 hours postapplication provided information to characterize fate of skin bound residues. Analysis of cumulative urine excretion data indicated that the magnitude of absorption decreased with time. As such, it was considered appropriate to derive a dermal absorption value from the groups of animals monitored for 168 hours (excluding skin bound residues). The dermal absorption value of 20% from the 0.01 mg/cm^2 dose level was considered appropriate for use in occupational exposure assessments.

The magnitude of residues in the protective covering was considered a study limitation as there is uncertainty as to whether these residues were available for dermal absorption.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

Individuals have potential for exposure to acequinocyl during mixing, loading and application. Exposure is expected to be short-to-intermediate term in duration for both end-use products. The application equipment used for applying both Shuttle 15 SC Miticide and Kanemite 15 SC Miticide is backpack, low-pressure hand wand and high-pressure hand wand. In addition, Kanemite 15 SC Miticide will also be applied using groundboom equipment on field grown ornamentals and airblast equipment for pome fruits.

Exposure estimates for mixers, loaders and applicators are based on data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. Appropriate subsets of A and B grade data (high confidence) were created from the database files of PHED for liquid open mixing/loading, open cab airblast, open cab ground boom and for backpack, low-pressure and high-pressure hand wand. All data were normalized for kilograms 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 which is most appropriate to the distribution of data for that body part. Exposure estimates are based on unit exposure values from PHED, coupled with application rate and typical area treated per day inputs (inputs provided in Table 3.4.2.1.1 and Table 3.4.2.1.2).

The exposure estimates are based on mixer/loaders/applicators (M/L/A) wearing a single layer of clothing (long pants and long sleeved shirt) plus gloves for hand held equipment and for mixer/loaders when using airblast and groundboom equipment. Exposure estimates were based on a single layer of clothing (no gloves) when applying using airblast and groundboom equipment.

Table 3.4.2.1.1 M/L/A Exposure and Risk Estimates for Shuttle 15 SC Miticide on Greenhouse and Shadehouse Container-Grown Ornamentals

Scenario	Application rate (g a.i./ha)	ATPD (ha/day)	Amount of a.i. handled per day (kg a.i./day) [1]	Dermal Exposure (µg a.i./kg bw/day) [2]	Dermal MOE [3]
Backpack M/L/A	0.69	1	0.69	53.68	3726
Low-pressure Hand Wand M/L/A				9.3	21508
High-pressure Hand Wand M/L/A				55.06	3537

[1] Amount of a.i. handled per day calculated using the application rate × Area Treated Per Day (ATPD)

[2] Daily exposure was calculated using amount of a.i. handled per day × PHED unit exposure value/body weight (70 kg)

[3] Exposure estimates were compared to a NOAEL of 200 mg/kg bw/day established in the 28-day dermal toxicity study in rats, target MOE = 100.

Table 3.4.2.1.2 M/L/A Exposure and Risk Estimates for Kanemite 15 SC Miticide on Field Grown Ornamentals and Pome Fruit

Scenario	Application rate (g a.i./ha)	ATPD (ha/day)	Amount of a.i. handled per day (kg a.i./day) [1]	Dermal Exposure (µg a.i./kg bw/day)[2]	Dermal MOE [3]
Backpack M/L/A	0.675	1	0.68	52.51	3809
Low-pressure Hand Wand M/L/A				9.1	21986
High-pressure Hand Wand M/L/A				53.86	3713
Groundboom M/L/A		32	21.6	25.96	7705
Farmer and Custom Airblast M/L/A	0.34	16	5.44	68.34	2927

[1] Amount of a.i. handled per day calculated using the application rate × Area Treated Per Day (ATPD)

[2] Daily exposure was calculated using amount of a.i. handled per day × PHED unit exposure value/body weight (70 kg)

[3] Exposure estimates were compared to a NOAEL of 200 mg/kg bw/day established in the 28-day dermal toxicity study in rats; target MOE = 100.

Dermal exposure estimates for individuals that mix/load/apply the end-use products were compared to a NOAEL of 200 mg/kg bw/day from a 28-day dermal toxicity study in rats. All MOEs exceed the target of 100 and are considered acceptable. An inhalation risk assessment was not conducted due to the limited exposure by the inhalation route (~3% of total exposure), the absence of toxicological endpoints for this route, as well as consideration of the magnitude of the MOE in the dermal risk assessment.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for intermediate-term exposure to workers entering orchards to perform pruning, scouting and harvesting and for workers entering field grown nurseries to perform scouting, pruning, harvesting and pinching activities. There is potential for long-term exposure to workers entering treated greenhouse and shadehouses to perform scouting, pruning, harvesting and pinching activities on greenhouse and shadehouse ornamentals (e.g. container grown plants).

The primary route of exposure for workers that enter treated areas is dermal through contact with residues on foliage. Inhalation exposure is expected to be negligible as the vapour pressure of acequinocyl is 1.7×10^{-6} Pa at 20°C, making it effectively non-volatile.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients. Chemical-specific dislodgeable foliar residue studies were submitted on apples and greenhouse chrysanthemums. Activity-specific transfer coefficients are based on Agricultural Reentry Task Force data, of which Arysta is a member.

The application regime for the greenhouse and shadehouse chrysanthemums DFR study consisted of two applications, 21 days apart, at a rate of 336 g a.i./ha. DFR samples were collected one day prior to application one, one day after application one, one day prior to application 2, immediately after application 2 (0, 4, 8, 12 and 24 hours after application) as well as 3, 7, 14, 21, 28 and 35 days after last application. Residues of both acequinocyl, and acequinocyl-OH, were analysed and reported as total acequinocyl. (Acequinocyl-0H was a minor contributor to the total residues.) No residues were found prior to the first application or in any of the control samples. After the first application, there was a decline in residues. Immediately after the second application, residues averaged 0.649 µg/cm^2 (range: 0.51–0.78 µg/cm^2). After the second application the residues slowly declined during the 35 days of sampling following the second application. This residue decline followed a byphasic curve and exhibited a half life of 0.75 days for the first phase of the curve and then did not show any decline for the second phase of the curve. The results indicate that the dislodgeable residues of acequinocyl do not decline rapidly with time. From this study, a time-weighted average DFR value (that is, the average of the daily exposure for the entire exposure duration) was derived for use in the Shuttle 15 SC Miticide exposure and risk assessment. The time weighted average is 0.152 µg/cm^2.

The application regime for the apple orchard DFR study consisted of two applications, at an application rate of 0.336 kg a.i./ha, at an interval of 21 (±1) days. Three sites were monitored (California, New York and Washington States) with three replicates per sampling time per site (total replicates per sampling time = 9). DFR samples were collected one day prior to application one, after the first application had dried, one day prior to application 2, after the second application had dried (0, 4, 8, 12 hrs after application) as well as 1, 3, 7, 14, 21, 28 and 35 days after last application. Residues of both acequinocyl and acequinocyl-OH, were analysed and reported as total acequinocyl (Acequinocyl-OH was a minor contributor of the total residues.). The results indicated that the dislodgeable foliar residues of acequinocyl declined with time in apple orchards. A linear regression of the data yielded an r^2 of 0.95 for both Washington and New York. The most appropriate value for use in the exposure and risk assessment is the peak average value from the New York study (0.69 µg/cm^2).

For the risk estimates, exposure was compared with the NOAEL of 0.35 mg/kg/day from the 2 year rat dietary study. The dermal absorption value of 20% was used to derive estimates of systemic exposure.

All margins of exposure are above the target MOE of 100 and are considered acceptable (Tables 3.4.2.2.1 and 3.4.2.2.2).

Table 3.4.2.2.1 Postapplication Exposure and Risk Estimates for Shuttle 15 SC Miticide

Activity	Exposure (mg a.i./kg bw/day)[a]	Margin of Exposure[b]
scouting, pruning, hand harvesting and pinching	0.001	252

[a] Estimate of exposure was calculated as 0.152 µg/cm^2 time weighted average DFR × transfer coefficient of 400 cm^2/hour × 8 hour/day × 20% dermal absorption / 70 kg body weight

[b] NOAEL of 0.35 mg a.i./kg bw/day (see section 3.4.1); target margin of exposure of 100.

Table 3.4.2.2.2 Postapplication Exposure and Risk Estimates for Kanemite 15 SC Miticide

Activity	Exposure (mg a.i./kg bw/day)[a]	Margin of Exposure[b]
scouting, pruning, hand harvesting and pinching	0.006	32407
pome fruit thinning	0.236	849
pome fruit pruning/scouting	0.039	5095
pome fruit handling irrigation	0.087	2306
pome fruit weeding	0.008	25473
pome fruit hand harvesting	0.118	1698

[a] Estimate of exposure was calculated as 0.152 µg/cm^2 time weighted average DFR × transfer coefficient × 8 hour/day × 20% dermal absorption / 70 kg body weight

[b] NOAEL of 0.35 mg a.i./kg bw/day (see section 3.4.1); target margin of exposure of 100.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement purposes in plant and animal commodities is acequinocyl and acequinocyl-OH. The metabolite AKM-15 is also included in the residue definition for risk assessment in liver and kidney. The data gathering/enforcement analytical methodology, liquid chromatography with tandem mass spectrometry (LC-MS/MS), is valid for the quantification of acequinocyl and acequinocyl-OH residues in pome fruit and ruminant livestock matrices (meat, milk, fat, liver and kidney). The residues of acequinocyl and acequinocyl-OH are stable when stored in a freezer at –20°C for at least 90 days. Apple samples were processed into apple juice and wet pomace using simulated commercial procedures. There was no concentration of residues in apple juice and a concentration of residues of 3.5-fold in

apple wet pomace. Supervised residue trials conducted throughout the United States and Canada using end-use products containing acequinocyl in or on pome fruit are sufficient to support the proposed MRLs.

3.5.2 Dietary Risk Assessment

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.0), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following assumptions were made in a chronic analysis: residues of pome fruit, citrus fruit, almonds and strawberries utilized are based on MRL values as are the MRL values for all animal by-product commodities. The refined chronic dietary exposure from all supported acequinocyl food uses (including acequinocyl-OH (and AKM-15 for liver and kidney only)) for the total population, including infants and children, and all representative population subgroups are $\leq$ 29% of the ADI. Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to acequinocyl (and metabolites) from food and water is 6.3% (0.001442 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all children 1 to 2 years old at 28.4% (0.005768 mg/kg bw/day) of the ADI.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for acequinocyl consists of exposure from food and drinking water sources only; there are no residential uses. Aggregate risks were calculated based on chronic endpoints. There was no acute endpoint identified for the general population, including infants and children.

3.5.4 Proposed Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

MRLs (ppm)	Foods
0.3	pome fruit
0.02	fat of cattle, sheep, goat, horse
0.02	meat byproducts of cattle, sheep, goat, horse
0.02	milk
0.02	liver of cattle, sheep, goat and horse

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

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the chronic dietary risk estimates are summarized in Tables 5 and 6, Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Acequinocyl reaches the soil when applied as a miticide on field grown ornamentals and pome fruit orchards. Under field conditions, its half-life in soil ranges from <1 to 4.7 days. Acequinocyl-OH (R1) is the major transformation product and its laboratory half-life in soil ranges from 7 to 37 days. Thus, acequinocyl is non-persistent to slightly persistent and R1 is slightly persistent in soil. Another non-persistent major transformation product was identified - AKM 18. Field data indicate that neither acequinocyl nor its major transformation products are expected to leach through the soil profile beyond 30 cm and, therefore, are not expected to enter ground water.

Acequinocyl can reach water bodies due to runoff from soil in treated pome fruit orchard areas. Although it is highly insoluble in water at pH 4 to pH 9, it may be present in runoff when sorbed to soil particles. Acequinocyl can also reach water bodies through spray drift. Its rate of dissipation from water systems is variable, with half-lives ranging from 14 minutes to 76 days under aerobic conditions. Thus, it ranges from non-persistent to slightly persistent in water.

The low vapour pressure and Henry's law constant indicate that acequinocyl is non-volatile in the environment. Therefore, acequinocyl residues are not expected in the atmosphere and long-range transport is not expected.

Data on the fate and behaviour of acequinocyl are summarized in Table 7, Appendix I.

4.2 Effects on Non-Target Species

To estimate risk of potential adverse effects on non-target species, a quotient method is used. The risk quotient (RQ) is calculated by dividing the exposure estimate by a value representing the most sensitive toxic endpoint. RQs are initially calculated for a screening-level assessment in order to obtain higher estimates of risk. The screening-level assessment is a realistic worst case scenario that is tending to worst case, but is not beyond the bounds of possibility. Negligible risk is predicted if the RQ is less than the trigger value of one. Risk increases with RQ values greater than one. If the trigger values are exceeded under the realistic worst-case scenario, then a refinement of the assessment is necessary to evaluate how frequently impacts might be expected in the range of conditions that occur in the field. A refined assessment takes into consideration more realistic exposure scenarios (e.g. drift to non-target habitats and runoff to water bodies) and may consider different toxicity endpoints.

4.2.1 Effects on Terrestrial Organisms

Risk of acequinocyl to terrestrial organisms was based upon evaluation of toxicity data for vertebrates, invertebrates and plants. Three bird species and two small mammal species (using

acute gavage, short and long-term dietary exposure scenarios) were used to represent terrestrial vertebrates. One honeybee species, four other arthropod species and one earthworm species were used to represent terrestrial invertebrates (using acute or chronic exposure). Ten crop species studied on a short-term exposure basis represented terrestrial vascular plants (Table 8, Appendix I).

Acequinocyl did not cause mortality to birds at the highest concentrations tested (2000 mg a.i./kg bw for acute exposure and 5000 mg a.i./kg diet for short-term dietary exposure). Sublethal effects, including reductions in food consumption and reductions in body weight gain (relative to control groups), were noted for birds exposed to 1500 and 5000 mg a.i./kg dw diet during short-term dietary exposure. Bird reproduction was affected due to an observed reduction in the number of eggs laid/hen at the 2500 mg a.i./kg dietary exposure level. Despite these observations of sublethal effects, RQs calculated under a realistic worst-case scenario are less then one for all three bird species tested under the different exposure scenarios. Thus, the level of concern is not exceeded and the risk posed to birds by exposure to acequinocyl is negligible.

Acequinocyl did not cause mortality in small mammals (rats and mice) at the highest concentration tested (5000 mg a.i./kg body weight) when administered acutely by gavage. The calculated RQs under the acute scenarios were less than one, indicating a negligible risk posed to small mammals by acequinocyl on an acute basis. Clinical signs of toxicity were observed at concentrations greater than or equal to 400 mg a.i./kg body weight/day during a 90-day dietary exposure period. The RQ values were 2.72 for the mouse on a chronic dietary basis and 2.74 for rat reproduction based on a chronic dietary basis. As there is a risk to small mammals based on longer term exposure scenarios (Table 9, Appendix I) a refined risk assessment was conducted.

The risk assessment in small mammals is initially conducted at a screening level incorporating a foliar dissipation half-life of 35 days. The 35 day default foliar half-lives are based on a data set of 447 foliar half-life estimates acquired from an extensive literature review conducted by Willis and McDowell (1987). Among this data set, 93% of the half-lives reported were less than 10 days, and 76% were less than 5 days. Since acequinocyl is not persistent in/on other media, a refined foliar dissipation rate of 10 days was included for assessment. Based on a refined foliar dissipation half life of 10 days, the resulting RQ values were: RQ - rat reproduction: 2.15 and RQ - mouse dietary: 2.14.

Although these two values are still greater than an RQ of 1, they are very conservative estimates, as they assume that the wild animals are consuming a diet that is 100% contaminated. Moreover, the results are based on chronic studies. In the dietary assessment, the mammals are exposed to contaminated feed for a period of 90 days. The reproductive study has an even longer exposure period (approximately 18 weeks for first generation individuals and approximately 22 weeks for second generation individuals). Taking into account that the soil half-lives of acequinocyl are 1.0, 3.9 days and 4.7 days in silty loam soil, sandy soil and clay loam soil (at 10°C), respectively, the concern for chronic exposure and for reproductive effects becomes negligible.

For terrestrial invertebrates, Kanemite 15 SC Miticide was not harmful to any of the beneficial arthropods tested: predatory mite, carabid beetle, lacewing and parasitic wasp at the highest

concentrations used 624–1050 g a.i./ha. The RQs calculated under realistic worst-case scenarios indicate that Kanemite 15 SC Miticide represents a negligible risk to beneficial arthropods after 14 days of exposure. Both acequinocyl and Kanemite 15 SC Miticide were relatively non-toxic to bees on an acute contact and acute oral basis. Thus, there is a negligible risk posed by acequinocyl and Kanemite 15 SC Miticide to honeybees following 48 hours and 72 hours exposure, respectively. For the earthworm, reductions in body weight were observed for acequinocyl at 1000 mg a.i./kg dw soil and no harmful effects were observed for Kanemite 15 SC Miticide at 156 mg a.i./kg dw soil (the highest concentration tested for the end-use product). There is a negligible risk posed by acequinocyl and Kanemite 15 SC Miticide to earthworms following 14 days exposure. No treatment-related mortalities were observed for any of the terrestrial invertebrates exposed to either acequinocyl or Kanemite 15 SC Miticide and all RQs for terrestrial invertebrates are less than one. Thus, level of concern is not exceeded and the risk posed to terrestrial invertebrates by exposure to acequinocyl and Kanemite 15 SC Miticide is negligible.

For terrestrial plants, no effects (i.e. < 25% reduction) on seedling emergence and vegetative vigour were observed in nine out of the ten plant species at 1500 g a.i./ha, the highest rate of Kanemite 15 SC Miticide tested. An EC_{25} of 11 000 g a.i./ha was observed in the carrot for seedling emergence. Despite this result, RQs calculated under a realistic worst-case scenario are less then one for vegetative vigour and seedling emergence for all ten terrestrial plant species tested. Thus, the level of concern is not exceeded and Kanemite 15 SC Miticide poses a negligible risk to plants (Table 9, Appendix I).

4.2.2 Effects on Aquatic Organisms

Risk of acequinocyl to aquatic organisms was based upon evaluation of toxicity data for four freshwater species (one invertebrate, two fish, and one alga) and three estuarine/marine species (two invertebrates and one fish) (Table 8, Appendix I).

There were no treatment-related mortalities and no sublethal effects observed at the highest concentrations tested in the acute studies with freshwater fish and freshwater algae (acequinocyl: 33 mg a.i./L for fish and 68.6 mg a.i./L for algae, Kanemite 15 SC Miticide: 90 mg a.i./L for fish). Thus, the risk posed to freshwater fish and freshwater algae from acute exposure to acequinocyl and Kanemite 15 SC Miticide is negligible. In the chronic fish study with acequinocyl, there were no mortality or sublethal effects on parent fish at any of the test concentrations (0.52–9.3 mg a.i./L). Larvae survival was significantly reduced compared to pooled controls at concentrations of 2.3, 4.6 and 9.3 mg a.i./L. Despite this effect on the offspring generation, the RQs calculated under a realistic worst-case scenario are less than one for fish on a chronic basis. Thus, the risk to fish remains negligible. The toxicity of acequinocyl to amphibians was estimated using endpoints from fish studies as surrogate data, based on these data, the level of concern is not exceeded for amphibians and the risk from acequinocyl exposure is negligible.

Acequinocyl is very highly toxic to the freshwater invertebrate on an acute basis. After 48 hours, significant immobilization/mortality of *Daphnia magna* was observed at 2.9–27 µg total [^{14}C] residues/L on an acute basis. After 48 hours, sublethal effects including lethargy were observed

at 48 hours for the 2.9, 4.8, and 17 µg total [^{14}C] residues/L treatments. At the highest concentration (27 µg total [^{14}C] residues/L), daphnids were lethargic and on the bottom of the test vessel after 24 hours and showed 100% mortality by 48 hours. On a chronic basis, significant immobilization / mortality of *Daphnia magna* was observed at the two highest test concentrations of 3.9 and 7.8 µg total [^{14}C] residues/L after 21 days. Treatment-related reductions in terminal growth measurements and in the mean number of offspring per adult were observed at the 1.8, 3.9, and 7.8 µg total [^{14}C]residues/L treatment levels. The RQ values for *Daphnia magna* were greater than one: 16.86 for acute exposure and 43.88 for chronic exposure. These RQ values indicate that the level of concern for daphnids is exceeded on both an acute and chronic basis.

For marine fish, on an acute exposure basis, there were no treatment-related mortalities and no sublethal effects observed at the highest concentrations tested in the acute studies (acequinocyl: 0.19 mg a.i./L and Kanemite 15 SC Miticide: 68 mg a.i./L). Thus, the level of concern is not exceeded and the risk posed to marine fish from acute exposure to acequinocyl and Kanemite 15 SC Miticide is negligible.

For the saltwater mysid, after 96 hours of exposure to acequinocyl, the cumulative percent mortality was 25% and 75% in the 0.71 and 1.2 µg a.i./L treatment groups, respectively. Lethargic swimming behaviour and loss of equilibrium were also observed in surviving mysids from the 0.50, 0.71, and 1.2 µg a.i./L treatment levels between 24 and 96 hours. For the eastern oyster, after 96 hours of exposure to acequinocyl, no mortalities or visible abnormalities were observed for any control or treatment group (0.11–2.4 µg a.i./L). However, all treatment groups were significantly reduced in the amount of shell deposition when compared to the controls. The RQ values for the estuarine/marine invertebrates were greater than one: 92.47 for the salt water mysid and 145.76 for the eastern oyster. These RQ values indicate that the level of concern for saltwater invertebrates is exceeded for acequinocyl on an acute basis.

RQs calculated under a realistic worst-case scenario exceeded the trigger value of one for all aquatic invertebrates. Thus, a refined risk assessment was conducted. The refined assessment considered that the most likely routes of entry of acequinocyl into water are through drift and runoff (Table 10, Appendix I). For drift, the screening level assumes 100% drift to a water body. The actual maximum drift deposition expected for airblast application at one metre downwind of a sensitive habitat is 74% (early application). Using the corresponding expected concentration of acequinocyl in water still led to RQs higher than one for all sensitive organisms identified. Therefore, buffer zones larger than one metre are required to mitigate the risk to aquatic invertebrates. Buffer zones have been calculated and added on the end-use product label under "Directions for Use". Their maximum width is 15 m and 35 m for freshwater and estuarine/marine habitats, respectively.

The refined risk assessment incorporating runoff first involved determining the geographic areas where the major crop (pome fruit) is grown. Next, the scenario that generated the highest expected acequinocyl concentration was chosen, assuming no drift. The calculated RQs were still well above one for acute exposure of both freshwater and marine invertebrates. No means to mitigate risk from run-off are currently available. Label statements providing instructions to

minimize run-off, as well as a label statement indicating the toxicity of this pesticide to aquatic organisms, have been added to the end-use product label.

5.0 Value

5.1 Effectiveness Against Pests

Data from a variety of trials were reviewed. These include:

- 10 studies conducted on various ornamentals in greenhouses between 2000 and 2001 in the United States (California, Illinois, Ohio, and New York);
- 2 studies conducted on outdoor ornamentals in 2001 in the United States (California);
- 24 studies conducted on apples between 1997 and 2002 in the United States (New York, Washington, California, Michigan, North Carolina, and Virginia) and Canada (Ontario); and
- 6 studies conducted on pears between 1999 and 2000 in the United States (New York, Michigan; California, and Washington).

Trials were not reviewed when pest pressure was too low to provide an adequate determination of efficacy. For each trial that was reviewed, an appropriate experimental design was employed, which included an untreated control and a miticide active ingredient that was considered as an industry standard.

Control of individual mite species was assessed and compared to an untreated control. Observations were made at various times throughout the growing season after treatment(s) were applied.

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Foliar applications of Shuttle 15 SC Miticide and Kanemite 15 SC Miticide

The reviewed efficacy data support the concentrations and rates outlined in Table 5.1.1. A rate effect was observed on pome fruit in the limited trials where the rate range tested included lower than the accepted rate of 0.21 L/ha. No consistent rate effect was observed on the ornamentals.

Table 5.1.1 Use claims for Shuttle 15 SC Miticide and Kanemite 15 SC Miticide

Crop	Pest	Concentration/Rate
Greenhouse and field grown ornamentals* (except roses)	Two-spotted spider mite	0.21–0.46 L product/500 L water (0.07–0.15 g a.i./L)
	Spruce spider mite	
Greenhouse and field grown roses**	Two spotted spider mite	0.21 L product/500 L water (0.07 g a.i./L)
Pome fruit (Crop Group 11)	Two spotted spider mite	2.07 L product/ha (0.34 kg a.i./ha)
	European red mite	

* Do not apply to impatiens.

** Do not apply to miniature-roses.

5.1.1.2 Insecticide Tank Mix Combinations

Tank mixes with Shuttle 15 SC Miticide and Kanemite 15 SC Miticide were not supported as no efficacy data were submitted.

5.2 Phytotoxicity to Host Plants

Non-safety adverse effects were summarized for studies conducted in the field on apples and roses. In the field, Kanemite 15 SC Miticide did not cause any adverse effects. Eight phytotoxicity studies conducted in greenhouses evaluated the effect of Shuttle 15 SC Miticide on 27 types of ornamental plants. The only crops which displayed any damage to acequinocyl were impatiens and miniature-roses. Damage to impatiens was minor with all damage occurring at concentrations higher (500 and 1000 mL Shuttle 15 SC Miticide/500 L water) than that accepted for use on roses. Foliage damage on miniature roses occurred at all concentrations tested (250, 500, and 1000 mL Shuttle 15 SC Miticide/500 L water), but was more prevalent at the high concentration. Due to the adverse effects noted in these trials, the applicant recommended prohibiting the application of Shuttle 15 SC Miticide and Kanemite 15 SC Miticide on impatiens and miniature roses. As roses are closely related to miniature roses, a conservative approach was adopted to prevent any possible phytotoxicity to roses. Therefore, the concentration for use on roses is limited to the lower range used on ornamentals.

5.2.1 Acceptable Claims for Host Plants

Only miniature roses and impatiens exhibited non-safety adverse effects when treated with acequinocyl as proposed on the label, therefore, the use of acequinocyl on miniature roses and impatiens is prohibited. Despite the lack of phytotoxic effects on crops other than impatiens and miniature roses, all species and varieties of crops listed on the label have not been evaluated. It is recommended to test Shuttle 15 SC Miticide and Kanemite 15 SC Miticide on a small scale basis before full scale use.

5.3 Impact on Succeeding Crops

The impact on succeeding crops was not evaluated in this application.

5.3.1 Acceptable Claims for Rotational Crops

The impact on rotational crops was not evaluated in this application.

5.4 Economics

Mites are common pests of ornamentals and pome fruit. In greenhouses and shadehouses, mites are persistent perennial pests with the potential of causing considerable damage to crops. Losses in the greenhouse industry would occur as a result of unmarketable ornamentals and reduced yields. Exact economic losses are not available, but would vary with the pest and value of the crop under consideration.

5.5 Sustainability

5.5.1 Survey of Alternatives

Alternative miticide active ingredients vary depending on the pest. Some of the currently available alternatives are older classes of insecticides/miticides, such as carbamates and organophosphates; however, these are coupled with some newer chemistries like spirodiclofen and spiromesifen. Other classes of insecticides/miticides include pyrethrins, avermectins and unclassified actives, such as soap, oil and sulphur. The major alternatives currently registered for control of mites on the labelled crops are listed in Table 11, Appendix I.

Acequinocyl belongs to the class of insecticides/miticides known to inhibit electron transport in the mitochondria (resistance management group 20B). There are no active ingredients from this resistance management group currently registered for control of mites in ornamentals and pome fruit in Canada, therefore, acequinocyl provides an active ingredient with a new mode of action for resistance management.

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Shuttle 15 SC Miticide and Kanemite 15 SC Miticide are compatible with current management practices. These products can be applied with conventional ground application equipment used in orchards and field grown ornamentals and on ornamentals grown in greenhouse and shadehouses. Growers are familiar with the monitoring techniques used to determine if and when miticide applications are needed. The new mode of action of these products offers growers an alternative for rotation with currently registered products.

The effect of Shuttle 15 SC and Kanemite 15 SC Miticides on beneficial/predacious insects and mites is unclear. Additional information is needed to determine if this product is safe for use in biological control programs, such as those prevalent in greenhouse and orchard production.

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

Repeated use of miticides having the same mode of action in a control program increases the probability of selecting biotypes (a group of mites within a species that has biological traits that are not common to the population as a whole) with less susceptibility to insecticides of the same mode of action. Therefore, Shuttle 15 SC Miticide and Kanemite 15 SC Miticide should be used in rotation with insecticides that have different modes of action.

The Shuttle 15 SC Miticide and Kanemite 15 SC Miticide labels include the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

5.5.4 Contribution to Risk Reduction and Sustainability

Acequinocyl is the first resistance management group 20B active ingredient registered for use on ornamentals and pome fruit. Acequinocyl will provide a new active ingredient for resistance management. As well, some of the registered broad spectrum active ingredients, such as the organophosphates, and the carbamates, are under re-evaluation and may no longer be available in the future.

6.0 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's *Toxic Substances Management Policy*, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

While reviewing acequinocyl, the PMRA took into account the federal Toxic Substances Management Policy and followed its Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of acequinocyl were also considered, including major transformation products formed in the environment (where data were available), microcontaminants in the technical product and formulants in the end-use products, Shuttle 15 SC Miticide and Kanemite 15 SC Miticide. The PMRA has reached the following conclusions:

- Based on experimental data, acequinocyl does not meet the criteria for persistence. Its values for half-life in water (≤ 74 days), soil (≤ 4.7 days) and sediment (≤ 4 days) are below the TSMP Track 1 cut-off criteria for water (≥ 182 days), soil (≥ 182 days) and sediment (≥ 365 days). The vapour pressure indicates that acequinocyl is non-volatile and Henry's law constant indicates that it is only slightly volatile from water or moist soil under field conditions. Thus, long-range atmospheric transport of acequinocyl is not likely to occur.

- In the aquatic environment, acequinocyl undergoes rapid phototransformation ($t_{½}$: 14 minutes). This compound also undergoes rapid hydrolysis under neutral and alkaline pH conditions ($t_{½}$: 76 minutes at pH 9 and 53 hours at pH 7). Acequinocyl is considered stable to hydrolysis under acidic conditions ($t_{½}$: 74 days at pH 4). Deacetylated acequinocyl (R1) is the major transformation product in aquatic systems.

- The *n*-octanol–water partition coefficient (log K_{ow}) of acequinocyl is 6.2, which is above the TSMP Track 1 cut-off criterion of ≥ 5.0 for bioaccumulation. However, the bioconcentration factor (BCF) of acequinocyl in whole fish is 370, which is well below the TSMP Track 1 cut-off criterion of BCF ≥ 5000. Thus, acequinocyl bioconcentrates in fish, but is readily depurated and, therefore, it does not meet the full criteria for bioaccumulation.

- Based on the experimental data available, acequinocyl does not form any major transformation products in the environment that meet TSMP Track 1 criteria. The half-life of R1 (36.67 days) in soil is below the TSMP Track 1 cut-off criteria for soil (≥ 182 days). Its persistence in water is not available and its toxicity could not be evaluated because organisms were tested by exposure to the parent compound only.

- Acequinocyl (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.

- The two formulated end-use products: Kanemite 15 SC Miticide and Shuttle 15 SC Miticide both contain chlorothalonil as a preservative at 0.05%. Chlorothalonil is contaminated with 2,3,7,8-substituted PCDDs/PCDFs, chlorinated benzenes and PCB. 1,2-Benzisothiazoline-3-one is contaminated with 2,3,7,8-substituted PCDDs/PCDFs which have been identified in the federal government's Toxic Substances Management Policy (TSMP, 1995) as Track 1 substances. As chlorothalonil is formulated as a preservative in this particular product, implementation of the TSMP policy falls under the *Formulants Policy and Implementation Guidance Document* (DIR2006-02).

Therefore, the use of acequinocyl is not expected to result in the entry of Track 1 substances into the environment.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for acequinocyl is adequate to define the majority of toxic effects that may result from human exposure to acequinocyl. In subchronic and chronic studies on laboratory animals, the primary target was the blood coagulation system, with effects on the liver also observed. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Acequinocyl is not considered to be a neurotoxicant.

The nature of the residue in apples and ruminant animals is adequately understood. The residue definition for enforcement purposes is acequinocyl and acequinocyl-OH. The residue definition for risk assessment is acequinocyl and acequinocyl-OH (AKM-15 is included in the risk assessment definition for liver and kidney only). The proposed use of acequinocyl on pome fruit does not constitute an unacceptable chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits to protect human health. The PMRA recommends that the following maximum residue limits be specified under the authority of the *Pest Control Products Act*:

- residues of acequinocyl in and on pome fruit (0.3 ppm);
- fat of cattle, sheep, goat, horse (0.02 ppm);
- meat byproducts of cattle, sheep, goat, horse (0.02 ppm);
- milk (0.02 ppm); and
- liver of cattle, sheep, goat and horse (0.02 ppm).

Mixer, loader, applicators and workers entering treated orchards, field grown nurseries, greenhouses and shadehouses are not expected to be exposed to levels of acequinocyl that will result in unacceptable risk when the Shuttle 15 SC Miticide or Kanemite 15 SC Miticide are used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

7.2 Environmental Risk

Acequinocyl and its associated end-use products, Shuttle 15 SC Miticide and Kanemite 15 SC Miticide, present a negligible risk to wild mammals, birds, earthworms, bees, terrestrial plants, fish, amphibians and algae. However, it poses a risk to aquatic invertebrates and is expected to adversely affect these organisms living in freshwater and estuarine/marine habitats in areas adjacent to application. Therefore, specific instructions to reduce spray drift to aquatic invertebrates are provided on the end-use product label. Also, buffer zones of 1 to 35 metres (depending on timing of application) are required to protect nearby freshwater and estuarine/marine habitats from the effects of spray drift.

7.3 Value

The data submitted to register Shuttle 15 SC Miticide and Kanemite 15 SC Miticide are adequate to describe its efficacy for use in greenhouse, shadehouses, field grown ornamentals and pome fruit. Shuttle 15 SC Miticide is for use in greenhouse and shadehouses on container grown ornamentals to control two spotted spider mites and spruce spider mites. Kanemite 15 SC Miticide is for use on field grown ornamentals and pome fruit to control two spotted spider mites, spruce spider mites and European red mites. Crop tolerance to Shuttle 15 SC Miticide and Kanemite 15 SC Miticide is acceptable though caution should be exercised when treating ornamentals as not all species and varieties have been tested. Shuttle 15 SC Miticide and Kanemite 15 SC Miticide must not be used on impatiens or miniature roses. Shuttle 15 SC Miticide and Kanemite 15 SC Miticide provide an alternative to currently registered organophospate, carbamate, and oranochlorine insecticides. Acequinocyl provides a new mode of action (group 20B) for use on the labelled crops, which can be used resistance management programs.

7.4 Unsupported Uses

Certain uses originally proposed by the applicant with this application are not supported by the PMRA because the value of theses uses had not been adequately demonstrated. Unsupported uses are outlined in Table 12, Appendix I.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and in accordance with the Pest Control Products Regulations, has granted conditional registration for the sale and use of the technical grade active ingredient acequinocyl and two end-use products. The end-use product Shuttle 15 SC Miticide is for the control of specific mites in commercial greenhouse and shadehouses on container-grown ornamental, floral, foliage and nursery crops. The end-use product Kanemite 15 SC Miticide is for the control of specific mites in field grown ornamentals and pome fruit.

An evaluation of current scientific data from the applicant, scientific reports and information from other regulatory agencies has resulted in the determination that, under the approved conditions of use, the end-use products have value and do not present an unacceptable risk to human health or the environment.

Although the risks and value have been determined to be acceptable when all risk reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant as a result of this evaluation. (For more details, refer to the Section 12 Notice associated with these conditional registrations.) The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a Consultation Document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

- **Environment**

    - Identification of the unknown major transformation product in the phototransformation on soil study. Submission of this information to the PMRA must be made no later than 1 December 2008.

    - An acute toxicity study and a chronic toxicity study using the major transformation product acequinocyl-OH (R1) with the freshwater invertebrate *Daphnia magna*. Submission of this information to the PMRA must be made no later than 1 December 2008.

    - An acute toxicity study using the major transformation product, acequinocyl-OH (R1), with two estuarine/marine invertebrates: saltwater mysid and eastern oyster. Submission of this information to the PMRA must be made no later than 1 December 2008.

List of Abbreviations

µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
atm	atmosphere
bw	body weight
CAS	chemical abstracts service
cm	centimetres
dw	dry weight
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in the test population)
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
ER_{25}	effective rate for 25% of the population
g	gram
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition 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
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry

N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RSD	relative standard deviation
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis in a Plant or Animal Matrix

Matrix	Method ID	Analyte	Method Type	LOQ	
Plant	Meth-133 Rev. 3 And Meth-135	acequinocyl and acequinocyl-OH	HPLC-MS/MS[1]	0.01 ppm (each analyte)	Apple Pear
Animal	Meth-139	acequinocyl and acequinocyl-OH	HPLC-MS/MS[1]	0.01 ppm	all matrices

[1] Acequinocyl transitions: 385 to 189 m/z and acequinocyl-OH transitions:343 to 189 m/z

Table 2 Residue Analysis in a Soil Sediment and Ground Water Matrix

Matrix	Method	Fortification Level	Overall Mean % Recovery (n)						LOQ	Method
			Acequinocyl (n = 10)	RSD (%)	Acequinocyl-OH (n = 10)	RSD (%)	AKM-18 (n = 10)	RSD (%)		
Soil, sediment	METH-136	0.01–0.1 µg/g	85.95	3.35	95.7	5.55	97.65	6.5	0.01 ppm	A
Ground water	AGK 076	0.1–1 µg/L	84.35	13	83.75	8.2			0.1 µg/L	A

Table 3 Acute Toxicity of Acequinocyl Technical and Its Associated End-Use Products (Shuttle 15 SC Miticide and Kanemite 15 SC Miticide)

Study Type	Species	Result	Comment
Acute Toxicity of Acequinocyl Technical			
Oral	Rat	LD_{50}>5000 mg/kg bw	Low Toxicity
Oral	Mouse	LD_{50}>5000 mg/kg bw	Low Toxicity
Dermal	Rat	LD_{50}>2000 mg/kg bw	Low Toxicity
Inhalation	Rat	LC_{50}>0.84 mg/l	Slight Toxicity
Skin irritation	Rabbit	MAS[a]=0 MIS[b]=1 at 24 hrs	Not a Dermal Irritant
Eye irritation	Rabbit	Unwashed: MAS=1;MIS=7 at 1hr Washed: MAS=0; MIS=3 at 1hr	Minimally Irritating
Skin sensitization (Buehler)	Guinea Pig	Negative	Not a Dermal Sensitizer

Study Type	Species	Result	Comment
Acute Toxicity of End-Use Products — Shuttle 15 SC Miticide and Kanemite 15 SC Miticide			
Oral	Rat	LD_{50}>5000 mg/kg bw	Low Toxicity
Oral	Mouse	LD_{50}>5000 mg/kg bw	Low Toxicity
Dermal	Rat	LD_{50}>5000 mg/kg bw	Low Toxicity
Inhalation	Rat	LC_{50}>4.65 mg/l	Low Toxicity
Skin irritation	Rabbit	MAS=0 MIS=0	Not a Dermal Irritant
Eye irritation	Rabbit	Unwashed: MAS=0; MIS=2.7 at 1 hr Washed: MAS=0; MIS=0	Not an Eye Irritant
Skin sensitization (Buehler)	Guinea pig	Negative	Not a Dermal Sensitizer

[a] MAS = maximum average score for 24, 28 and 72 hours
[b] MIS = maximum irritation score

Table 4 Toxicity Profile of Acequinocyl Technical

Study Type	Species	Results (mg/kg/day in ♂/♀)
28-day dermal	Rat	NOAEL= 200 mg/kg bw/day LOAEL= 1000 mg/kg bw/day; based on:↑APTT, ↑ PT, fibrinogen, absolute and relative heart weights in males
90-day dietary	Rat	NOAEL= 30.4/32.3 mg/kg bw/day LOAEL= 119.5/129.2 mg/kg bw/day; based on increased prothrombin times in males, increased activated partial thromboplastin times in both sexes, and eye effects in females
90-day dietary	Mouse	Effect levels based on data available in the EPA DER: NOAEL = 100 ppm (16/21 mg/kg bw/day) LOAEL = 500 ppm (81/100 mg/kg bw/day); based on hepatocyte vacuolation, increased liver weight in males, WBC effects in females and the death of one male
90-day dietary/capsule	Dog	LOAEL = 40 mg/kg bw/day; based on decreased body weight gain in males, increased platelets in females, and changes in thymus and thyroid weights in both sexes. NOAEL not established

Study Type	Species	Results (mg/kg/day in ♂/♀)
12-month capsule	Dog	NOAEL(♂) = 5 mg/kg bw/day LOAEL (♂) = 20 mg/kg bw/day; based on increased platelets and decreased thyroid weight NOAEL(♀) = 80 mg/kg bw/day LOAEL(♀) = 320 mg/kg bw/day; based on premature sacrifice due to body wt. loss and inappetence
78-week dietary (Oncogenicity study)	Mouse	NOAEL = 20 ppm (2.7/3.5 mg/kg bw/day) LOAEL = 50 ppm (7.0/8.7 mg/kg bw/day); based on increased liver enzyme levels and microscopic non-neoplastic lesions in the liver (brown pigmented cells, perivascular inflammatory cells, and fat in hepatocytes)
2-year dietary	Rat	NOAEL(♂) = 50 ppm (2.25 mg/kg bw/day); LOAEL(♂) = 200 ppm (9.02 mg/kg bw/day); based on hypertrophy of the eyeball and corneal abnormalities NOAEL (♀) = 800 ppm (46.20 mg/kg bw/day) LOAEL (♀) = 1600 ppm (93.56 mg/kg bw/day); based on hypertrophy of the eyeball, increased clotting times, increased platelets, changes in organ weights, congestion/pigmentation of the spleen
Multi-generation	Rat	**Parental toxicity** Males: NOAEL = 100 ppm (8.2 mg/kg bw/day) LOAEL = 800 ppm (65.5 mg/kg bw/day);based on clinical signs of toxicity in F_1 parental males Females: NOAEL = 1500 ppm (135.9 mg/kg bw/day in F_1 parental ♀) **Offspring toxicity** NOAEL = 100 ppm (7.3/8.7 mg/kg bw/day) LOAEL = 800 ppm (58.9/69.2 mg/kg bw/day) Based on clinical signs of toxicity after weaning in both F_1 and F_2 pups, cerebral hemorrhage in F_2 pups, an increase in the number of deaths PND 22–30 in F_2 pups, and delayed eye opening and reduced startle response in F_2 pups **Reproductive toxicity** NOAEL=1500 ppm (111.2/133.5 mg/kg bw/day) LOAEL not established

Study Type	Species	Results (mg/kg/day in ♂/♀)
Developmental toxicity	Rat	**Maternal** NOAEL= 150 mg/kg bw/day LOAEL= 500 mg/kg bw/day; based on clinical signs and internal haemorrhage **Developmental** NOAEL= 500 mg/kg bw/day LOAEL= 750 mg/kg bw/day; based on increased early resorptions
Developmental toxicity	Rabbit	**Maternal** NOAEL= 60 mg/kg bw/day LOAEL= 120 mg/kg bw/day; based on clinical signs leading to premature sacrifice and gross necropsy findings **Developmental** NOAEL= 60 mg/kg bw/day LOAEL= 120 mg/kg bw/day; based on complete resorptions in sacrificed animals.
Gene mutations in bacteria	*Salmonella typhimurium*; *E. Coli*	Negative (with and without metabolic activation)
Gene mutations in mammalian cells in vitro	Mouse lymphoma L5178Y (TK locus)	Negative (with and without metabolic activation)
Chromosome aberrations in vitro	Chinese hamster lung fibroblasts	Negative
Micronucleus assay (in vivo)	Male and female CD-1 mice	Negative

Study Type	Species	Results (mg/kg/day in ♂/♀)
Metabolism	Rat	**Absorption** Rapid and low (13–16% of a single or repeated low-dose; saturated at 8–9% at the high-dose). Peak plasma concentrations at 2–6 hours (low-dose) and 24 hours (high-dose). No evidence of binding to red blood cells. **Distribution** Widely distributed with the highest concentrations in the gastrointestinal tract and liver. No difference noted between dosing regimens or gender, and no evidence of sequestration in any tissues. **Excretion** No difference in the elimination half-lives between dosing regimens or sexes. Major route of elimination is via the feces (81–91% over 168 hours). Urinary excretion accounted for 12–15% within 24 hours and fecal excretion accounted for 84–87% within 72 hours. Biliary excretion accounted for 20% (low-dose) and 3–5% (high-dose) of the radioactivity in the feces. **Metabolism** Metabolic profiles similar for urine, feces, bile, and plasma, and regardless of label position or dose regimen. Parent compound is extensively metabolized (<1% in plasma, bile, urine; 0.5–8.3% in feces). In addition to the parent compound, eleven metabolic compounds were detected. The major metabolite in plasma (33–40%) was 2-hydroxy-3-dodecyl-1,4-naphthalenedione ®-1), with the hexanoic (AKM-15), butanoic (AKM-14), and benzoic acid (AKM-18) derivatives present in lesser amounts (16–27%). The benzoic acid derivative (AKM-18) was the major metabolite in feces (<0.6–40%). In urine, the hexanoic (AKM-15) and butanoic acid (AKM-14) naphthalenedione derivative represented the major metabolite (1.2–6%). The metabolic profile in the bile was similar to that in the feces and urine except for the presence of a glucuronide conjugation product (AKM-05) of deacylated parent compound which represented the majority of radioactivity (4.1–8.3% (low-dose), <1% (high-dose)). AKM-14 and AKM-15 are identified as red-coloured metabolites.

Table 5 Integrated Food Residue Chemistry

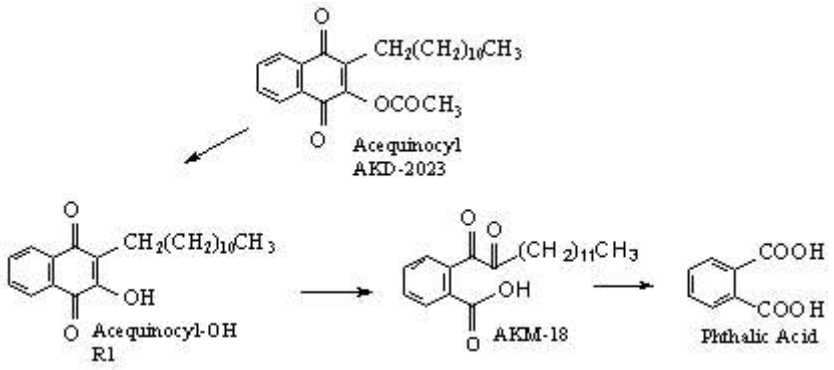
NATURE OF THE RESIDUE IN APPLES	
Radiolabel Position	**[Phenyl-U-^{14}C]**
Test site	Outdoors, trees in containers
Main Study	
Treatment	Single broadcast foliar application.
Rate (g a.i./ha)	760 to 776
End-use product	Kanemite 15 SC Miticide
Preharvest interval (days)	0, 14, 21, 30
Translocation of ^{14}C-residues from leaves to fruits was minimal. The majority of the TRR in/on fruit and leaves consisted of surface residues. ^{14}C-residues were less than 7.1% of the TRR in flesh at all time intervals.	

Metabolites Identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	**[^{14}C-Phenyl]**	**[1-^{14}C-Dodecyl]**	**[^{14}C-Phenyl]**	**[1-^{14}C-Dodecyl]**
Day 0				
Surface rinse- fruit	Acequinocyl	Acequinocyl	R1, AKM-18	R1, AKM-18
Peel	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity
Flesh	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity
Leaves: surface rinse	Acequinocyl	Acequinocyl	R1, AKM-18	R1, AKM-18
Leaves: extract	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity
Day 14				
Surface rinse- fruit	Acequinocyl	Acequinocyl	R1, AKM-18 , phthalic acid	R1, AKM-18 , phthalic acid
Peel	-	-	Acequinocyl, R1, AKM-18, phthalic acid	Not identified, low radioactivity
Flesh	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity
Leaves: surface rinse	Not Analyzed at Day 14			
Leaves: extract				
Day 21				
Surface rinse- fruit	Acequinocyl	Acequinocyl	R1, AKM-18 , phthalic acid	R1, AKM-18 , phthalic acid
Peel	-	-	Acequinocyl, R1, AKM-18, phthalic acid	Not identified, low radioactivity
Flesh	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity
Leaves: surface rinse	Not Analyzed At Day 21			
Leaves: extract				

Day 30				
Surface rinse- fruit	Acequinocyl	Acequinocyl	R1, AKM-18 , phthalic acid	R1, AKM-18 , phthalic acid
Peel	-	-	Acequinocyl, R1, AKM-18, phthalic acid	Acequinocyl, R1, AKM-18, phthalic acid
Flesh	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity	Not identified, low radioactivity
Leaves: surface rinse	Acequinocyl	Acequinocyl	R1, AKM-18 , phthalic acid	R1, AKM-18 , phthalic acid
Leaves: extract	-	-	Acequinocyl, R1, AKM-18, phthalic acid	Acequinocyl, R1, AKM-18 , phthalic acid

Based on the predominant residues and toxicological significance, the residue definition is acequinocyl and the metabolite R1 (acequinocyl-OH). Although acequinocyl-OH is considered a minor metabolite, it is included in the residue definition since it retains the naphthaquinone moiety believed to be responsible for blood coagulation effects. The metabolism of acequinocyl in apples involves the loss of the acetyloxy moiety to form acequinocyl-OH, opening of the quinone ring to form AKM-18, and subsequent degradation of the quinone ring to yield phthalic acid.

Proposed Metabolic Pathway



NATURE OF THE RESIDUE IN LACTATING GOAT

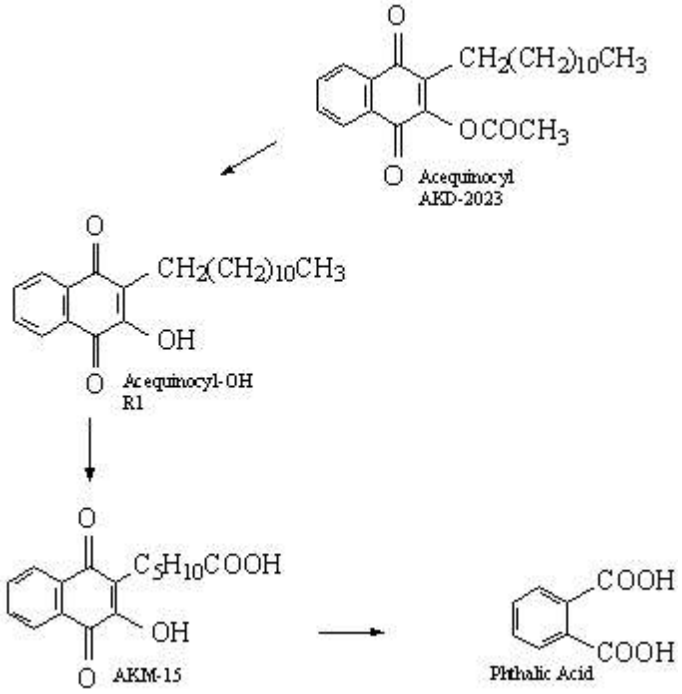
One lactating goat (British Saanen) was dosed for 5 consecutive days at levels of 11.3 mg/kg ([U^{14}C-phenyl]-acequinocyl). The goat was sacrificed 23 hours after the final dose was administered. Identification and characterization of ^{14}C-residues was limited and problematic in some instances due to poor separation of components.

Matrices	% of Administered Dose
	[^{14}C-Phenyl]
Urine	9.9
Feces	64.2
Gastrointestinal tract contents	10.8
Cage rinse	0.12
Liver	0.2
Bile	<0.1
Blood	0.2
Plasma (T_{max} 12 hours post dose) Day 1 Day 2–5	0.06 ppm 0.093–0.104 ppm
Foreleg & Rump Muscle	0.2
Subcutaneous, omental & perirenal fat	0.1

Metabolites Identified	Major Metabolites (> 10% TRR)	Minor Metabolites (< 10% TRR)
Radiolabel Position	**^{14}C-Phenyl**	**^{14}C-Phenyl**
Liver	None	Acequinocyl; R1; AKM-15; AKM-18
Kidney	Acequinocyl/R1(combined)	AKM-15; AKM-18
Fat	Acequinocyl/R1(combined)	None
Milk	The TRR in milk was <0.01 ppm, therefore no further analyses were conducted.	

Based on the predominant residues and toxicological significance, the residue definition for enforcement purposes is acequinocyl and acequinocyl-OH (R1). Although the metabolite AKM-15 and R1 are minor metabolites in liver and kidney, they should be included for risk assessment purposes because the retain the naphthaquinone structure. The naphthaquinone structure is believed to be responsible for blood coagulation effects.

Proposed Metabolic Scheme in Livestock



The metabolism of acequinocyl in goat involves the loss of the acetyloxy moiety to form acequinocyl-OH and partial cleavage of the dodecyl chain to form AKM-15. Opening and degradation of the quinone ring yields AKM-18 and phthalic acid.

CROP FIELD TRIALS ON PEARS

Pear trees received two broadcast foliar applications of Kanemite 15 SC for a total of 684 g a.i./ha/season. Samples of pears were harvested at a PHI of 14 days. Samples were also harvested at 0, 7, 14 and 21 DALA.

Commodity	Total Rate (g a.i./ha)	Preharvest Interval (days)	Residue Levels (ppm)			
			n	Min.	Max.	HAFT
Acequinocyl and acequinocyl-OH						
Pears	684	14	20	0.02	0.046	0.05

RESIDUE DECLINE

Samples were collected at 0, 7, 14 and 21 DALA for the residue decline study. Average residues at day 0 and day 21 were 0.168 ppm and 0.034 ppm, respectively, accounting for a total decrease of 79.8%.

CROP FIELD TRIALS ON APPLES

Apple trees received two broadcast foliar applications of Kanemite 15 SC for a total of 684 g a.i./ha/season. Samples of apples were harvested at a PHI of 14 days. Samples were also harvested at 0, 7, 14 and 21 DALA.

Commodity	Total Rate (g a.i./ha)	Preharvest Interval (days)	Residue Levels (ppm)			
			n	Min.	Max.	HAFT
Acequinocyl and acequinocyl-OH						
Apples	684	14	30	0.029	0.23	0.217

RESIDUE DECLINE

Samples were collected at 0, 7, 14 and 21 DALA for the residue decline study. Average residues at day 0 and day 21 were 0.23 ppm and 0.122 ppm, respectively, accounting for a total decrease of 47% was observed.

PROCESSED FOOD AND FEED IN APPLES

Processing data was gathered concurrently with the magnitude of the residue trials of apple. Samples were processed using simulated commercial practices and stored frozen. The actual storage duration was supported by the demonstrated storage stability.

Commodity	Processing Factor
Apple wet pomace	3.5
Apple juice	0.06

STORAGE STABILITY APPLES

Freezer storage stability of acequinocyl and acequinocyl-OH residues in/on apples and apple processed commodities was conducted concurrently with the magnitude of the residue study. Control samples were spiked with 1 ppm of either acequinocyl or acequinocyl-OH. No residues above the LOQ were found in control samples.

Matrix	Storage Interval (months)
Apple whole fruit	5
Apple juice	5
Apple wet pomace	5

LIVESTOCK FEEDING							
Encapsulated acequinocyl was administered once daily to thirteen Holstein dairy cows for 28 days. Dosing levels were equivalent to 5 ppm, 15 ppm and 50 ppm of acequinocyl in the diet. The maximum dietary burden (MTDB) of acequinocyl and the metabolite acequinocyl-OH to beef and dairy cattle were calculated to be 0.8 ppm and 0.4 ppm, respectively. The MTDB for dairy and beef cattle results from a diet comprised solely apple pomace which does not constitute 100% of their diet; 40% for beef and 20% dairy cattle.							
Matrix	Feeding Level (ppm)	Residue Levels (ppm)					
		MTDB	Combined Residues[1]	Mean	STMR	R/F[2]	Anticipated Residues[3] (AR)
Acequinocyl and acequinocyl-OH							
Muscle	5	0.8	0.02	0.005	0.005	0.004	0.003
Liver	5	0.8	0.08	0.037	0.029	0.016	0.013
Kidney	5	0.8	0.036	0.016	0.012	0.0072	0.006
Fat	5	0.8	0.119	0.035	0.019	0.024	0.019
Whole Milk	5	0.4	0.02	0.003	0.002	0.004	0.002

[1] Acequinocyl and acequinocyl-OH
[2] Residue to feed ratio= combined residue/feeding level
[3] AR=(R/F)(MTDB)

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT **Primary crops (pome fruit)**	Acequinocyl and acequinocyl-OH
METABOLIC PROFILE IN DIVERSE CROPS	Only an apple metabolism study was considered for the Canadian registration.
ANIMAL STUDIES	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	Acequinocyl and acequinocyl-OH
RESIDUE DEFINITION FOR RISK ASSESSMENT	Acequinocyl, acequinocyl-OH and AKM-15
METABOLIC PROFILE IN ANIMALS (goat)	Only ruminant (goat) was evaluated and considered.
FAT SOLUBLE RESIDUE	Yes

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)	
		Food Only	Food and Water
Refined chronic non-cancer dietary risk ADI = 0.023 mg/kg bw Estimated chronic drinking water concentration = 0.000247 ppm	All infants < 1 year	12.7	12.8
	Children 1–2 years	28.4	28.4
	Children 3–5 years	19.7	19.7
	Children 6–12 years	10.1	10.1
	Youth 13–19 years	5.6	5.6
	Adults 20–49 years	3.7	3.7
	Adults 50+ years	3.9	3.9
	Females 13–49 years	4.1	4.1
	Total population	6.2	6.3

Table 7 Fate and Behaviour in the Environment

Terrestrial Environment			
Property (study length)	Test substance	Half life Value	Comments [a,b]
Abiotic transformation			
Phototransformation on soil (13 days)	Acequinocyl	5.3 days (The calculation of a half-life for phototransformation is not relevant, as the half-life in irradiated soil was longer than that in the dark controls.)	Not an important route of transformation

Biotransformation			
Biotransformation in aerobic soil (up to 365 days)	Acequinocyl	sand (20°C): 3.9 days clay loam (20°C): 2.3 days clay loam (10°C): 4.7 days	Non-persistent
	R1	sand (20°C): 20 days clay loam (20°C): 6 days clay loam (10°C): 19 days	Non-persistent
	AKM-18	sand (20°C): 6 days clay loam (20°C): 10 days clay loam (10°C): 10 days	Non-persistent
Biotransformation in aerobic soil (up to 180 days)	Acequinocyl	Milton: 1.3 days Malham: 1 day	Non-persistent
Mobility			
Adsorption or desorption in soil	Acequinocyl	Milton: 34 087 mL/g Malham: 263 982 mL/g Speyer: 104 486 mL/g	Immobile according to McCall et al. (1981)
	R1	Milton: 228 312 mL/g Malham: 1175 mL/g Speyer: 56 306 mL/g	Immobile according to McCall et al. (1981) except for Malham which has low mobility
Soil TLC	Acequinocyl	<1% AR in leachate	Limited mobility
Field studies			
Field dissipation	Acequinocyl	< 1 day	An important route of transformation

[a] Classification of Goring et al. 1975.
[b] Classification of McCall et al. 1981.

Aquatic Environment			
Property (study length)	**Test material**	**Half life Value**	**Comments** [c]
Abiotic transformation			
Hydrolysis (up to 30 days)	Acequinocyl	pH 1.2: 19 days pH 4: 74 days pH 7: 53 hours pH 9: 76 minutes	An important route of transformation in neutral and basic conditions
Phototransformation in water (up to 14 days)	Acequinocyl	14 minutes	An important route of transformation in neutral and basic conditions
Biotransformation			
Biotransformation in aerobic water systems (100 days)	Acequinocyl	System: < 1 day in both Bury pond and Houghton meadow	Non-persistent
Biotransformation in anaerobic water systems (365 days)	Acequinocyl	System: 4 days	Non-persistent
Bioaccumulation (14 days)	Acequinocyl	whole fish BCF 290 -370	Acequinocyl bioconcentrates and is readily depurated (89% in 1day)

[c] Classification of McEwan and Stephenson 1979.

Table 8 Toxicity to Non-Target Species

Terrestrial Species				
Organism	**Exposure**	**Test substance**	**End point value**	**Degree of toxicity[a]**
Invertebrates				
Earthworm	Acute	TGAI: AKD-2023 (Acequinocyl)	LC_{50}:>1000 mg/kg NOEC (body weight gain): 500 mg/kg	No classification
	Acute	EP: Kanemite 15 SC Miticide	LC_{50}: > 156 mg a.i./kg NOEC: 156mg a.i./kg	No classification
	Contact	TGAI: AKD-2023 (Acequinocyl)	LC_{50}: >100 µg a.i./bee NOEC: 100 µg a.i./bee	Relatively non-toxic according to Atkins (1981)
	Oral	EP: Kanemite 15 SC Miticide	LC_{50}:> 315 µg a.i./bee NOEC (lethargy / uncoordinated movements): 175 µg a.i./bee	Relatively non-toxic according to Atkins (1981)
	Contact	EP: Kanemite 15 SC Miticide	LC_{50}:> 315 µg a.i./bee NOEC (lethargy / uncoordinated movements): 87.5 µg a.i./bee	Relatively non-toxic according to Atkins (1981)
Predators and Parasites	Predatory Mite	EP: Kanemite 15 SC Miticide	LR_{50}: > 624 g a.i./ha NOEC (mortality and reproduction): 624 g a.i./ha	No classification
	Carabid beetle	EP: Kanemite 15 SC Miticide	LR_{50}: > 1050 g a.i./ha NOEC (mortality and food consumption): 1050 g a.i./ha	No classification
	Lacewing	EP: Kanemite 15 SC Miticide	LR_{50}: > 1050 g a.i./ha NOEC (mortality and reproduction): 1050 g a.i./ha	No classification
	Parasitic Wasp	EP: Kanemite 15 SC Miticide	LR_{50}: > 1050 g a.i./ha NOEC (mortality and reproduction): 1050 g a.i./ha	No classification

Terrestrial Species				
Organism	**Exposure**	**Test substance**	**End point value**	**Degree of toxicity[a]**
Birds				
Bobwhite Quail	Acute oral	EP: Kanemite 15 SC Miticide	LD_{50}: > 2000 mg a.i./kg bw NOEL: 2000 mg a.i./kg bw	Practically non-toxic
	Reproduction	TGAI: AKD-2023 (Acequinocyl)	LOEL: >2500 mg a.i./kg diet NOEL: 2500 mg a.i./kg diet	No classification
Japanese Quail	Acute oral	TGAI: AKD-2023 (Acequinocyl)	LD_{50}: > 2000 mg a.i./kg bw NOEC: 2000 mg a.i./kg bw	Practically non-toxic
	Acute dietary	TGAI: AKD-2023 (Acequinocyl)	LD_{50}: >5000 mg a.i./kg diet NOEL (body weight gain and mean food consumption): 1000 mg a.i./kg diet	Moderately toxic
Mallard Duck	Acute oral	TGAI: AKD-2023 (Acequinocyl)	LC_{50}: > 500 mg a.i./kg bw NOEC (female body weight): 500 mg a.i./kg bw NOEC (male body weight): 1000 mg a.i./kg bw	Slightly toxic
	Acute dietary	TGAI: AKD-2023 (Acequinocyl)	LD_{50}: > 5000 mg a.i./kg diet NOEL (mortality and sublethal effects): 488 mg a.i./kg diet	Practically non-toxic
	Reproduction	TGAI: AKD-2023 (Acequinocyl)	LD_{50}: >500 mg a.i./kg diet NOEL (female body weight gain): 100 mg a.i./kg diet	No classification
Mammals				
Rat	Acute oral	TGAI: AKD-2023 (Acequinocyl)	LD_{50}: > 5000 mg/kg bw NOEL (mortality): 5000 mg/kg bw NOEL (watery feces): < 5000 mg/kg bw	Low toxicity
	Acute oral	EP: Kanemite 15 SC Miticide	LD_{50}: > 5000 mg/kg bw NOEL (mortality): 5000 mg/kg bw NOEL (diarrhea): < 5000 mg/kg bw	Low toxicity
	Dietary (90 day)	TGAI: AKD-2023 (Acequinocyl)	NOEL (sublethal effects in blood, liver, lung, pancreas and eyes): 400 mg/kg diet	No classification
	Reproduction (multi-generation)	TGAI: AKD-2023 (Acequinocyl)	NOEL (poor physical condition in F_1 and F_2 pups): 100 mg/kg diet	No classification

Terrestrial Species				
Organism	**Exposure**	**Test substance**	**End point value**	**Degree of toxicity[a]**
Mouse	Acute oral	TGAI: AKD-2023 (Acequinocyl)	LD_{50}: > 5000 mg/kg bw NOEL (mortality): 5000 mg/kg bw NOEL (watery feces): < 5000 mg/kg bw	Low toxicity
	Acute oral	EP: Kanemite 15 SC Miticide	LD_{50}: > 5000 mg/kg bw NOEL (mortality and sublethal effects): 5000 mg/kg bw	Low toxicity
	Dietary (90 day)	TGAI: AKD-2023 (Acequinocyl)	NOEL (mortality and sublethal effects in blood and liver): 100 mg/kg diet	No classification
Vascular plants				
Vascular Plant	Seedling emergence	EP: Kanemite 15 SC Miticide	NOEC: 15 kg/ha for all monocot species tested, EC_{25} > 15 kg/ha NOEC: 5 kg/ha for carrot (dicot), EC_{25}: 11 kg/ha	No classification
	Vegetative vigour	EP: Kanemite 15 SC Miticide	NOEC: 15 kg/ha for all species tested, except for beet and cabbage shoot height - NOEC: 5 kg/ ha; EC_{25} > 15 kg/ha for all species tested	No classification

[a] Atkins et al. (1981) for bees, and US EPA classification for others, where applicable.

Aquatic Species				
Organism	**Exposure**	**Test substance**	**End point value**	**Degree of toxicity[a]**
Freshwater species (limit of solubility: 6.67 µg a.i./L)				
Daphnia magna	48 hr acute	TGAI: AKD-2023 (Acequinocyl)	EC50: 5.1 µg total [^{14}C] residues/L NOEC: 2.2 µg total [^{14}C] (Immobilization) NOEC: 2.2 µg total [^{14}C] residues/L (behavioural effects, eg. lethargy)	Very highly toxic
	21-day chronic	TGAI: AKD-2023 (Acequinocyl)	EC50: 5.49 µg total [^{14}C] residues/L NOEC: 1.8 µg total [^{14}C] residues/L (Immobilization) NOEC: 0.98 µg total [^{14}C] residues/L (length, weight, and mean number of young per adult)	No classification
Rainbow Trout	96 hr acute	TGAI: AKD-2023 (Acequinocyl)	LC_{50}: > 33 mg a.i./L NOEC: 33 mg a.i./L	Slightly toxic
		EP: Kanemite 15% SC Miticide	LC_{50}: 67 mg a.i./L NOEC: 33 mg a.i./L (mortality)	Slightly toxic
	88-day chronic	TGAI: AKD-2023 (Acequinocyl)	EC50: 5.3 mg a.i./L NOEC: 1.1 mg a.i./L (larval survival)	No classification
Bluegill Sunfish	96 hr acute	TGAI: AKD-2023 (Acequinocyl)	LC_{50}: > 1.1 mg a.i./L NOEC: 1.1 mg a.i./L	Moderately toxic
		EP: Kanemite 15 SC Miticide	LC_{50}: > 90 mg a.i./L NOEC: 90 mg a.i./L	Slightly toxic
Freshwater Alga (green alga)	72 hr acute	TGAI: AKD-2023 (Acequinocyl)	EC50: > 68.6 mg a.i./L NOEC: 68.6 mg a.i./L	No classification
Marine species				
Crustacean (mysid)	96 hr acute	TGAI: AKD-2023 (Acequinocyl)	LC_{50}: > 0.93 µg a.i./L NOEC: 0.27 µg a.i./L (abnormal behaviour)	Very highly toxic
Mollusk (eastern oyster)	96 hr acute	TGAI: AKD-2023 (Acequinocyl)	EC50: 0.59 µg a.i./L NOEC:< 11 µg a.i./L (shell growth)	Very highly toxic

Aquatic Species				
Organism	**Exposure**	**Test substance**	**End point value**	**Degree of toxicity[a]**
Sheepshead Minnow	96 hr acute	TGAI: AKD-2023 (Acequinocyl)	LC_{50}: > 0.19 mg a.i./L NOEC: 0.19 mg a.i./L	Very highly toxic
	96 hr acute	EP: Kanemite 15 SC Miticide	LC_{50}: > 68 mg a.i./L NOEC: 68 mg a.i./L	Slightly toxic

[a] EPA classification scheme, where applicable

Table 9 Screening Level Risk Assessment on Non-target Species

Terrestrial Species					
Organism	**Exposure: Test substance**	**End point value**	**EEC**	**RQ**	**Level of Concern**
Invertebrates					
Earthworm	Acute: TGAI Acequinocyl	LC_{50}:>1000 mg a.i./kg	0.16 mg a.i./kg soil	0.0003	Not exceeded
	Acute: EP Kanemite 15 SC	LC_{50}: > 156 mg a.i./kg	0.16 mg a.i./kg soil	0.002	Not exceeded
Bee	Acute contact: TGAI Acequinocyl	LC_{50}: >100 µg a.i./bee; NOEC: 100 µg a.i./bee	572.6 g a.i./ha	0.0051	Not exceeded
	Acute contact: EP Kanemite 15 SC	LC_{50}:> 315 µg a.i./bee; NOEC (lethargy / uncoordinated movements): 87.5 µg a.i./bee	572.6 g a.i./ha	0.0058	Not exceeded
	Acute oral: EP Kanemite 15 SC	LC_{50}:> 315 µg a.i./bee; NOEC (lethargy / uncoordinated movements): 175 µg a.i./bee	572.6 g a.i./ha	0.0029	Not exceeded
Predatory Mite	Acute Contact: EP Kanemite 15 SC	LR_{50}: > 624 g a.i./ha NOEC (mortality and reproduction): 624 g a.i./ha	572.6 g a.i./ha	0.91	Not exceeded
Carabid Beetle	Acute Contact: EP Kanemite 15 SC	LR_{50}: > 1050 g a.i./ha	572.6 g a.i./ha	0.55	Not exceeded
Lacewing	Acute Contact: EP Kanemite 15 SC	LR_{50}: > 1050 g a.i./ha	572.6 g a.i./ha	0.55	Not exceeded
Parasitic Wasp	Acute Contact: EP Kanemite 15 SC	LR_{50}: > 1050 g a.i./ha	572.6 g a.i./ha	0.55	Not exceeded

Terrestrial Species					
Organism	**Exposure: Test substance**	**End point value**	**EEC**	**RQ**	**Level of Concern**
Birds					
Bobwhite Quail	Acute oral: EP Kanemite 15 SC	LD_{50}: > 2000 mg a.i./kg bw NOEL: 2000 mg a.i./kg bw	6.03 mg a.i./kg bw	0.003	Not exceeded
	Reproduction: TGAI Acequinocyl	LOEL: >2500 mg a.i./kg diet NOEL: 2500 mg a.i./kg diet	95 mg a.i./kg diet	0.038	Not exceeded
Japanese Quail	Acute oral: TGAI Acequinocyl	LD_{50}: > 2000 mg a.i./kg bw NOEC: 2000 mg a.i./kg bw	95 mg a.i./kg diet	0.0047	Not exceeded
	Acute dietary: TGAI Acequinocyl	LD_{50}: >5000 mg a.i./kg diet NOEL (body weight gain and mean food consumption): 1000 mg a.i./kg diet	95 mg a.i./kg diet	0.095	Not exceeded
Mallard Duck	Acute oral: TGAI Acequinocyl	LC_{50}: > 500 mg a.i./kg bw NOEC (female body weight): 500 mg a.i./kg bw	18.35 mg a.i./kg diet	0.0034	Not exceeded
	Acute dietary: TGAI Acequinocyl	LD_{50}: > 5000 mg a.i./kg diet NOEL: 488(mortality and sublethal effects) mg a.i./kg diet	18.35 mg a.i./kg diet	0.038	Not exceeded
	Reproduction: TGAI Acequinocyl	LD_{50}: >500 mg a.i./kg diet NOEL (female body weight gain): 100 mg a.i./kg diet	18.35 mg a.i./kg diet	0.184	Not exceeded
Mammals					
Rat	Acute oral: TGAI Acequinocyl	NOEL: 5000 mg a.i. /kg bw (mortality)	22.32 mg a.i./kg bw	0.0045	Not exceeded
	Acute oral: EP Kanemite 15 SC	NOEL: 5000 mg a.i./kg bw (mortality)	32.85 mg a.i./kg bw	0.0066	Not exceeded
	Dietary (90 day): TGAI Acequinocyl	NOEL (sublethal effects in blood, liver, lung, pancreas and eyes): 400 mg a.i./kg diet	273.74 mg a.i./kg diet	0.68	Not exceeded
	Reproduction TGAI Acequinocyl	NOEL (poor physical condition of F_1 and F_2 pups): 100 mg a.i./kg diet	273.74 mg a.i./kg diet	2.74	EXCEEDED

Terrestrial Species					
Organism	**Exposure: Test substance**	**End point value**	**EEC**	**RQ**	**Level of Concern**
Mouse	Acute oral: TGAI Acequinocyl	NOEL: 5000 mg a.i./kg bw (mortality)	66.63 mg a.i./kg bw	0.0133	Not exceeded
	Acute oral: EP Kanemite 15 SC	NOEL: 5000 mg a.i./kg bw (mortality and sublethal effects)	64.78 mg a.i./kg bw	0.0129	Not exceeded
	Dietary (90 day): TGAI Acequinocyl	NOEL (sublethal effects in blood and liver): 100 mg a.i./kg diet	272.09 mg a.i./kg diet	2.72	EXCEEDED
Vascular plants					
Vascular Plant	Seedling emergence: EP Kanemite 15 SC	NOEC: 15 kg/ha for all monocot species tested, EC_{25} > 15 kg/ha NOEC: 5 kg/ha for carrot (dicot), EC_{25}: 11 kg/ha	572.6 g a.i./ha	0.052 (carrot) 0.038 (remaining species)	Not exceeded
	Vegetative vigour: EP Kanemite 15 SC	NOEC: 15 kg/ha for all species tested, except for beet and cabbage shoot height - NOEC: 5 kg EP/ha EC_{25} > 15 kg/ha for all species tested	572.6 g a.i./ha	0.11 (beet and cabbage) 0.038 (remaining species)	Not exceeded Not exceeded

Aquatic Species					
Organism	**Exposure: Test Substance**	**End point value**	**EEC**	**RQ**	**Level of Concern**
Freshwater species					
Daphnia magna	Acute (48 h): TGAI Acequinocyl	EC50: 5.1 µg total [^{14}C] residues/L	0.043 mg a.i./L	16.86	EXCEEDED
	Chronic (21 day): TGAI Acequinocyl	NOEC: 0.98 µg total [^{14}C] residues/L (length, weight, and mean number of young per adult)	0.043 mg a.i./L	43.88	EXCEEDED
Rainbow Trout	Acute (96 h): TGAI Acequinocyl	LC_{50}: > 33 mg a.i./L	0.043 mg a.i./L	0.013	Not exceeded
	Acute (96 h): EP Kanemite 15 SC	LC_{50}: 67 mg a.i./L	0.043 mg a.i./L	0.0064	Not exceeded
	Chronic (88 day): TGAI Acequinocyl	NOEC: 1.1 mg a.i./L (larval survival)	0.043 mg a.i./L	0.039	Not exceeded
Bluegill Sunfish	Acute (96 h): TGAI Acequinocyl	LC_{50}: > 1.1 mg a.i./L	0.043 mg a.i./L	0.39	Not exceeded
	Acute (96 h): EP Kanemite 15 SC	LC_{50}: > 90mg a.i./L	0.043 mg a.i./L	0.0047	Not exceeded
Freshwater Alga (green alga)	Acute (72 h): TGAI Acequinocyl	EC50: > 68.6 mg a.i./L	0.043 mg a.i./L	0.0013	Not exceeded
Amphibians	Acute (based on 96 h acute rainbow trout study): TGAI Acequinocyl	LC_{50} for rainbow trout: > 33 mg a.i./L	0.23 mg a.i./L	0.07	Not exceeded
	Chronic (based on 88 day chronic rainbow trout study): TGAI Acequinocyl	NOEC for rainbow trout: 1.1 mg a.i./L (larval survival)	0.23 mg a.i./L	0.209 (low)	Not exceeded

Aquatic Species					
Organism	**Exposure: Test Substance**	**End point value**	**EEC**	**RQ**	**Level of Concern**
Saltwater species					
Crustacean (saltwater mysid)	Acute (96 h): TGAI Acequinocyl	LC_{50}: > 0.93 µg a.i./L	0.043 mg a.i./L	92.47	EXCEEDED
Mollusc (eastern oyster)	Acute (96 h): TGAI Acequinocyl	EC50: 0.59 µg a.i./L	0.043 mg a.i./L	145.76	EXCEEDED
Sheepshead Minnow	Acute (96 h): TGAI Acequinocyl	LC_{50}: > 0.19 mg a.i./L	0.043 mg a.i./L	0.226	Not Exceeded
	Acute (96 h): EP Kanemite 15 SC	LC_{50}: > 68 mg a.i./L	0.043 mg a.i./L	0.0063	Not exceeded

Table 10 Refined Risk Assessment on Non-Target Species

Organism (exposure)	Test Substance	Endpoint Value	EEC based on 74% drift for an early airblast application	Risk Quotient (RQ)	Level of Concern
Freshwater species					
Daphnia magna 48-h Acute	TGAI Acequinocyl	EC50: 5.1 µg total [^{14}C] residues/L	0.032 mg a.i./L (32 µg a.i./L)	12.48	EXCEEDED
Daphnia magna 21-day Chronic	TGAI Acequinocyl	NOEC (length, weight, and mean number of young per adult): 0.98 µg total [^{14}C] residues/L	0.032 mg a.i./L (32 µg a.i./L)	32.65	EXCEEDED
Saltwater species					
Crustacean (saltwater mysid) 96-h Acute	TGAI Acequinocyl	LC_{50}: > 0.93 µg a.i./L	0.032 mg a.i./L (32 µg a.i./L)	68.82	EXCEEDED
Mollusc (eastern oyster) 96-h Acute	TGAI Acequinocyl	EC50: 0.59 µg a.i./L	0.032 mg a.i./L (32 µg a.i./L)	108.47	EXCEEDED

Table 11 Alternative Insecticides for Mite Control in the Labelled Crops

Pest Claim	Resistance Management Group	Active Ingredient	Comments
Mites on ornamentals	1B	Diazinon	Field grown ornamentals
		Malathion	
		Chlorpyrifos	
		Dimethoate	Field grown ornamentals
		Naled	Greenhouse roses and flowers
	3 and 27A	Pyrethrin & piperonyl butoxide	Field grown ornamentals
	6	Abamectin	Greenhouse ornamentals
	10 A	Clofentezine	Field grown nursery stock
	12 B	Fenbutatin oxide	
	21	Pyridaben	
	23	Spiromesifen	
	25	Bifenazate	
	Unclassified	Oil	Dormant application Field grown ornamentals
	Unclassified	Potassium salt of fatty acids (soap)	
		Calcium polysulphide	Dormant application
Mites on pome fruit	1 A	formetanate hydrochloride	Apple and pear only
	1 B	Malathion	Apple only
		Diazinon	European red mite only
		Phosalone	Apple and Pear
		Phosmet	Apple and Pear
	3	Pyrethrins	
	6	Abamectin	Apple and pear
	10 A	Clofentezine	Apple and pear
	23	Spirodiclofen	
	21	Pyridaben	
	Unclassified	Dicofol	
	Unclassified	Mineral oil	Dormant application
	Unclassified	Paraffinic base oil	Dormant application Apple and pear

Table 12 Label Claims Proposed by Applicant Not Supported by Value

Applicant-proposed Label Claim	Accepted Label Claim	Unsupported Label Claim and Comment
Pests of ornamentals: Two spotted spider mite and spruce spider mite on greenhouse and field grown roses	Two spotted spider mite on roses	Spruce spider mite is not a pest of roses

Appendix II Supplemental Maximum Residue Limit (MRL) Information - International Situation and Trade Implications

Eight of the specified Canadian MRLs are the same as those in the U.S. In one case (pome fruit), the MRL differs from the tolerance established in the U.S. www.access.gpo.gov/nara/cfr/waisidx_04/40cfr180_04.html:

Differences Between Canadian MRLs and Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Apple, wet pomace		1.0	
Cattle, fat		0.02	
Cattle, liver		0.02	
Fruit, pome, group 11	0.3	0.4	
Goat, fat		0.02	Not reviewed by Codex
Goat, liver		0.02	
Horse, fat		0.02	
Horse, liver		0.02	
Sheep, fat		0.02	
Sheep, liver		0.02	

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. The Canadian MRL for pome fruit is different from the reported U.S. MRL since the Canadian MRL was derived from the use of the MRL calculator.

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

Appendix III Crop Groups: Numbers and Definitions

Crop Group Number	Name of the Crop Group	Commodity
11	Pome fruit	apples, crabapple, loquat, mayhaw, pear, oriental pear and quince

References

1.0 The Active Ingredient, Its Properties and Uses

1140651 Product Chemistry Data. 2004. DACO: 2.1,2.2,2.3,2.4,2.5,2.6,2.8,2.9.

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