Proposed Registration Decision PRD2026-03

Acynonapyr and Kodama Miticide

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Overview

Proposed registration decision for acynonapyr

Health Canada's Pest Management Regulatory Agency (PMRA), pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of Acynonapyr Technical and Kodama Miticide, containing the active ingredient acynonapyr, to control Tetranychid mites on Crop Group 11-09: Pome Fruits.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science evaluation provides detailed technical information on the human health, environmental and value assessments of acynonapyr and Kodama Miticide.

What does Health Canada consider when making a registration decision?

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

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

Before making a final registration decision on acynonapyr and Kodama Miticide, Health Canada's PMRA will consider any written comments received from the public directly related to the proposed decision in this consultation document.[3]

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

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

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

Health Canada will then publish a Registration Decision[4] on acynonapyr and Kodama Miticide, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What is acynonapyr?

Acynonapyr is a new conventional acaricide with a new mode of action (MOA) that acts on the nervous system of mites. Acynonapyr acts by contact to provide rapid knockdown of adult and larval Tetranychid mites on Crop Group 11-09: Pome Fruits.

Health considerations

Can approved uses of acynonapyr affect human health?

Kodama Miticide, containing acynonapyr, is unlikely to affect your health when used according to proposed label directions.

Potential exposure to acynonapyr may occur through the diet (food and drinking water), when handling and applying the end-use product, or when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: 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 selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

In laboratory animals, the active ingredient acynonapyr was of low acute toxicity orally, dermally, and through inhalation exposure. It was minimally irritating to the eyes and was non-irritating to the skin. Although results in laboratory animals suggested that acynonapyr did not cause an allergic skin reaction, issues were noted with the conduct of the study. For this reason, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label of Acynonapyr Technical.

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

The acute toxicity of the end-use product, Kodama Miticide, containing acynonapyr, was low via the oral, dermal, and inhalation routes of exposure. It was non-irritating to the eyes and skin, but did cause an allergic skin reaction; consequently, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests were assessed for the potential of acynonapyr to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other health effects. The most sensitive endpoints for risk assessment were effects on body weight and the blood in both adult and young animals, an increase in the number of stillbirths and early death of young animals, and clinical signs of toxicity in the young. There was no evidence to suggest that acynonapyr damaged genetic material. Acynonapyr did, however, cause tumours of the liver and lymphatic system of male mice and tumours of the thyroid, lymphatic system, skin, and brain of male rats. There was no evidence of increased sensitivity of the young compared to adult animals. The risk assessment protects against the effects previously noted in this section and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Residues in food and drinking water

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

Aggregate acute dietary (food plus drinking water) intake estimates indicated that females 13–49 years, infants and children up to 12 years old are exposed to less than 34% of the acute reference dose (ARfD), and therefore, are not of health concern.

Aggregate chronic dietary (food plus drinking water) intake estimates indicated that the general population and all population subgroups are exposed to less than 3% of the acceptable daily intake (ADI), and therefore, are not of health concern.

The lifetime cancer risk from the use of acynonapyr on Crop Group 11-09: Pome Fruits is not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Given that dietary risks from the consumption of foods are shown to be acceptable when acynonapyr is used according to the supported label directions, an MRL is being proposed as a result of this assessment (refer to *PMRL2026-05*, acynonapyr).

The MRL for acynonapyr, determined from the acceptable residue trials conducted throughout the United States, including growing regions representative of Canada, on apples and pears, can be found in the Science evaluation of this document.

Occupational risks from handling Kodama Miticide

Occupational risks are not of health concern when Kodama Miticide is used according to the proposed label directions, which include protective measures.

Workers mixing, loading, or applying Kodama Miticide and workers entering recently treated orchards can be exposed to acynonapyr residues through direct skin contact or through inhalation. Therefore, the label specifies that anyone mixing and loading Kodama Miticide, engaging in clean-up and repair activities, and applying Kodama Miticide using handheld application equipment must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. For applicators using airblast application equipment, workers must wear a long-sleeved shirt, long pants, socks and shoes when using closed cab equipment, or a long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes, and chemical-resistant headgear when using open cab equipment (chemical-resistant headgear includes Sou'Wester hat, chemical-resistant rain hat, or large-brimmed waterproof hat and hood with sufficient neck protection). The label also requires that workers do not enter or be allowed entry into treated orchards during the restricted-entry intervals (REIs) of 6 days to perform hand thinning activities in pome fruits, and 12 hours for all other postapplication activities. Taking into consideration the label statements, the number of applications, and the duration of exposure for handlers and postapplication workers, the risks to these individuals from exposure to Kodama Miticide are not of health concern when the end-use product is used according to the proposed label directions.

Health risks in residential and other non-occupational environments

Risks in residential and other non-occupational environments are not of health concern when Kodama Miticide is used according to the proposed label directions and REIs are observed.

Residential aggregate (dermal and dietary) exposure to Kodama Miticide during pick-your-own (PYO) fruit activities in treated orchards are not of health concern when the end-use product is used according to the proposed label directions.

There is the potential for aggregate exposure, as the general public may be exposed via the dermal and dietary routes simultaneously. Dermal exposure occurs when contacting trees in residential settings that may have been treated by a commercial applicator, to perform activities such as hand harvesting of fruit, pruning and thinning. Dietary exposure occurs from background residues in food and drinking water. The aggregate non-cancer risk is not of health concern, when the product is used according to the proposed label directions; however, the aggregate lifetime cancer risk is above the PMRA's level of concern (LOC) (1E-6).

Health risks to bystanders

Bystander risks are not of health concern when Kodama Miticide is used according to the proposed label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is on the label. Therefore, health risks to bystanders are not of concern when the end-use product is used according to the proposed label directions.

Environmental considerations

What happens when acynonapyr is introduced into the environment?

When acynonapyr is used according to the label directions, the risks to the environment have been determined to be acceptable.

Acynonapyr enters the environment when applied as a foliar spray to pome fruit to control Tetranychid mites. Acynonapyr and its breakdown products may persist on land, but are expected to have limited movement to groundwater. In water bodies, acynonapyr breaks down rapidly, but its breakdown products may persist and move from water to sediment. Acynonapyr may bioaccumulate; however, minimal exposure is expected due to its rapid breakdown to compounds that do not build up in the tissues of organisms. Acynonapyr is not expected to travel long distances from where it was applied. It is not expected to be taken up by plants and move inside plant tissues.

When used according to the proposed label directions, acynonapyr poses acceptable risk to small wild mammals, birds, beneficial insects, bees, earthworms, and terrestrial and aquatic plants. Exposure to acynonapyr may affect freshwater and marine animals if they are exposed to high enough levels; therefore, standard precautionary label statements, standard best management practice statements to reduce runoff, and spray buffer zones for protection of aquatic habitats are required on the end-use product label.

Value considerations

What is the value of Kodama Miticide?

Kodama Miticide provides a new MOA for resistance management and control of adult and larval Tetranychid mites, which are important pests of Crop Group 11-09: Pome Fruits.

As it is a new MOA, Kodama Miticide will aid in resistance management of Tetranychid mites. The development of resistance is a major concern for Tetranychid mites, which are well documented to have resistance to various MOAs. Kodama Miticide is expected to be compatible with current management practices, including Integrated Pest Management (IPM).

Measures to minimize risk

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

The key risk-reduction measures being proposed on the labels of Acynonapyr Technical and Kodama Miticide to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

To reduce the potential exposure of workers to acynonapyr through direct skin contact or inhalation of sprays, workers mixing, loading, and applying Kodama Miticide and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. For applicators using airblast application equipment, workers must wear a long-sleeved shirt, long pants, socks and shoes when using closed cab equipment, or a long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes, and chemical-resistant headgear when using open cab equipment (chemical-resistant headgear includes Sou'Wester hat, chemical-resistant rain hat, or large-brimmed waterproof hat and hood with sufficient neck protection).

The end-use product label also requires that workers do not enter or be allowed entry into treated orchards during the REIs of 6 days to perform hand thinning activities in pome fruits and 12 hours for all other postapplication activities. Risks to workers are not of health concern when Kodama Miticide is used according to the proposed label directions and REIs are observed.

The aggregate lifetime cancer risk from dermal exposure, while hand harvesting fruit, pruning and thinning residential fruit trees that may have been treated by a commercial applicator, and dietary (food and drinking water) exposure from eating treated foods (background diet) is above the PMRA's LOC (1E-6). As such, the proposed end-use product label will prohibit use in residential areas.

Environment

Standard precautionary label statements are required to inform users of the toxicity of acynonapyr to aquatic organisms.

Standard best management practice statements are required to instruct users to reduce runoff of Kodama Miticide into sensitive aquatic habitats.

Spray buffer zones of up to 15 metres are required to protect sensitive aquatic habitats.

Next steps

Before making a final registration decision on acynonapyr and Kodama Miticide, Health Canada's PMRA will consider any written comments received from the public that are directly related to this proposed decision, such as comments directed to the Science evaluation, in response to this consultation document up to 30 days from the date of publication of this document (by 12 March 2026). If more time is required to provide comments, a request for an extension of up to an additional 15 days can be made. Your request must be submitted in writing to the PMRA's Publications Section (pmra.publications-arla@hc-sc.gc.ca) within the 30-day consultation period. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRL will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to PMRA Publications, through the Public Engagement Portal (Public Engagement Portal forms – Consultation Comment). Health

Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

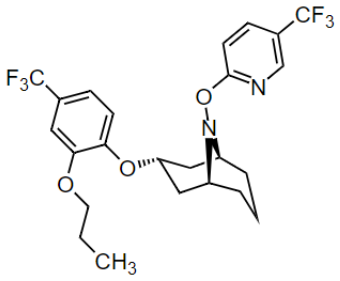
When Health Canada's PMRA makes its registration decision, it will publish a Registration Decision on acynonapyr and Kodama Miticide (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information or if you have questions, please contact the PMRA's Pest Management Information Service.

Science evaluation

Acynonapyr and Kodama Miticide

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Acynonapyr
Function	Acaricide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	3-*endo*-[2-propoxy-4-(trifluoromethyl)phenoxy]-9-{[5-(trifluoromethyl)-2-pyridyl]oxy}-9-azabicyclo[3.3.1]nonane
2. Chemical Abstracts Service (CAS)	(3-*endo*)-3-[2-propoxy-4-(trifluoromethyl)phenoxy]-9-[[5-(trifluoromethyl)-2-pyridinyl]oxy]-9-azabicyclo[3.3.1]nonane
CAS number	1332838-17-1
Molecular formula	$C_{24}H_{26}F_6N_2O_3$
Molecular weight	504.47
Structural formula	
Purity of the active ingredient	99.5%

1.2 Physical and chemical properties of the active ingredient and end-use product

Technical product—Acynonapyr Technical

Property	Result
Colour and physical state	Pale yellow powder
Odour	Odourless
Melting point	80.3°C
Boiling point or range	NA
Density	0.72–0.74 g/mL at 20°C

Property	Result
Vapour pressure	1.13E-6 Pa (20.0°C)
Ultraviolet (UV)-visible spectrum	λ_{max} (nm) / ε (L*mol^{-1}*cm^{-1}) neutral 222.4 / 1.53E+4 275.3 / 7.40E+3 acidic 231.1 / 1.50E+4 275.8 / 7.51E+3 alkaline 225.7 / 1.51E+4 275.3 / 7.46E+3 No absorption at λ>300 nm
Solubility in water at 20°C	0.889 µg/L
Solubility in organic solvents at 20°C	Insoluble in acetone and methanol
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 6.5 (25°C)
Dissociation constant (pK_a)	Estimated pK_a = 1.0
Stability (temperature)	Stable for 2 weeks at 54°C

End-use product—Kodama Miticide

Property	Result
Colour	White
Odour	Faint
Physical state	Opaque liquid
Formulation type	Suspension
Label concentration	20.09%
Container material and description	High-density polyethylene (HDPE) bottle, 1–20 L
Density	1.068 g/mL at 20°C
pH of 1% dispersion in water	5.71
Oxidizing or reducing action	Compatible with water, 10% monoammonium phosphate, iron powder and kerosene; incompatible with 10% potassium permanganate.
Storage stability	The product was stable for 2 weeks when stored in HDPE bottles at 54°C.
Corrosion characteristics	No corrosion to the HDPE bottle was observed after 2 weeks storage at 54°C.
Explodability	Not explosive

1.3 Directions for use

For control of Tetranychid mites such as twospotted spider mite, European red mite, McDaniel spider mite, and Pacific spider mite in Crop Group 11-09: Pome Fruits, Kodama Miticide is applied at a rate of 0.58 L of product per hectare by ground application, no more than once per year.

1.4 Mode of action

Acynonapyr, the active ingredient of Kodama Miticide, is an acaricide classified as Insecticide Resistance Action Committee (IRAC) Group 33 (calcium-activated potassium (KCa2) channel modulators). Acynonapyr and IRAC Group 33 are a new MOA that act by the negative modulation of KCa2, causing hyperexcitation and convulsions. Calcium-activated potassium channels are activated by an increase of the intracellular calcium concentration and are involved in the regulation of action potentials. Acynonapyr is active through contact with the target pest.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

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

2.2 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

Environmental media: 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 (LOQ). Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis in environmental media are summarized in Appendix I, Table 1a.

Plant matrices: HPLC-MS/MS methods were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy, and precision at the LOQ (0.01 ppm). Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement methods were successfully validated by an independent laboratory. Extraction solvents used in the methods were similar to those used in the metabolism studies; therefore, the proposed enforcement methods appear suitable to extract bioincurred residues of acynonapyr and its associated metabolites. Methods for residue analysis in plant matrices are summarized in Appendix I, Table 1b.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Acynonapyr (also identified as NA-89) is an acaricide that contains a unique azabicyclic ring and oxyamine structure. It has a novel pesticidal MOA as a KCa2 channel modulator (Group 33 of the IRAC MOA classification). The negative modulation of KCa2 causes hyperexcitation and convulsions in insects. Calcium-activated potassium channels are activated by an increase of the intracellular calcium concentration and are involved in the regulation of action potentials.

A detailed review of the toxicology database for acynonapyr was conducted. A comprehensive database, consisting of the full array of standard toxicity studies currently required for hazard assessment purposes, was provided. An acute oral neurotoxicity study and a number of neurotoxicity assessments (for example, functional observational battery (FOB), rearing, and motor activity) within the 28-day and 90-day dietary studies in rats were also conducted. Thyroid hormone measurements were performed in a 90-day dietary study in rats as well as in a 7-day dietary study in rats conducted to assess hepatic enzyme induction. Acute and subchronic oral toxicity studies were conducted with various metabolites of acynonapyr. In addition, select studies performed with acynonapyr (the 28-day oral studies in the dog, rat, and mouse; 3-day and 28-day dermal studies in rats; 7-day oral nephrotoxicity study in rats) included an evaluation of toxicokinetics for acynonapyr and the mammalian metabolites identified as AP and AY and their related compounds. A number of mechanistic studies were also submitted to support the proposed MOA for the thyroid and liver tumours, which were proposed to be the result of induction of liver metabolizing enzymes and activation of the constitutive androstane receptor/pregnane X receptor (CAR/PXR), respectively. In addition, a mechanistic study was conducted in Wistar and Sprague Dawley rats to understand the high-dose effects on the kidneys and to elucidate potential differences between strains used by two different contracting laboratories. Based on the pesticidal MOA as well as the endocrine and thyroid effects that were observed in the rat reproductive toxicity study, it was determined that the database is lacking, as it does not contain a developmental neurotoxicity study or an assessment of thyroid hormone perturbation in the young. This deficiency was accounted for by applying an additional uncertainty factor (UF) when establishing the toxicology reference values. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). Overall, the scientific quality of the toxicology database is acceptable, and the database is considered adequate to characterize the majority of the toxic effects that may result from exposure.

The toxicokinetics of acynonapyr in the rat were investigated with acynonapyr radiolabelled at either the phenyl or pyridine position. Another study using azabicyclo-radiolabelled acynonapyr was available but provided limited information. In the more robust studies, rats were administered the radiolabelled compound either as a single oral low dose (all three label positions), a single oral high dose (pyridine and phenyl labels), or a repeated oral low dose for 14 days (phenyl label only). The extent of absorption 48 hours following oral dosing varied depending on the position of the radiolabel. Greater absorption was reported following administration of both single low and single high doses when acynonapyr was labelled at the

pyridine position (up to 68% and 39% of the administered dose (AD) following a single low or single high dose, respectively) compared to when labelled at the phenyl position (up to 25% and 15% of the AD following a single low or a single high dose, respectively). These differences in absorption likely reflect differences in the absorption of the metabolites AY (containing the pyridine label) and AP (containing the phenyl label). Systemic exposure, based on area-under-the-curve (AUC) estimates, was slightly higher in females than in males following administration of both pyridine- and phenyl-labelled acynonapyr.

In the rat toxicokinetics studies, results suggest that acynonapyr is cleaved into the pyridine portion, represented by the metabolite AY, and the phenyl portion, represented by the metabolite AP, prior to absorption from the gastrointestinal tract. Given that the available toxicokinetics studies tested acynonapyr when radiolabelled on either the pyridine ring or the phenyl ring, the absorption of acynonapyr as a whole molecule could not be determined with a high level of certainty. The absorption of the AY-related compounds and AP-related compounds can only be determined separately, and results from the toxicokinetics studies demonstrated that the degree of absorption differed when acynonapyr was radiolabelled on the pyridine ring versus the phenyl ring. Based on the recovered radioactivity in urine, bile, and tissues, the absorption of the metabolite AP and its related metabolites, such as AP-2, is relatively low based on an absorption rate of approximately 24% of the AD, as seen with the low-dose phenyl label. Absorption of the metabolite AY and its related compounds was moderately higher, at approximately 65% of the AD, based on radioactivity recovered from the urine, bile, and tissues after administration of the low-dose pyridine label.

Additionally, it cannot be excluded that most of the toxic effects observed in the database are due to the metabolite AP, and AP-related compounds, deriving from the phenyl portion of the molecule. Based on comparative results of the repeat-dose oral toxicity studies in rats conducted with acynonapyr and metabolites AP and AY (discussed later in this section), the metabolite AP, and AP-related compounds, appear to be the major contributors of the toxicity seen in the acynonapyr toxicology database. Consequently, the oral absorption of acynonapyr was estimated based on that observed with the AP label, which was estimated to be approximately 25%.

Both radiolabels were rapidly and widely distributed, with the highest concentration found in the fat. Tissue distribution was similar in both sexes, although concentrations were often higher in females. Additionally, after multiple low doses, tissue distribution in females was similar to that after a single oral administration.

Most of the radioactivity (>90% of the AD) was eliminated in urine and feces within 48 hours. When labelled at the pyridine position, elimination of radioactivity in intact rats occurred primarily via urine at the low dose and via feces at the high dose. When labelled at the phenyl and the azabicyclo positions, elimination of radioactivity in intact rats occurred primarily via feces and, to a lesser extent, in the urine at both doses. Bile was not a major route of elimination with either label. The longest half-life of elimination was observed in the fat.

Unchanged acynonapyr was the main component detected in feces for all dose groups and radiolabels. With the pyridine label, the metabolite AY was detected in feces and was the main component in urine. With the phenyl and azabicyclo labels, the metabolite AP was detected in feces, and AP-4-glucuronide was the main component in urine. Some sex differences were noted, as levels of unchanged acynonapyr were higher in males and some metabolites were more prevalent in females. The identification of select metabolites is presented in Appendix I, Table 2.

In acute toxicity testing, acynonapyr was of low toxicity via the oral, dermal, and inhalation routes of exposure in rats. It was minimally irritating to the eyes and non-irritating to the skin in rabbits. It was not a dermal sensitizer in guinea pigs when tested using the maximization method; however, due to study limitations and the observation that the formulated end-use product, Kodama Miticide, produced an allergic skin reaction, acynonapyr is considered a potential dermal sensitizer. In acute oral toxicity studies of select metabolites, high acute oral toxicity was demonstrated for metabolites AP, AP-2, and AY, whereas AY-1-Glc, AY-5, and AH were shown to have low acute oral toxicity.

Kodama Miticide was of low acute toxicity via the oral, dermal, and inhalation routes of exposure in rats. It was non-irritating to the eyes and skin of rabbits, and was considered a potential dermal sensitizer in guinea pigs via the Buehler method.

Repeat-dose oral toxicity studies with acynonapyr were available in mice and rats via dietary administration, and in dogs via capsule administration. In the repeat-dose dietary studies conducted in mice, the most sensitive indicators of toxicity were decreased body weights and body weight gain, red blood cell effects such as decreased hemoglobin, hematocrit, and red cell counts, as well as increased reticulocytes, higher white blood cell count, increased adrenal, liver and spleen weights, and correlating histopathological effects in the adrenal gland (cortical hypertrophy), liver (hepatocellular hypertrophy), and spleen (increased erythropoiesis).

Similar to mice, repeated dietary administration in rats resulted in decreased body weights and body weight gain, decreases in hemoglobin, hematocrit, and red cell counts, and increased reticulocytes. Increases in liver and spleen weight were also observed in rats, as well as increases in kidney and thyroid weight. Correlating histopathological effects in these organs included hepatocellular hypertrophy, erythropoiesis in the spleen, follicular cell hypertrophy in the thyroid, cortical cell hypertrophy in the adrenals, inflammatory cell infiltration in the kidneys, and accumulation of foamy cells in the lungs, mesenteric, and submaxillary lymph nodes. Neurotoxicity parameters were examined in the 90-day oral toxicity studies in rats, and effects were observed at the highest dose level tested, which also resulted in other toxic effects. The treatment-related findings stemming from these neurotoxicity assessments included rolling gait, walking on tiptoes, decreased foot splay, and decreased forelimb and hindlimb grip strength in Wistar rats, as well as increased activity level and rearing count in Sprague Dawley rats. In a study comparing toxic effects on the kidneys and liver of Wistar and Sprague Dawley rats after short-term dietary exposure, evidence of strain differences were observed, with Wistar rats showing increased susceptibility compared to Sprague Dawley rats, but study limitations precluded a more definitive comparison.

Repeat-dose dietary studies in the rat were also conducted with select metabolites of acynonapyr (AP-2 and AY). Following dietary administration of AP-2 for 28 days, some signs of toxicity were similar to those observed following dosing with the parent compound, such as decreased

body weight and histopathological findings, including hepatocellular hypertrophy, accumulation of foamy cells in the lungs, and follicular cell hypertrophy in the thyroid. Additionally, single cell necrosis in the kidney was observed, and one male at the highest dose level was found dead on Day 23. In the 28- and 90-day dietary studies conducted with the AY metabolite, signs of toxicity at the highest dose tested included decreased body weights and body weight gain, nuclear inclusion bodies in proximal tubules of the kidneys, and hepatocellular hypertrophy (28-day study only). Based on the results from these studies, it was determined that AY did not demonstrate increased toxicity relative to the active ingredient. Although AP-2 demonstrated increased toxicity relative to acynonapyr, when considering relative molecular weights, the toxicology reference values for acynonapyr were determined to provide sufficient coverage for potential toxicity from exposure to AP-2 (in other words, the dose levels showing toxicity from AP-2, when converted to parent equivalents on a molecular weight basis, are comparable to those for the parent compound).

In repeat-dose oral toxicity studies in the dog via capsule administration for 90 days or one year, the most sensitive indicators of toxicity were decreased body weights and body weight gain, decreases in hemoglobin, hematocrit, and red cell counts, and increased mean corpuscular volume, reticulocytes, and alkaline phosphatase. Effects in dogs also included increases in liver, adrenal, and spleen weights. Correlating histopathological effects in these organs included hepatocellular hypertrophy, increased hemopoiesis or extramedullary hemopoiesis in the spleen, and vacuolation, capsular fibrosis, and tingible body macrophages of the splenic white pulp, as well as cortical vacuolation of the adrenal zona fasciculata. Additionally, dogs were noted with lymphocytolysis and vacuolation in the mandibular and mesenteric lymph nodes and increased numbers of brown-pigmented and tingible body macrophages in mandibular and mesenteric lymph nodes. One male and one female were sacrificed early, on Days 40 and 344, respectively, in the 1-year study due to clinical signs of toxicity and convulsions.

A battery of genotoxicity studies was submitted for acynonapyr. Bacterial reverse mutation assays were also available for several metabolites (AP, AP-2, AY, AY-1-Glc, AY-5, and AH) and an in vivo mouse micronucleus assay and a gene mutation assay in the Muta Mouse were also available for metabolite AY. With the exception of positive results in two strains with and without metabolic activation in a bacterial reverse mutation assay with the metabolite AY, the overall weight of evidence for acynonapyr and its metabolites did not suggest genotoxic potential. In a 78-week dietary carcinogenicity study in mice with acynonapyr, an increased incidence of liver tumours (hepatocellular adenomas) was observed in males at the highest dose level tested, and a dose-related increased incidence of hemolymphoreticular tissue lymphomas was observed in males at all dose levels. In the 2-year dietary carcinogenicity study in rats with acynonapyr, increased incidences of thyroid tumours (follicular cell adenomas) and lymph node tumours (mesenteric lymph node hemangioma and hemangioma/hemangiosarcoma combined) were observed in males at the highest dose level tested. Male rats also had an increased incidence of skin tumours (fibroma and fibroma/fibrosarcoma combined) and brain tumours (malignant astrocytoma) at the highest dose level tested.

An MOA involving activation of the CAR/PXR was proposed for both the liver tumours in mice and the thyroid tumours in rats. A description of key events addressing dose and temporal relationship was presented by the applicant, and several mechanistic studies to support the MOAs for both tumours were provided. For the thyroid tumours, the proposed MOA suggested

that activation of the CAR/PXR receptors in the liver results in induction of liver metabolizing enzymes, in particular uridine-5'-diphospho-glucuronosyltransferase (UDP-GT), leading to a decrease in levels of thyroxine (T4), followed by a subsequent increase in the production of thyroid stimulating hormone (TSH), ultimately resulting in thyroid follicular hyperplasia and cell proliferation and the formation of thyroid tumours. The proposed MOA was deemed to be not adequately supported, as there was insufficient data to demonstrate the temporal relationship between the key events and the tumour response, specifically a lack of clear induction of UDP-GT, increase in TSH, or increase in thyroid follicular cell proliferation and hyperplasia. There were also limitations in demonstrating the dose-response relationship between the key events and the tumour response. Additionally, alternative MOAs were not examined.

For the liver tumours, the proposed MOA of CAR/PXR activation was suggested to result in altered CAR-specific gene expression, resulting in an increase in hepatocellular proliferation leading to altered hepatic foci, and ultimately resulting in liver tumours. The proposed MOA for liver tumours was deemed plausible; however, residual uncertainties remained, including evidence that CAR activation was only observed at one time point in one study, which was not conducted according to GLP, and results related to hepatocellular proliferation were conflicting.

Although considered plausible, the overall weight of evidence to support the proposed MOA for both the thyroid tumours in rats and the liver tumours in mice was considered inadequate, and a linear low dose extrapolation (cancer potency factor, known as the q_1*) approach to the cancer risk assessment was taken for these tumour types, as well as for the hemolymphoreticular tissue lymphomas observed in male mice and the hemangiomas in the lymph nodes, fibroma/fibrosarcomas in the skin, and malignant astrocytomas in the brain of male rats.

Based on the results of the available studies, the dog appeared to be the most sensitive species to the toxicity of acynonapyr, followed by the rat and mouse. There was no clear evidence of increased toxicity with increased duration of dosing in the rat or dog. However, there was some evidence of increased toxicity with prolonged duration of oral dosing in the mouse. This was supported by the lower lowest observed adverse effect level (LOAEL) in the 78-week dietary carcinogenicity study in mice compared to the 28- and 90-day dietary mouse studies, in addition to the progression of histopathological changes in the liver (liver masses and hepatocellular adenomas) in male mice following the 78-week dietary exposure, which were noted at a lower dose level compared to the hepatocellular and centrilobular hypertrophy observed in the 28- and 90-day mouse studies, respectively.

In a 2-generation reproductive toxicity study in which rats were administered acynonapyr via the diet, decreased body weight and body weight gain were observed in parental animals at the mid-dose level during the pre- and post-mating, gestation, and lactation periods, along with red blood cell effects such as decreased hemoglobin, hematocrit, and red cell counts and lung histopathology. At the highest dose tested, parental animals were noted with increased incidence of kidney histopathology. Reproductive effects were noted at the highest dose tested and all occurred in the presence of parental systemic toxicity. These effects included a decrease in the number of females that successfully mated, an increased duration of gestation, an increased incidence in the number of dams with stillborn pups and pups dying on postnatal day (PND) 0, as well as reductions in the number of pups delivered and mean litter size at birth. A decrease in the combined male and female anogenital distance was also observed at birth that persisted to

weaning. The most sensitive endpoints in the offspring included decreased pup weight and clinical signs (dehydration, cold to touch), observed at the mid-dose level. At the highest dose tested, additional clinical signs (pale whole body, no milk band present) were observed, as well as a decrease in viability index, an increased number of pups dying, and an overall decrease in mean litter size. As part of the pre-weaning assessment of developmental landmarks, decreases in motor activity, air righting reflex, and acoustic startle response were observed. There was also a delay in sexual maturation in both sexes. Effects in the offspring occurred at dose levels that were toxic to the parental animals, suggesting no evidence of increased sensitivity of the young compared to the adult animal. Although serious effects in the young were observed, these were observed at the highest dose tested in the presence of significant parental toxicity.

In oral gavage developmental toxicity studies in rats and rabbits, there was no evidence of increased sensitivity of the young compared to the adult animal, as effects in the developing fetus were observed at the same dose levels at which maternal animals also exhibited toxicity. In the study in rats, maternal and fetal toxicity were observed at the highest dose level only. Maternal animals exhibited a decrease in body weight and body weight gain, and developing fetuses were noted with a decrease in body weight as well as reduced skeletal ossification sites for metatarsals and hindlimb phalanges. In rabbits, maternal and fetal toxicity were observed beginning at the mid dose, which in maternal animals was evidenced by the early sacrifice of one doe following abortion, body weight loss, and clinical signs of toxicity, as well as a decrease in overall body weight gain for the whole group. Additional effects seen in maternal animals at the highest dose included further mortality following abortion and clinical signs, as well as body weight loss, decreased motor activity, and gross pathology findings in the lung. Effects on developing fetuses starting at the mid-dose level, at which maternal animals were affected, included a decrease in the number of ossification sites of the caudal vertebrae and a decrease in fetal body weight (females). A single incidence of spina bifida was observed in one fetus at the highest dose level tested, a dose level at which significant maternal toxicity was also observed; this finding was deemed to be equivocally related to treatment.

A waiver request was submitted for the 90-day dermal toxicity study in rats on the basis that there were no significant treatment-related findings in the 3-day or 28-day dermal toxicity studies conducted in the rat. Similarly, a waiver request was submitted for the 90-day neurotoxicity study in the rat based on the lack of treatment-related effects in the acute neurotoxicity study, as well as the fact that some effects suggestive of neurotoxicity were seen only at high doses in the 90-day and 2-year dietary studies in rats that also resulted in significant systemic toxicity. Waiver requests were also provided for the 90-day inhalation toxicity study in rats, based on low volatility potential and the low acute inhalation toxicity; and for the immunotoxicity study, based on the overall lack of immunotoxicity in the acynonapyr toxicology database. The waivers for these studies were considered acceptable based on the weight of evidence presented.

Based on the available information, there was some concern identified with respect to the lack of a developmental neurotoxicity (DNT) study as well as other gaps in endocrine or thyroid hormone assessments in the young. This was due to several lines of evidence, including: the pesticidal MOA for acynonapyr, which involves the modulation of KCa2 channels that regulate neuronal excitability in insects; the noted effects on certain developmental landmarks in F2 pups in the 2-generation reproductive toxicity study (for example, impaired air righting reflex

response); and the observed thyroid effects in adult animals in the database. This concern was accounted for through the application of a database UF of threefold in the risk assessment. Otherwise, the database for acynonapyr was considered adequate to characterize potential human health hazards.

The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 3. Results of the toxicology studies conducted on laboratory animals with acynonapyr, with relevant metabolites and with its associated end-use product, are summarized in Appendix I, Tables 4, 5, and 6, respectively.

3.1.2 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.[5]

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the required studies, including developmental toxicity studies in the rabbit and rat, and a 2-generation reproductive toxicity study in the rat. Although the database lacks a DNT study evaluating the potential for acynonapyr to elicit neurotoxicity and testing of thyroid hormone perturbation in the young, this concern was addressed through the application of a database UF in the risk assessment, as previously noted in this section.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of fetuses or offspring compared to parental animals in the dietary reproductive or gavage prenatal developmental toxicity studies. In the 2-generation rat reproductive toxicity study, the serious endpoints of reduced pup viability, pup deaths, as well as decreased acoustic startle and air righting reflex in the F2 generation offspring, were observed at the highest dose tested and in the presence of maternal toxicity (decrease in body weight and food consumption, red blood cell effects, kidney histopathology). In the oral gavage rabbit developmental toxicity study, the serious effect of spina bifida in one fetus was deemed equivocally related to treatment and was observed at the highest dose tested in the presence of maternal toxicity (mortality, clinical signs, body weight loss, decreased motor activity). There was no evidence of serious endpoints in the young identified in the rat developmental toxicity study.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young, as effects in the young are well-characterized and occurred in the presence of maternal toxicity. Concern for the serious fetal and offspring effects previously noted in this section was tempered by the presence of maternal toxicity.

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

Therefore, a threefold *Pest Control Products Act* (PCPA) factor was retained when using a point of departure for serious effects in the young from the 2-generation rat reproductive toxicity study or the rabbit developmental toxicity study in the human health risk assessment. Otherwise, the PCPA factor was reduced to onefold.

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

Occupational exposure to acynonapyr is characterized as short- and intermediate-term in duration and is predominantly by the dermal and inhalation routes. Short-term aggregate residential exposure is also expected by the oral and dermal routes. Acute and chronic dietary exposure to acynonapyr is also expected.

For mixers, loaders, and applicators, occupational exposure to Kodama Miticide is characterized as short-term (<30 days) in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure to Kodama Miticide is characterized as short-term in duration and is predominantly by the dermal route. For residential and non-occupational exposure scenarios, contact with trees treated with Kodama Miticide would primarily occur via the dermal route of exposure and for a short-term duration. For the cancer risk assessments, the number of days of exposure per year is 5 days for mixer/loaders/applicators and 15 days for both occupational and non-occupational postapplication assessments.

3.2.2 Occupational and residential toxicology reference values

Short- to intermediate-term dermal and inhalation – occupational

For the short- and intermediate-term occupational exposures via the dermal and inhalation routes, the offspring no observed adverse effect level (NOAEL) of 5.9 mg/kg bw/day was selected from the 2-generation dietary reproductive toxicity in the rat. At the offspring LOAEL of 30 mg/kg bw/day, decreased pup weight and clinical signs in pups (dehydration and cold to touch) were observed. Worker populations could include pregnant or lactating women; therefore, these endpoints were considered appropriate for the occupational risk assessment. A short-term inhalation toxicity study was not available and the existing short-term dermal toxicity study did not address endpoints of concern in the young, thus necessitating the use of an oral study for risk assessment.

Since a point of departure from an oral study was selected to assess risks from dermal and inhalation exposure, consideration was given to any correction required for oral absorption in order to account for differences in bioavailability between the different routes of exposure. As noted previously, the oral absorption of acynonapyr was estimated to be approximately 25% based on the calculated uptake of the AP label of acynonapyr. To account for this relatively low oral absorption noted in the animal database, the offspring NOAEL was adjusted by the estimated oral absorption value of 25%. Therefore, the point of departure for use in the human health risk assessment for short to intermediate-term dermal and inhalation routes is the adjusted offspring NOAEL of 1.5 mg/kg bw/day.

The target margin of exposure (MOE) for these scenarios is 300, which includes UFs of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a threefold database UF to reflect the lack of neurotoxicity and hormone measurements in the young.

The selection of this study and target MOE provide sufficient margins (over 1000) to the points of departure for serious effects in the young in the 2-generation reproductive toxicity study in rats and the developmental toxicity study in rabbits, and are thus considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short- term dermal – residential

For the short-term residential exposure via the dermal route, the adjusted offspring NOAEL of 1.5 mg/kg bw/day was selected from the 2-generation dietary reproductive toxicity in the rat, as previously discussed in this section for the occupational exposure scenarios. The target MOE is 300, which includes UFs of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a threefold database UF to reflect the lack of neurotoxicity and hormone measurements in the young. The PCPA factor was reduced to onefold as discussed in the *Pest Control Products Act* hazard characterization section. The selection of this study and the target MOE provide adequate margins (over 1000) to the points of departure for serious effects in the young in the 2-generation reproductive toxicity study in rats and the developmental toxicity study in rabbits, and are thus considered to be protective of all populations, including nursing infants and the unborn children of exposed women.

3.2.3 Acute reference dose (ARfD)

For females 13 to 49 years of age, infants, and children up to 12 years old, the most appropriate study endpoint for assessing risk following acute dietary exposure to acynonapyr was from the 2-generation dietary reproductive toxicity study in the rat. A reproductive NOAEL of 30 mg/kg bw/day was determined based on stillbirths and early post-natal death of pups (PND 0) at the LOAEL of 74 mg/kg bw/day. It was considered possible that these deaths were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard UFs of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, a threefold PCPA factor was retained for serious effects in the young, and an additional threefold database UF was applied to reflect the lack of neurotoxicity and hormone measurements in the young. The composite assessment factor (CAF) is thus 1000.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{30 \text{ mg/kg bw}}{1000} = 0.03 \text{ mg/kg bw of acynonapyr}$$

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 4 mg/kg bw/day from the 1-year oral (capsule) toxicity study in the dog was selected. At the LOAEL of 20 mg/kg bw/day, reductions in body weights, body weight gains, and food consumption were observed. This study provides the lowest NOAEL in the database. Standard UFs of 10-fold for interspecies

extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to onefold. An additional threefold database UF was applied to account for the lack of neurotoxicity and hormone measurements in the young. The CAF is thus 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{4 mg/kg bw/day}}{300} = 0.01 \text{ mg/kg bw/day of acynonapyr}$$

The ADI provides margins of 3000 and 5000 to the NOAELs for serious effects in the young observed in the 2-generation reproductive toxicity study in rats and the developmental toxicity study in rabbits, respectively.

3.2.5 Cancer assessment

Acynonapyr is considered to have tumourigenic potential based on the weight of evidence. There was evidence of tumourigenicity in rodents in the form of an increased incidence of liver tumours and lymphomas in male mice, and lymph node, thyroid, skin, and brain tumours in male rats. A linear low-dose extrapolation (non-threshold) approach was deemed appropriate for all tumour types since the MOA data provided for the liver and thyroid tumours were deemed to be insufficient to support both proposed MOAs. Additionally, there was no MOA proposed for the other treatment-related tumours. For the oral route, a q_1* of 2.5E-2 $(\text{mg/kg bw/day})^{-1}$ was derived based on the combined incidence of mesenteric lymph node hemangioma and hemangiosarcoma in male rats treated with acynonapyr. For assessing cancer risk via the dermal and inhalation routes, an adjusted q_1*) of 4.9E-2 $(\text{mg/kg bw/day})^{-1}$ was derived based on the combined incidence of mesenteric lymph node hemangioma and hemangiosarcoma in male rats treated with acynonapyr, and the application of a fourfold adjustment factor to account for the low (25%) oral absorption. This q_1* was selected as it reflected the most conservative potency factor for the various tumour types and was considered relevant to all exposure routes.

3.2.6 Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). Short-term aggregate exposure to acynonapyr may be comprised of food, drinking water, and residential exposure via the oral and dermal routes. The toxicology endpoint selected for aggregation for all populations was the decreased pup weight and clinical signs in pups (dehydration and cold to touch) observed at the LOAEL of 30 mg/kg bw/day from the 2-generation dietary reproductive toxicity in the rat. For oral exposure, the offspring NOAEL of 5.9 mg/kg bw/day was selected. For dermal exposure, the adjusted offspring NOAEL of 1.5 mg/kg bw/day (based on a NOAEL of 5.9 mg/kg bw/day corrected for 25% oral absorption) was selected. The target MOE for these scenarios is 300, which includes UFs of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a threefold database UF to account for the lack of neurotoxicity and hormone measurements in the young. The PCPA factor was reduced to onefold, as outlined in the *Pest Control Products Act* hazard characterization section.

3.3 Dermal absorption

Three dermal absorption studies were submitted as part of a triple pack for acynonapyr: a rat in vivo study, and a rat and human in vitro study (PMRA# 3630579).

Limitations were identified with the studies, including the use of a Geiger counter to determine the end of the skin wash. This is a limitation as it results in a more vigorous skin wash than what is in the test guidelines and what would be expected in the field, which could underestimate dermal absorption. Low recoveries were determined for some low-dose groups, but these losses were determined to be from the skin wash, and no correction for the missing radioactivity was required. There were some issues with the homogeneity of the doses and dose calculations; however, this was not expected to underestimate dermal absorption.

Overall, all components of the study were considered acceptable for the selection of dermal absorption values for the exposure and risk assessment. The doses and tested formulation were representative of the proposed product, Kodama Miticide. The triple pack showed that the in vitro model was a conservative estimate of absorption in vivo, which supports the current PMRA position of accepting in vitro studies alone, when conducted using the standard methodology. However, due to the limitations of the study and to allow the use of this value for a wider range of products/formulations for acynonapyr, the rat in vivo data was used to determine the dermal absorption value. As such, the dermal absorption value for acynonapyr is 10% based on the in vivo rat dermal absorption study.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use product and mitigation measures

Kodama Miticide

The acute hazard assessment indicated that Kodama Miticide is of low acute toxicity to rats via the oral, dermal, and inhalation routes of exposure. It was non-irritating to the eyes and the skin of rabbits, and was a potential dermal sensitizer in guinea pigs via the Buehler method. Based on these acute hazards, a long-sleeved shirt, long pants, socks, shoes and chemical-resistant gloves are required for workers during mixing, loading, application, clean-up, and repair.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader and applicator exposure and risk assessment

Individuals have potential for exposure to acynonapyr during mixing, loading, application, clean-up, and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database and the Pesticide Handlers Database (PHED, v1.1) for mixers, loaders, and applicators applying Kodama Miticide using airblast and various handheld equipment including backpack sprayers, manually pressurized handwands, and mechanically pressurized handguns (Appendix I, Table 7).

The PPE in the risk assessment is based on handlers wearing a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes, with the exception that chemical-resistant gloves are not required for applicators using closed cab equipment, and applicators using open cab equipment must also wear chemical-resistant headgear (Appendix I, Table 7).

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and the dermal absorption value of 10%. Inhalation exposure was estimated by combining the unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

For the non-cancer risk assessment, exposure estimates were compared to the toxicology reference values to obtain the MOE; the target MOE is 300. Dermal and inhalation MOEs were combined, since the dermal and inhalation toxicology reference values are based on the same toxicological effects. Calculated MOEs are greater than the target MOE of 300 for all chemical handler scenarios and are, therefore, not of health concern (Appendix I, Table 8).

A cancer risk assessment was conducted for workers mixing, loading and applying acynonapyr. Absorbed daily doses (ADDs) were used as the basis for calculating lifetime average daily dose (LADD) values. Lifetime average daily dose values were calculated by amortizing exposure over the lifetime of the worker. The treatment frequency was assumed to be 5 days per year, with an exposure duration of 40 years. Cancer risk was calculated by multiplying the estimated LADD by a q_1*; the target threshold is 1.0E-5. The calculated cancer risks are below the threshold and are therefore not of health concern (Appendix I, Table 9).

3.4.2.2 Postapplication exposure and risk assessment

There is potential for exposure to workers entering areas treated with Kodama Miticide to complete tasks such as hand thinning and hand harvesting. Given the nature of activities performed, exposure is primarily via dermal contact with treated foliage. Inhalation exposure is not expected, as acynonapyr is considered non-volatile with a vapour pressure of 1.13E-9 kPa (at 20°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios (1E-4 kPa at 20–30°C). As such, a quantitative inhalation risk assessment was not required. Inhalation risk is not of health concern for postapplication workers, as acynonapyr is considered to be non-volatile and the minimum REI of 12 hours will allow residues to dry, suspended particles to settle, and vapours to dissipate.

Dermal exposure to workers entering treated areas is estimated by combining dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients (TCs). Activity TCs are based on data from the Agricultural Re-entry Task Force (ARTF). As chemical-specific DFR data were not submitted, a standard DFR value of 25% of the application rate coupled with 10% daily dissipation of residues were used in the exposure assessment.

For the non-cancer risk assessment, exposure estimates were compared to the toxicology reference value to obtain the MOE; the target MOE is 300. Calculated MOEs are greater than the target MOE of 300 and are, therefore, not of health concern, provided a 6-day REI is applied to thinning in pome fruit and a 12-hour REI is prescribed for all other postapplication activities (Appendix I, Table 10).

A cancer risk assessment was conducted for workers entering areas treated with acynonapyr. The ADD was used as the basis for calculating LADD values. The exposure frequency was assumed to be equivalent to 15 days per year based on a single application per year and professional judgement. A career duration of 40 years was assumed for postapplication workers. The calculated cancer risk for workers entering areas treated with acynonapyr was at the threshold of 1E-5 for hand thinning and 5E-6 for hand harvesting (Appendix I, Table 11). Therefore, potential exposure to postapplication workers is not expected to result in cancer risks of concern when the product is used according to label directions.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

Kodama Miticide is not a domestic class product and is not permitted for use in residential settings; therefore, a residential handler exposure assessment was not required.

3.4.3.2 Postapplication exposure and risk assessment

Kodama Miticide is proposed for use on PYO farms and on pome fruit trees grown in residential areas. As such, a postapplication residential risk assessment was required.

Pick-your-own (PYO) activities

Given that pome fruit can be treated with acynonapyr, there is potential for exposure during PYO activities. The postapplication occupational risk assessment is protective of the risks associated with dermal exposure to the patrons in a PYO facility; therefore, a quantitative risk assessment was not required.

Trees in residential areas treated with Kodama Miticide

When a commercial applicator is hired to treat pome fruit trees in a residential area or when a farmer treats pome fruit trees adjacent to residential areas, there is potential for residential postapplication dermal exposure to homeowners and their families.

For the non-cancer risk assessment, the residential postapplication dermal risk assessment was conducted for adults (16+ years), youth (11 < 16 years), and children (6 < 11 years) when contacting treated fruit trees to perform activities such as hand harvesting, thinning, and pruning.

Dermal exposure was estimated using the standard DFR values, transfer coefficients, durations of exposure, and body weights from the United States Environmental Protection Agency's (USEPA) *Residential Standard Operating Procedures for Residential Pesticide Exposure Assessment* (revised October 2012). Using the dermal absorption and toxicological reference values, calculated MOEs were greater than the target MOE of 300 (Appendix 1, Table 12) for all residential postapplication dermal exposures on Day 0.

A lifetime cancer risk was estimated for adults (16+ years), youth (11 < 16 years), and children (6 < 11 years) contacting treated fruit trees to perform activities such as hand harvesting, thinning, and pruning. As there is only a single application of the end-use product per season, the

days of exposure per year were assumed to be 15 based on professional judgement. The time-weighted average (TWA) DFR value for 15 days after a single application was used for all life stages and the lifetime cancer risk was less than the threshold of 1E-6 (Appendix 1, Table 13).

As such, health risks are not of concern and individuals can contact treated pome fruit trees once the sprays have dried.

3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible, as application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools, and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.

Therefore, bystander exposure and risk are not of health concern since the potential for drift is expected to be minimal.

3.5 Dietary exposure and risk assessment

3.5.1 Exposure from residues in food of plant and animal origin

The residue definition in primary fruit crops for enforcement purposes is acynonapyr + AP, expressed as parent equivalents, and for risk assessment is acynonapyr + AP + AP-2, expressed as parent equivalents. The data gathering and enforcement analytical methods are valid for the quantitation of residues of acynonapyr and its metabolites AP, AP-2, AY, AY-3, and AY-1-Glc in plant commodities. The residues of acynonapyr + AP are stable in apple fruit for up to 182 days, when stored in a freezer at -10 to -25°C. Crop field trials conducted throughout the United States, including growing regions representative of Canada, using an end-use product containing acynonapyr and applied at approved rates on apples and pears are sufficient to support the proposed MRL. Field rotational crop studies were not conducted since pome fruits are not considered a rotational crop.

3.5.2 Exposure from residues in drinking water

3.5.2.1 Concentrations in drinking water

For the human health risk assessment, estimated environmental concentrations (EECs) in potential drinking water sources are calculated for both groundwater and surface water using the Pesticide Water Calculator (PWC; version 2.0). The drinking water residue definition was determined as the combined residue of acynonapyr and its major transformation products AP, AY, AP-suc, AP-fum, AP-mal, and AY-4.

For surface water, PWC calculates the amount of pesticide entering the water body by runoff and drift, and the subsequent degradation of the pesticide in the water system. EECs are calculated by modelling a total land area of 173 hectares draining into a 5.3-hectare reservoir with a depth of 2.7 metres. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the 1 metre below the water table.

Drinking water modelling follows a tiered approach consisting of progressive levels of refinement. Level 1 EECs are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using conservative inputs with respect to application rate, application method, application timing, and geographic scenario.

Modelling was performed at Level 1. The EECs for surface water were calculated based on a single standard scenario, which was run for 50 years. The EECs in groundwater were calculated for several scenarios representing different regions of Canada; only the highest EECs from across these scenarios are reported. All groundwater scenarios were run for 100 years due to slow leaching. The drinking water model input parameters and Level 1 EECs are reported in Appendix I, Tables 14 and 15, respectively.

3.5.3 Dietary risk assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 4.02, 05-10-c), which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005–2010.

3.5.3.1 Acute dietary exposure results and risk characterization

The following assumptions were applied in the basic acute analysis for acynonapyr: 100% crop treated, default processing factors, and the MRL for pome fruits. The basic acute dietary exposure (food alone) is estimated to be 2% of the ARfD (0.03 mg/kg bw) for females 13–49 years old and 8–31% of the ARfD for infants and children up to 12 years old (95th percentile, deterministic). Aggregate exposure from food and drinking water (EEC value = 21 µg a.i./L, Level 1, groundwater) is considered acceptable: 5% of the ARfD for females 13–49 years old and 9–33% of the ARfD for infants and children up to 12 years old.

3.5.3.2 Chronic dietary exposure results and risk characterization

The following assumptions were applied to the refined chronic analysis for acynonapyr: projected percent crop treated for pome fruits, supervised trial median residue (STMdR) values for apples and pears, anticipated residues in processed commodities (where available), and a refined Level 1 EEC value. The refined chronic dietary exposure (food alone) to pome fruits for the total population, including infants and children, and all representative population subgroups is less than 0.2% of the ADI. Aggregate exposure from food and drinking water (EEC value = 2.6 µg a.i./L, refined Level 1, groundwater) is considered acceptable. The PMRA estimates that refined chronic (non-cancer) dietary exposure to acynonapyr from food and drinking water is <2% of the ADI for the total population. The highest exposure and risk estimate is for all infants (<1 year) at 2% of the ADI (0.000209 mg/kg bw/day).

The refined chronic cancer risk assessment was conducted using the same residue inputs as those for the chronic non-cancer assessment. The lifetime cancer risk from exposure to acynonapyr in food and drinking water was estimated to be 1E-6 for the general population, which is not of health concern.

3.6 Aggregate exposure and risk assessment

There is potential for individuals to be exposed to acynonapyr via different routes and sources of exposure concurrently. As such, the following scenarios were considered:

For the non-cancer risk assessment, aggregate chronic dietary (food and drinking water) and dermal exposure to acynonapyr from harvesting, pruning, and thinning of trees in residential settings was conducted. When comparing the total (dietary and dermal) exposures to the aggregate toxicology reference values, calculated MOEs were greater than the target MOE of 300 (Appendix I, Table 18) for all life stages.

An aggregate lifetime cancer risk assessment was conducted for adults (16+ years), youth (11 < 16 years), and children (6 < 11 years) by combining the lifetime dermal cancer risk with the lifetime dietary cancer risk. As the highly refined lifetime dietary cancer risk is at the PMRA's LOC (1E-6), aggregating with the lifetime dermal cancer risk exceeds the threshold for residential cancer risk (Appendix I, Table 19). As such, application of Kodama Miticide to pome fruit trees in residential settings will be prohibited.

3.7 Cumulative assessment

The *Pest Control Products Act* requires the PMRA to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for acynonapyr. Acynonapyr's pesticidal MOA as a KCa2 channel modulator is novel, and it is the only chemical included in this IRAC group. Additionally, acynonapyr has not been grouped with other pesticides based on its chemical structure according to the Compendium of Common Pesticide Names maintained by the British Crop Production Council.[6] Overall, for the current evaluation, the PMRA did not identify information indicating that acynonapyr shares a common mechanism of toxicity with other pest control products.

3.8 Health risk assessment of a common metabolite from multiple pesticides

The transformation product AY of acynonapyr has been identified as a transformation product, identified as Compound 10, of another active ingredient, fluazifop-p-butyl. For both acynonapyr and fluazifop-p-butyl, this common transformation product was considered to be of toxicological relevance but not of greater toxicity than the unchanged active ingredient. As such, it was determined that an assessment of the potential exposure and risk to this transformation product was required, and the toxicology reference values established for each active ingredient were considered adequate to account for potential toxicity from exposure to the transformation product.

For the purposes of the proposed registration of acynonapyr, a qualitative approach was used to assess risks from the combined exposure to the common transformation product from the use of acynonapyr and fluazifop-p-butyl.

[6] British Crop Production Council. 2025. Compendium of Pesticide Common Names, http://www.bcpcpesticidecompendium.org/index.html [accessed 30 April 2024].

Acynonapyr is proposed for use on pome fruits to provide rapid knockdown of adult and larval Tetranychid mites, whereas fluazifop-p-butyl is registered for use as a herbicide for a wide range of crops.

Exposure to the common transformation product from food is limited for the following reasons:

- Its residues were not quantifiable in acynonapyr pome fruit field trials.
- Although it is part of the fluazifop-p butyl residue definition for rotational crops, the registered label contains a plant-back interval of 12 months and there is no expectation of residues of the transformation product in secondary crops planted 12 months after the initial treatment.

However, exposure to the common transformation product from drinking water is possible, as it is part of the drinking water residue definition for both acynonapyr and fluazifop-p butyl. Risk estimates from the individual dietary exposure assessments of the two pesticides, taking into account the parent and transformation products, were used to assess the health risk of the common transformation product.

Acute exposure from drinking water represented ≤5.2% of the ARfD (all subpopulations, including 2.6% of the ARfD for females 13–49 years old) in the basic acute dietary exposure assessment for acynonapyr and 6.1% of the ARfD (females 13–49 years old only) of the refined acute dietary exposure assessment for fluazifop-p butyl. The sum of the individual risk estimates for females 13–49 year old for both acynonapyr and fluazifop-p butyl is 8.6% of the risk cup.

Chronic exposure from drinking water represented ≤2.0% of the ADI in the refined chronic dietary exposure assessment for acynonapyr and ≤56% of the ADI of the refined chronic dietary exposure assessment for fluazifop-p butyl. The sum of the individual risk estimates of the highest exposed subpopulation (all infants) for both acynonapyr and fluazifop-p butyl is 58% of the risk cup.

Cancer risk was estimated for acynonapyr; however, no cancer endpoint was established for fluazifop-p-butyl. As such, it is not applicable to the common transformation product.

The acute and chronic risk estimates from the individual dietary exposure assessments were calculated using the most conservative points of departure for acynonapyr and fluazifop-p butyl, which were considered adequate to account for potential toxicity from exposure to the common transformation product. In addition, the drinking water exposure estimates for acynonapyr and fluazifop-p butyl consist of residues of the parent compound and other metabolites, in addition to those of the common transformation product. As such, the summing of the individual risk estimates overestimates the combined risk of the common transformation product from the two pesticides.

Therefore, based on this qualitative assessment, the combined risks of the common transformation product from acynonpyr and fluazifop-p butyl through food and drinking water, where relevant, are acceptable.

3.9 Maximum residue limit

Dietary risks from the consumption of pome fruits, as listed in Table 3.9.1, were shown to be acceptable when acynonapyr is used according to the supported label directions. Therefore, pome fruits containing residues at this level are safe to eat, and the PMRA recommends that the following MRL be specified for residues of acynonapyr.

Table 3.9.1 Recommended maximum residue limit

MRL (ppm)	Food commodity
0.2	Crop Group 11-09: Pome Fruits

The MRL is proposed for each commodity included in the listed crop grouping in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and pest management Section of Canada.ca.

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

The nature of the residues in plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1b, 16, and 17.

3.10 Health incident reports

Acynonapyr is a new active ingredient pending registration for use in Canada. As of 6 June 2025, no human or domestic animal incidents involving acynonapyr had been submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

The fate and behaviour of acynonapyr and its transformation products in the environment is summarized in Appendix I, Table 20. A summary of the transformation products of acynonapyr detected in the environmental fate studies is provided in Appendix I, Table 21. A summary of the leaching assessment for acynonapyr is provided in Appendix I, Table 22.

Abiotic processes of hydrolysis and phototransformation are important routes of dissipation for acynonapyr in the environment. Biotransformation in terrestrial and aquatic environments is also an important route of dissipation for acynonapyr. Acynonapyr is classified as slightly to moderately persistent in soils and non-persistent in aquatic systems. The major transformation products (>10% formed) of acynonapyr in soil and aquatic systems include: AP, AY, AY-4, AY-5, AP-suc, AP-fum, AP-mal, AH, and UK-15. The two major transformation products, AP and AY, represent the cleavage of the parent, acynonapyr. Only AP and AY were considered in the residue definition for the environment, based on the potential for exposure and ecotoxicity.

Based on available aerobic soil biotransformation studies, AP is persistent, whereas AY is moderately persistent. Depending on the soil or aquatic system, biotransformation of acynonapyr may result in mineralization to carbon dioxide (CO_2) and residues that are strongly bound to soil or sediment.

Acynonapyr and its transformation products are not expected to be volatile under field conditions. Terrestrial field dissipation studies indicate that acynonapyr dissipates relatively rapidly, demonstrating agreement between laboratory and field degradation rates and an unlikelihood for acynonapyr to carry over to the next growing season. No residues were detected below a 15 cm soil depth, with a few exceptions for the transformation products, suggesting limited movement to groundwater at the sites evaluated. Overall, taking into consideration the results of laboratory studies, assessments using groundwater ubiquity scores (GUS) and the criteria of Cohen et al. (1984), and field studies, acynonapyr and its residues are expected to have limited mobility to groundwater.

Based on the log K_{ow} of acynonapyr and measured bioconcentration factors, there is a potential for bioaccumulation; however, due to its rapid cleavage to the transformation products AP and AY, exposure to acynonapyr is considered minimal. The estimated log K_{ow} and measured bioconcentration value for the two major transformation products, AP and AY, respectively, suggest they are unlikely to bioaccumulate. Bioaccumulation studies involving dietary exposure of fish and sediment exposure of worms suggest that acynonapyr and its transformation products are not expected to bioaccumulate.

4.2 Environmental risk characterization

An environmental risk assessment was conducted as described in the PMRA guidance document, *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products*, to estimate the potential for adverse effects on non-target species. Environmental exposure and ecotoxicology information were integrated by comparing EECs to effects-based values used to assess risk (effects metrics). The EECs were estimated using standard models that consider application rate(s) and chemical and environmental fate properties, including pesticide dissipation between applications. The EECs used in this risk assessment are presented in Appendix I, Table 23.

Acute and chronic ecotoxicological data for non-target terrestrial, freshwater, and marine organisms are summarized in Appendix I, Tables 24 and 25. In the risk assessment, toxicity endpoints were adjusted via a UF to calculate the effects metrics. The effects metrics account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). The toxicity endpoints and UFs used to establish the effects metrics, along with the LOC used in the risk assessment, are presented in Appendix I, Table 26.

Initially, a screening-level risk assessment was performed to identify specific uses that do not pose a risk to non-target organisms. The screening-level risk assessment used simple methods, conservative exposure scenarios, and sensitive effects metrics. A risk quotient (RQ) was calculated by dividing the EEC by the effects metric and was then compared to the LOC.

When the screening-level RQ was below the LOC, the risk was considered to be acceptable, and no further risk characterization was necessary. When the screening-level RQ was equal to or greater than the LOC, a refined risk assessment was performed to further characterize the risk.

The refined risk assessment evaluated additional and more realistic exposure scenarios, including consideration of spray drift and runoff, as well as effects metrics that were more reflective of potential exposure in the environment. Refinements to the risk assessment continued until the risk was adequately characterized or until the available data did not permit further refinements.

4.2.1 Risks to terrestrial organisms

Terrestrial organisms such as earthworms, bees, birds, mammals, and terrestrial vascular plants may be exposed to acynonapyr through direct contact with spray or spray drift, contact with sprayed surfaces, or from ingestion of contaminated food. A risk assessment for acynonapyr and its end-use product formulation was conducted for terrestrial organisms based on available toxicity data. Screening-level RQs were calculated based on the maximum application rate. The screening-level risk assessment for acynonapyr is presented in Appendix I, Table 27, for terrestrial organisms other than birds and mammals, and in Appendix I, Table 28, for birds and mammals.

Earthworms: Acynonapyr was not toxic to earthworms on an acute or chronic basis at concentrations as high as 1000 mg a.i./kg soil dw. The RQs for earthworms resulting from acute and chronic exposure to acynonapyr do not exceed the LOC at the screening level. The risk to earthworms from the use of acynonapyr has been determined to be acceptable.

Bees: Acynonapyr may be found on pollen and nectar, as spray droplets are deposited onto open flowers during foliar application. Acynonapyr is not systemic and is expected to be found mainly on the leaves when the application is made before or after bloom; therefore, a pre-bloom or post-bloom application is expected to result in minimal exposure to bees. Application during bloom may result in exposure to both adult forager bees, and also to bees in the hive, from contaminated pollen and nectar being brought back to the hive for consumption.

Acynonapyr was practically nontoxic to honey bees on an acute contact and oral basis. No significant effects from chronic exposure to acynonapyr were observed in adult bees; however, effects on pupal mortality and emergence were observed in larval bees from chronic exposure, resulting in a no observed effect dose (NOED) of 12.2 µg a.i./bee/day. Exposure estimates for bees were calculated using default values and consumption rates for adult and larval honey bees. The screening-level RQs for adult bees from acute contact, acute oral, and chronic exposure, and for larval bees from acute oral and chronic exposure do not exceed the LOC. The risk to bees from the use of acynonapyr has been determined to be acceptable.

Beneficial arthropods: In laboratory studies involving exposure to residues on glass plates, acynonapyr was toxic to the beneficial arthropod species *Typhlodromus pyri* but not to *Aphidius rhopalosiphi*, with LR_{50} values of 13 g a.i./ha and >100 g a.i./ha, respectively. In extended laboratory studies, exposure to residues of the end-use product formulation on plant leaves or soil did not affect the survival and reproduction of six different species of beneficial arthropods. All reported ER_{50}/LR_{50} values were >269 g a.i./ha, with the exception of the predatory bug, *Orius laevigatus,* with an ER_{50} >53.7 g a.i./ha for effects on fertility.

The RQs for the standard beneficial species, *T. pyri*, resulting from exposure to acynonapyr on glass plates, exceeded the LOC at the screening level. The risk to beneficial arthropods was further characterized using results from higher tier, extended laboratory toxicity studies, and by adjusting the amount of exposure on-field and off-field by considering deposition fractions and vegetation distribution factors (Appendix I, Table 29).

The refined RQs for the **on-field assessment**, based on Tier I effect metrics, only exceeded the LOC for a glass plate study with acynonapyr and the standard beneficial species, *T. pyri* (RQ = 7.8). In an extended laboratory study with the end-use product and *T. pyri*, no significant effects on survival or reproduction were observed up to the highest treatment level. When using Tier II (extended laboratory) effect metrics, the refined RQs only slightly exceeded the LOC for fertility effects on the predatory bug, *O. laevigatus* (RQ < 1.9). In this study with *O. laevigatus*, there were no statistically significant effects on mortality or fecundity at any test item application rate, resulting in an ER_{50}/LR_{50} of >268.6 g a.i./ha for those endpoints. Significant effects were only observed for fertility (nymphal hatching rate), resulting in a non-definitive ER_{50} for fertility of >53.7 g a.i./ha, due to an insufficient dose-response. The refined RQs for the **off-field assessment**, based on Tier I and Tier II (extended laboratory) effect metrics, did not exceed the LOC for any of the tested species.

When considering all laboratory studies with standard species of beneficial arthropods (predatory mite, *T. pyri*, and parasitic wasp, *A. rhopalosiphi*) and additional beneficial arthropod species, including the predatory bug (*O. laevigatus*), ladybird beetle (*Coccinella septempunctata*), lacewing (*Chrysoperla carnea*), and rove beetle (*Aleochara bilineata*), minimal toxicity is expected from acynonapyr exposures both on-field and off-field. The risk to beneficial arthropods from the use of acynonapyr has been determined to be acceptable.

Birds: Acynonapyr was practically non-toxic to slightly toxic to birds by sub-acute dietary consumption or through acute oral administration. Mortalities and body weight effects were observed for two of the three avian species tested. Significant reproductive effects were observed in duck and quail, with the lowest avian reproductive no observed effect level (NOEL) being 4.01 mg a.i./kg bw/day. The screening-level RQ for birds resulting from reproductive exposure to acynonapyr exceeded the LOC at the screening level. The risks to birds were further characterized, considering other feeding guilds, on-field and off-field exposures, and maximum and mean residue levels (Appendix I, Table 30). Looking at multiple feeding guilds, RQs only slightly exceeded the LOC for reproductive effects in small- and medium-sized insectivorous birds when considering mean residue levels on-field and off-field.

The risk assessment assumes that 100% of the diet consumed is comprised of contaminated items; however, diets are likely to be composed of both contaminated and uncontaminated items. The RQs also only exceeded the LOC for reproductive effects. Endpoints from reproductive studies consider repetitive consumption, and given the proposed use pattern of a single application, it is unlikely that residues will be maintained on the insects in the diet for a long duration. Insects move around and with a single application, the likelihood of repeated exposure is low. When considering the timing of application required for effects (in other words, during the breeding season), time spent in treated fields, foraging behaviour, and diet during the exposure time period (in other words, mixed diets, particularly over longer-term exposure), the likelihood of effects is low. Furthermore, for the risk assessment, the effects metric used was the

most sensitive endpoint from the reproductive toxicity studies, which corresponds to a NOEL of 4.01 mg a.i./kg bw/day. To further characterize the potential risk to birds, the lowest observed effect level (LOEL) was considered. When considering the LOEL, all RQs are <0.5. Based on these results and considerations, the risk to birds from the use of acynonapyr has been determined to be acceptable.

Mammals: Acynonapyr and its end-use product were both practically non-toxic to rats on an acute basis, with oral LD_{50} values of >2000 mg/kg bw. Acynonapyr transformation products were moderately toxic to practically non-toxic to rats on an acute basis. A 2-generation rat reproduction study with acynonapyr resulted in a NOEL of 24 mg a.i./kg bw/day due to significant treatment-related effects on parents, offspring, and other endpoints describing reproductive performance. The RQs for mammals resulting from acute and reproductive exposure to acynonapyr and its transformation products did not exceed the LOC at the screening level. The risk to mammals from the use of acynonapyr has been determined to be acceptable.

Terrestrial vascular plants: In the seedling emergence and vegetative vigour studies with an acynonapyr end-use product formulation, little or no effect on the germination, emergence, and survival of ten plant species was observed up to the maximum application rate of 200 g a.i./ha. The calculated RQs do not exceed the LOC at the screening level. The risk to terrestrial vascular plants from the use of acynonapyr has been determined to be acceptable.

4.2.2 Risks to aquatic organisms

Aquatic organisms could be exposed to acynonapyr through spray drift or runoff that enters aquatic habitats. A risk assessment for acynonapyr, its end-use product formulation, and its transformation products was conducted for freshwater and marine aquatic organisms based on available toxicity data. Screening-level RQs were calculated based on the maximum application rate. For groups where the RQ exceeds the LOC, a refined Tier I assessment was conducted to determine risk resulting from spray drift and runoff separately. The screening-level and Tier I refined RQs for acynonapyr are summarized in Appendix I, Tables 31 to 33.

Acute aquatic toxicity endpoints are largely attributed to the functional solubility of the technical grade active ingredient, with many endpoints for aquatic species reported as non-definitive (in other words, greater than values), with no effects observed at the highest tested concentration. The reported water solubility for acynonapyr is 0.00228 mg/L (25°C); however, the functional solubility was higher, and varied amongst the available aquatic studies. Nevertheless, even with a solvent, it was not feasible to achieve exposure concentrations high enough to cause acute toxicity for many species. Acute toxicity tests were conducted on rainbow trout, *Daphnia*, and aquatic plants and algae using the formulated end-use product, in which higher concentrations of acynonapyr were achieved, demonstrating that the true acute toxicity endpoints are likely higher than those resulting from the solubility-restricted studies conducted using the technical grade active ingredient. Therefore, where available for the same species and study duration, studies conducted using the end-use product were used to better characterize the risk. It is noted that unlike the acute studies, chronic exposure to acynonapyr resulted in significant effects on growth or reproduction of both pelagic and benthic invertebrates at levels within the functional solubility of the technical grade active ingredient.

Invertebrates: No significant mortality in acute studies with freshwater and marine invertebrates was observed for either acynonapyr or its end-use product, with the highest acute LC_{50}/EC_{50} of >1.9 mg a.i./L for *Daphnia magna* in a study with the end-use product formulation. In chronic studies with aquatic invertebrates, significant effects on growth and reproduction were observed, with the most sensitive endpoint being a no observed effect concentration (NOEC) of 0.00083 mg a.i./L for *D. magna*. Acynonapyr's major transformation products, AP and AY, were moderately toxic and practically nontoxic, respectively, to *D. magna* on an acute basis, with LC_{50}/EC_{50} values of 3.2 mg AP/L and >96 mg AY/L, respectively. Three spiked whole-sediment sub-chronic studies were conducted with freshwater and marine benthic species. No lethal effects were observed in any test group in any of the three studies. A sublethal effect (larval weight reduction) was identified in the *Chironomus dilutus* study.

The RQs for acute exposure of freshwater *D. magna* to the transformation products AP and AY do not exceed the LOC at the screening level. The RQ for acute exposure of *D. magna* to acynonapyr exceeds the LOC at the screening level due to the solubility constraints previously explained in this section; however, the RQ resulting from acute exposure to the end-use product does not exceed the LOC at the screening level. The RQ for chronic exposure of *D. magna* to acynonapyr exceeds the LOC at the screening level, as do the RQs for acute and chronic exposure of marine invertebrates. The acute and chronic risks of acynonapyr to freshwater and marine invertebrates were further characterized, as were risks to benthic invertebrates, through the refined risk assessment for runoff. The refined RQs indicate that the LOC is exceeded through spray drift and runoff. In order to mitigate potential exposure of acynonapyr to freshwater and marine invertebrates, spray buffer zones, standard precautionary label statements, and standard best management practice statements to reduce runoff entering sensitive aquatic habitats, are required on the label of Kodama Miticide.

Fish: No significant effects in any of the fish acute studies were observed for either acynonapyr or its end-use product, with the highest acute LC_{50} > 4.5 mg a.i./L for rainbow trout in a study with the end-use product formulation. The acynonapyr major transformation product, AP, was moderately toxic to rainbow trout and bluegill sunfish on an acute basis, with LC_{50} values of 3.7 and 6.3 mg AP/L, respectively. In chronic early-life stage studies with freshwater and marine fish, no statistically significant treatment-related effects were observed, with the highest NOEC value being ≥ 0.0067 mg a.i./L for the sheepshead minnow.

The RQs for freshwater fish resulting from acute exposure to the end-use product (study available with rainbow trout only), and transformation product, AP, do not exceed the LOC at the screening level. The RQs for freshwater and marine fish resulting from acute and early-life stage (ELS) exposure to acynonapyr exceed the LOC at the screening level due to the solubility constraints previously explained in this section. The acute and chronic risks of acynonapyr to freshwater and marine fish were further characterized. The refined RQs indicate that the LOC is exceeded through spray drift and runoff. In order to mitigate potential exposure of acynonapyr to freshwater and marine fish, spray buffer zones, standard precautionary label statements, and standard best management practice statements to reduce runoff entering sensitive aquatic habitats, are required on the product label of Kodama Miticide.

Amphibians: Using the effects metrics from acute and ELS studies with fish as a surrogate, along with an EEC for acynonapyr in a 15-cm deep body of water, the RQs for amphibians resulting from acute and ELS exposure to acynonapyr exceed the LOC at the screening level due to the solubility constraints previously explained in this section. The RQ for amphibians resulting from acute exposure to the transformation product, AP, does not exceed the LOC at the screening level. The acute and chronic risks of acynonapyr to amphibians were further characterized. The refined RQs indicate that the LOC is exceeded through spray drift, but not through runoff. In order to mitigate potential exposure of acynonapyr to amphibians, spray buffer zones, standard precautionary label statements, and standard best management practice statements to reduce runoff entering sensitive aquatic habitats, are required on the label of Kodama Miticide.

Algae: No significant effects on freshwater and marine algae were observed for acynonapyr up to its functional solubility under the test conditions. The acynonapyr end-use product formulation inhibited the growth rate and yield of algae, with the most sensitive definitive EC_{50} = 0.16 mg a.i./L. The acynonapyr major transformation product, AP, inhibited the growth rate and yield of freshwater algae, with an EC_{50} of 0.025 mg AP/L. The RQ for algae resulting from exposure to the transformation product, AP, does not exceed the LOC at the screening level. The RQs for freshwater and marine algae resulting from exposure to acynonapyr exceed the LOC at the screening level due to the solubility constraints previously explained in this section; however, the RQs resulting from exposure to the end-use product do not exceed the LOC at the screening level. The risk to freshwater and marine algae from the use of acynonapyr has been determined to be acceptable.

Aquatic vascular plants: No significant effects on aquatic vascular plants were observed for acynonapyr up to its functional solubility under the test conditions. The acynonapyr end-use product formulation inhibited the growth rate and yield of aquatic plants; however, the EC_{50} remained greater than the highest tested concentration of 2.9 mg a.i./L. The RQ for aquatic vascular plants resulting from exposure to acynonapyr exceeds the LOC at the screening level due to the solubility constraints previously explained in this section; however, the RQ resulting from exposure to the end-use product does not exceed the LOC at the screening level. The risk to aquatic vascular plants from the use of acynonapyr has been determined to be acceptable.

4.3 Environmental incident reports

Acynonapyr is a new active ingredient pending registration for use in Canada. As of 6 June 2025, no environmental incidents involving acynonapyr had been submitted to the PMRA.

5.0 Value

Value information reviewed in support of Kodama Miticide consisted of 27 efficacy trials, which included 23 field trials on European red mite, twospotted spider mite, McDaniel spider mite, and Pacific spider mite; and 4 laboratory bioassays on twospotted spider mite. Overall, the submitted trials were sufficient to demonstrate that Kodama Miticide provides control of Tetranychid mites at an application rate of 0.58 L of product per hectare. As product performance was tested against four different Tetranychid mite species, the information provided was sufficient to support a general claim of Tetranychid mites. The submitted laboratory trials were sufficient to

support a claim that Kodama Miticide provides knockdown of Tetranychid mites. As many of the submitted trials demonstrated extended control following one application of Kodama Miticide, a residual control claim was also supported. Non-safety adverse effects (for example, phytotoxicity) were not observed in any of the submitted efficacy trials.

Alternative active ingredients for controlling various Tetranychid mites on pome fruits include mineral oil, spirodiclofen, acequinocyl, cyflumetofen, fenpropathrin, fenazaquin, pyridaben, abamectin, cyantraniliprole, phosmet, fluazinam, and clofentezine. Kodama Miticide has value, as it is a new active ingredient with a novel MOA that will aid in resistance management. The development of resistance is a major concern for Tetranychid mites, which are well documented to have resistance to various MOAs. Kodama Miticide is expected to be compatible with current management practices, including IPM.

The submitted value information was sufficient to support a claim that Kodama Miticide will provide knockdown and residual control of Tetranychid mites (including European red mite, twospotted spider mite, McDaniel spider mite, and Pacific spider mite) with one application of 0.58 L of product per hectare in Crop Group 11-09: Pome Fruits.

Supported uses are summarized in Appendix I, Table 34.

6.0 Pest Control Product Policy considerations

6.1 Assessment of the Active Ingredient under the Toxic Substances Management Policy

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

During the review process, acynonapyr and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[7] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that acynonapyr and its transformation products do not meet all of the TSMP Track 1 criteria.

Please refer to Appendix I, Table 35, for further information on the TSMP assessment.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[8] The list is

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

[8] SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

used as described in the PMRA Science Policy Note SPN2020-01[9] and is based on existing policies and regulations, including the *Toxic Substances Management Policy* and *Formulants Policy*,[10] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under CEPA, 1999, (substances designated under the *Montreal Protocol*).

The PMRA has reached the conclusion that Acynonapyr Technical does not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. The end-use product, Kodama Miticide, contains the preservative 1,2-benzisothiazolin-3-one which contains low levels of dioxins and furans. These are being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of the TSMP.

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

7.0 Proposed regulatory decision

Health Canada's PMRA, pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of Acynonapyr Technical and Kodama Miticide, containing the active ingredient acynonapyr, to control Tetranychid mites on Crop Group 11-09: Pome Fruits.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

Additional information being requested

Since this technical product is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production will be required as post-market information after registration.

[9] PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under paragraph 43(5)(b) of the *Pest Control Products Act.*

[10] DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

List of abbreviations

^{14}C	carbon-14 radioactive isotope
♀	female
♂	male
ε	molar absorption coefficient
∑	sum
λ	wavelength
λ_{max}	wavelength of maximum absorption
±	plus-or-minus
↑	increased
↓	decreased
=	equal to
>	greater than
<	lesser than
≥	greater than, or equal to
≤	lesser than, or equal to
µg	microgram
%	percent
#	number
µg	microgram
°C	degree Celsius
°N	degree North
A	applicator
AB	airblast
abs.	absolute
a.i.	active ingredient
AD	administered dose
ADD	absorbed daily dose
ADI	acceptable daily intake
AEROWIN	Aerosol Sorption Program for Microsoft Windows
A/G	albumin/globulin
AHETF	Agricultural Handlers Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AOPWIN	Atmospheric Oxidation Program for Microsoft Windows
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	area under the curve
AUGC	area under the growth curve
BAF	bioaccumulation factor
BAF_K	kinetic bioaccumulation factor
BBCH	Biologische Bundesanstalt, Bundessortenamt and Chemical industry (scale is used to identify the phenological development stages of plants)
BCF	bioconcentration factor

BCF_{KGL}	growth-corrected kinetic bioconcentration factor normalized for lipid content
BMF_{Lg}	growth and lipid-corrected biomagnification factor
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CA	California
CAF	composite assessment factor
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
cm	centimetre
cm^2	square centimetre
cm^3	cubic centimetre
CO_2	carbon dioxide
CR	chemical-resistant
CTA	comparative thyroid assay
d	day(s)
DAT	days after treatment
DBH	days before harvest
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DFOP	double first-order in parallel
DIR	Regulatory Directive
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
ELS	early-life stage
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
F1	first filial generation
F2	second filial generation
fc	food consumption
FIR	food ingestion rate
FOB	functional observational battery
g	gram
GD	gestation day
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practices
GPT	glutamic pyruvic transaminase
GUS	groundwater ubiquity score
h	hour(s)
ha	hectare
HAFT	highest average field trial
HC	historical control
HCT	hematocrit

HDPE	high-density polyethylene
HDT	highest dose tested
HGB	hemoglobin
HPLC-MS/MS	High-performance liquid chromatography method with tandem mass spectrometry
ID	identification
IORE	indeterminate order rate equation
IPM	Integrated Pest Management
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
J	Joules
K	potassium
KCa2	calcium-activated potassium (channel)
kg	kilogram
K_d	soil-water partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
KOWWIN	Octanol-Water Partition Coefficient Program for Microsoft Windows
kPa	kilopascal
L	litre
LADD	lifetime average daily dose
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LDH	lactate dehydrogenase
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	lowest observed effect concentration
LOED	lowest observed effect dose
LOEL	lowest observed effect level
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m^2	square metre
m^3	cubic metre
MAS	maximum average score
MBq	megabecquerel
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MIS	maximum irritation score
mg	milligram
mL	millilitre
M/L	mixer/loader
M/L/A	mixer/loader/applicator
MOA	mode of action
MOE	margin of exposure
mol	mole
MPHG	mechanically-pressured handgun
MPHW	manually-pressurized handwand
MRL	maximum residue limit

MW	molecular weight
n	number of independent trials
NA	not applicable
NAFTA	North American Free Trade Agreement
NHANES/ WWEIA	National Health and Nutrition Examination Survey/What We Eat in America
ND	not detected
NER	non-extractable residues
nm	nanometres
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOER	no observed effect rate
NY	New York
OC	organic carbon content
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
P	parental generation
Pa	Pascal
PCPA	*Pest Control Product Act*
PES	post extraction solids
pH	measure of the acidity or basicity of an aqueous solution
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PMRL	Proposed Maximum Residue Limit
PND	postnatal day
PPE	personal protective equipment
ppb	parts per billion
ppm	parts per million
PRO	Regulatory Proposal
PROD	7-pentoxyresorufin-O-depentylase
PXR	pregnane X receptor
PWC	Pesticide Water Calculator
PYO	pick-your-own
q_1*	cancer potency factor
RAC	raw agricultural commodity
RBC	red blood cells
REI	restricted-entry interval
rel.	relative
RQ	risk quotient
S9	mammalian metabolic activation system
SC	suspension concentrate
SDEV	standard deviation
SFO	single first-order
SI	Statutory Instrument
SMILES	Simplified Molecular Input Line Entry System

SPN	Science Policy Note
STMdR	supervised trial median residue
T3	triiodothyronine
T4	thyroxine
TC	transfer coefficient
T_{max}	time of maximum concentration
TP	transformation product
t_R	representative half-life
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	*Toxic Substances Management Policy*
TWA	time-weighted average
UDP-GT	uridine diphosphate glucuronyltransferase
UF	uncertainty factor
UK	United Kingdom
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
WBC	white blood cells
WD	work days
wk	week(s)
w/v	weight per volume
wt	weight
yr	year(s)

Appendix I Tables

Table 1a Residue analysis in environmental media

Matrix	Method ID	Analyte	Method type	LOQ	Reference
Soil	12791.6381	Acynonapyr	HPLC-MS/MS	5 ppb	PMRA No. 3324582 and 3324584
		AP			
		AY			
Sediment	12791.6333	Acynonapyr		0.05 ppm	PMRA No. 3324581
		AP			
		AY			
Water	12791.6382	Acynonapyr		0.1 µg/L	PMRA No. 3324580 and 3324585
		AP			
		AY			

Table 1b Residue analysis in plant matrices

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ	Reference
Plant commodities					
Enforcement/ data-gathering method	Apple (whole apple fruit, wet apple pomace and apple juice) and pear (whole pear fruit)	Acynonapyr, AP, AP-2	HPLC-MS/MS	0.01	Study No. 12791.6393, PMRA No. 3324404
	Almond nutmeat, almond hulls, roasted almond, and almond oil		HPLC-MS/MS	0.01	Study No. 12791.6387, PMRA No. 3386721
	Dried hop cones, hop flocs, spent hops, yeast, and beer		HPLC-MS/MS	0.01	Study No. 12791.6389, PMRA No. 3386717
	Orange whole fruit, lemon whole fruit, grapefruit whole fruit, orange juice, dried orange pulp, and orange oil		HPLC-MS/MS	0.01	Study No. 12791.6390, PMRA No. 3386718

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ	Reference
Independent laboratory validation of enforcement method	Whole orange, whole lemon, whole grapefruit, dried orange pulp, orange juice, orange oil, almond nutmeat, almond hulls, roasted almond, almond oil, dried hops, spent hops, brewers' yeast, spent yeast (flocs), and beer	Acynonapyr, AP, AP-2	HPLC-MS/MS	0.01	Study No. 3202886, PMRA No. 3386719 and 3386720
Radiovalidation	Extraction solvents used in the proposed enforcement method were similar to those used in the metabolism studies (acetone: ultra-purified water). Given the similarities of these extraction solvents, it is assumed that the enforcement method will be successful in extracting bioinccured residues of acynonapyr, AP, and AP-2.				

Table 2 Identification of select metabolites of acynonapyr

Metabolite	Chemical name	Source
AY	2-hydroxy-5-(trifluoromethyl)pyridine	Identified in the rat, crop residue, and environmental fate studies (formed by photolysis on plant leaves, soil, and water)
AY-glucuronide	2-hydroxy-5-(trifluoromethyl)pyridine-glucuronide	Identified in the rat and crop residue studies
AY-1	3-hydroxy-5-(trifluoromethyl)-2-pyridine	Identified in the rat and crop residue studies
AY-1-glucuronide	3-hydroxy-5-(trifluoromethyl)-2-pyridine-glucuronide	Identified in the rat
AY-1-sulphate	3-hydroxy-5-(trifluoromethyl)-2-pyridine-sulphate	Identified in the rat
AY-1-Glc	5-(trifluoromethyl)-2-pyridon-3-yl ß-D-glucopyranoside	Identified in the rat and crop residue studies
AY-5	6-hydroxynicotinic acid	High pH hydrolysis product – not found in soil, water, or crops
AP	3-*endo*-[2-propoxy-4(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonane	Identified in the rat, crop residue, and environmental fate studies (formed by photolysis on plant leaves, soil, and water)
AP-1	3-*endo*-[2-hydroxy-4-(trifluoromethyl) phenoxy]-9-azabicyclo[3.3.1]nonane	Identified in the rat

Metabolite	Chemical name	Source
AP-OH	3-*endo*-[2-propoxy-4(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonane-hydroxide	Identified in the rat
AP-1-OH	3-*endo*-[2-hydroxy-4-(trifluoromethyl)-phenoxy]- 9-azabicyclo[3.3.1]nonane-hydroxide	Identified in the rat
AP-1-OH glucuronide	3-*endo*-[2-hydroxy-4-(trifluoromethyl)-phenoxy]- 9-azabicyclo[3.3.1]nonane-hydroxide-glucuronide	Identified in the rat
AP-4	3-*endo*-[2, 5-dihydroxy-4-(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonane	Identified in the rat
AP-4-glucuronide	3-*endo*-[2, 5-dihydroxy-4-(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonane -glucuronide	Identified in the rat
AP-2	3-*endo*-[2-propoxy-4-(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonane-9-carbaldehyde	Identified in the rat and crop residue studies
AH	2-propoxy-4-(trifluoromethyl)phenol	Low pH hydrolysis product – not found in soil, water, or crops

Table 3 Toxicology reference values for use in health risk assessment for acynonapyr

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
Acute dietary (females 13–49 yrs old; infants, and children up to 12 yrs old)	2-generation dietary reproductive toxicity in the rat	Reproductive NOAEL (♀) = 30 mg/kg bw/day Based on stillbirths, and early post-natal death of pups (PND 0)	1000[2,3]
ARfD (females 13–49 yrs old; infants, and children up to 12 yrs old) = 0.03 mg/kg bw			
Chronic dietary	1-yr oral (capsule) toxicity in the dog	NOAEL = 4 mg/kg bw/day Based on reduced bw and bwg	300[3]
ADI = 0.01 mg/kg bw/day			
Dermal and inhalation (short- to intermediate-term)[4]	2-generation dietary reproductive toxicity in the rat	Adjusted offspring NOAEL = 1.5 mg/kg bw/day, based on a NOAEL of 5.9 mg/kg bw/day corrected for 25% oral absorption	300[3]

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
		Based on reduced pup bw and clinical signs in pups (dehydration, cold to touch)	
Aggregate residential – oral and dermal[4] (short-term)	2-generation dietary reproductive toxicity in the rat	Common endpoints: reduced pup bw and clinical signs in pups (dehydration, cold to touch) Oral: offspring NOAEL = 5.9 mg/kg bw/day Dermal: adjusted offspring NOAEL = 1.5 mg/kg bw/day	Oral: 300[3] Dermal: 300[3]
Cancer	Evidence of treatment-related tumours in mice (hepatocellular adenomas and hemolymphoreticular tissue lymphomas in males) and rats (thyroid follicular cell adenomas, mesenteric lymph node hemangiomas combined with hemangiosarcomas, skin fibromas combined with fibrosarcomas, and brain astrocytomas in males). The overall weight of evidence to support a proposed MOA involving CAR/PXR activation for both the liver tumours in mice and the thyroid tumours in rats was considered inadequate. Overall, a linear low dose extrapolation (q_1*) approach to the cancer risk assessment was deemed appropriate. Oral route: q_1* = 2.5E-2 (mg/kg bw/day)$^{-1}$ based on the combined incidence of mesenteric lymph node hemangioma and hemangiosarcoma in male rats. Dermal and inhalation routes: q_1* = 4.9E-2 (mg/kg bw/day)$^{-1}$ based on the combined incidence of mesenteric lymph node hemangioma and hemangiosarcoma in male rats and the application of a fourfold adjustment factor to account for the low (25%) oral absorption.[4]	

1 CAF refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

2 A threefold PCPA factor was applied when using a point of departure for serious effects in the young.

3 A threefold database UF was applied for the potential uncertainties due to the lack of a DNT study or an assessment of potential endocrine/thyroid hormone perturbation in the young.

4 Since an oral NOAEL was selected, a dermal absorption factor of 10%, based on the in vivo rat dermal absorption data, and an inhalation absorption factor of 100% (default value) were used in route-to-route extrapolation. The oral dose administered in the toxicity study was corrected by a factor of 25% to account for low oral absorption in order to extrapolate to the dermal and inhalation routes.

Table 4 Toxicity profile of technical acynonapyr

Effects observed in both sexes are presented first, followed by sex-specific effects in males, then in females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights, unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Unless otherwise specified, studies listed in this table are considered acceptable according to the PMRA Information Note: Determining Study Acceptability for use in Pesticide Risk Assessments (28 March 2024 (Amended from 2019 version)).

Study type / Animal / PMRA No.	Study results
Toxicokinetic studies	
Toxicokinetics (excretion kinetics) Wistar rat PMRA No. 3324370	**Acceptable with limitations** Acynonapyr radiolabelled at the [azabicyclo-1,5-^{14}C] position was administered as a single oral dose of 3 mg/kg bw via gavage. **Excretion:** The majority of radioactivity was excreted in the feces in both sexes (77/83% of the AD in ♂/♀). Urinary excretion accounted for 18/13% of the AD in ♂/♀. Excretion was rapid, with the majority of recovered radioactivity excreted in the first 48 h. No radioactivity was recovered in expired air. Unchanged acynonapyr was detected in feces at up to 23% of the AD. The metabolite AP was also detected in fecal samples at up to 31% of the AD. **Metabolism:** The main radioactive component detected in urine was a di-hydroxylated AP conjugate, identified as AP-4-glucuronide, accounting for up to 10% of the AD. At least 18 other radiolabelled components were detected (not further identified), but all were minor in nature (none were >4.6% of the AD). The results of this study suggest that [azabicyclo-1,5-^{14}C]-acynonapyr is metabolized by cleavage of the trifluoromethyl pyridinol moiety to give AP. AP is then metabolized by hydroxylation to give AP-4 (not detected), then conjugated to give AP-4-glucuronide. **Limitations:** Only one dose level used, examinations were limited.
Toxicokinetics (absorption, distribution, metabolism, elimination) Wistar rat	Acynonapyr radiolabelled at the [pyridine-2,6-^{14}C] position was administered as a single oral dose of 3 or 300 mg/kg bw via gavage. **Absorption:** Absorption was rapid at the low dose, with plasma T_{max} of 1 h in both sexes. Absorption was slightly slower at the high dose, with plasma T_{max} of 6/14 h in ♂/♀.

Study type / Animal / PMRA No.	Study results
PMRA No. 3328880 and 3328884	Absorption was higher at 3 mg/kg bw than at 300 mg/kg bw. Based on radioactivity recovered in urine, bile, and carcass in bile duct-cannulated rats, absorption at 48 h post-dose was 65/68% of the AD in ♂/♀ at 3 mg/kg bw, and 29/39% of the AD in ♂/♀ at 300 mg/kg bw. AUC values were slightly higher in ♀ than in ♂ (1.4-fold in plasma, 1.7-fold in whole blood). **Distribution:** Radiolabel was rapidly and widely distributed, with the highest concentration found in the fat at the end of sampling. Tissue distribution was similar in both sexes, although concentrations were often higher in ♀. **Elimination:** Most of the radioactivity (>90% of the AD) was eliminated in urine and feces within 48 h. In intact rats, elimination of radioactivity occurred primarily via urine at 3 mg/kg bw (64/52% of the AD in ♂/♀ after 168 h), and via feces at 300 mg/kg bw (80/75% of the AD in ♂/♀ after 168 h). In bile duct-cannulated rats, 6/7% and 4/1% of the AD was eliminated in bile in ♂/♀ at 3 and 300 mg/kg bw, respectively. The half-life of elimination from plasma was 11–12 h for all dose groups. The half-life of elimination from tissues was about 20–60 h for most tissues in all groups. The longest half-life was observed in the fat (289/158 h and 134/595 h in ♂/♀ at the low and high dose, respectively). **Metabolism:** Unchanged acynonapyr was the main component detected in feces for all dose groups, and accounted for a maximum of 38% and 65% of the AD for 3 and 300 mg/kg bw dose groups, respectively. AY was the only metabolite identified in feces, accounting for 8–11% of the AD. The main component detected in urine was AY (59/35% of AD in ♂/♀ at 3 mg/kg bw, 20/19% of AD in ♂/♀ at 300 mg/kg bw). Other metabolites in urine included AY-1-sulphate, AY-1, AY-1-glucuronide, and AY-glucuronide. There was evidence of a sex difference in metabolite distribution, as AY-1/AY-glucuronide was more prevalent in ♀ (8.3% and 5.1% of the AD at 3 and 300 mg/kg bw, respectively), compared to ♂ (0.9% of the AD at 3 and 300 mg/kg bw). Metabolites detected in bile included AY, AY-1, and AY-glucuronide (AY-glucuronide considered to be most abundant). AY-glucuronide was the main component detected in plasma. Unchanged acynonapyr was also detected in plasma, more so in ♂ (6.4% of the TRR) compared to ♀ (1.6% of the TRR) at 300 mg/kg bw. AY was the main component in liver, kidney, and fat samples (AY-glucuronide was also detected). A distinct minor metabolite, hydroxylated acynonapyr (NA-89-OH), was detected in fat only.

Study type / Animal / PMRA No.	Study results
	Unchanged acynonapyr was also detected in fat only, with a larger portion in ♀ compared to ♂ (15/40% of the TRR in ♂/♀ at 3 mg/kg bw; 24/34% of the TRR in ♂/♀ at 300 mg/kg bw). This corresponds with the lower portion of AY in the fat of ♀ compared to ♂ at 3 mg/kg bw (76/56% of the TRR in ♂/♀) and lower portion of NA-89-OH in the fat of ♀ compared to ♂ at 300 mg/kg bw (7.4% of the TRR in ♂ and not detected in ♀). [Pyridine-2,6-^{14}C]-Acynonapyr is metabolized by cleavage of the trifluoromethyl phenol azabicyclic moiety to give AY, which is then metabolized by glucuronide conjugation and hydroxylation to give AY-glucuronide and AY-1. AY-1 is further metabolized by conjugation, resulting in the formation of AY-1-sulphate and AY-1-glucuronide. Hydroxylation of acynonapyr to give NA-89-OH is a minor pathway. Cleavage of the trifluoromethyl phenol azabicyclic moiety on NA-89-OH may also result in the formation of AY.
Toxicokinetics (absorption, distribution, metabolism, elimination) Wistar rat PMRA No. 3328882 and 3328886	Acynonapyr radiolabelled at the [phenyl-U-^{14}C] position was administered via gavage as a single oral dose of 3 or 300 mg/kg bw, or as repeated doses at 3 mg/kg bw for 14 d. **Absorption:** Absorption was rapid following a single low dose, with plasma T_{max} of 2–3 h, but was slightly slower at the high dose with a plasma T_{max} of 9–10 h. Absorption was higher following a single dose at 3 mg/kg bw than at 300 mg/kg bw. Based on radioactivity recovered in urine, bile, and carcass in bile duct-cannulated rats, absorption at 48 h was 25/23% of the AD in ♂/♀ at 3 mg/kg bw, and 15/13% of the AD in ♂/♀ at 300 mg/kg bw. AUC values in ♀ were slightly higher than in ♂ at the high dose (1.6-fold in plasma, 1.8-fold in whole blood). **Distribution:** Radiolabel was rapidly and extensively distributed, with the highest concentration found in the fat at the end of sampling. Distribution was similar in both sexes following single oral low and high doses. After multiple low doses, tissue distribution in ♀ was similar to that after single oral administration, but mean concentrations of radioactivity were higher in most tissues. **Elimination:** Following single oral doses, the majority of the administered radioactivity was eliminated in urine and feces within 48 h (>90% of AD). In intact rats, the majority of the radioactivity was eliminated in feces in both sexes (81/82% of the AD in ♂/♀ at 168 h after a single low dose and 95/97% of the AD in ♂/♀ at 168 h after a single high dose). Urinary excretion accounted for 14/13% of the AD in ♂/♀ at 168 h after a single low dose and 6/7% of the AD in ♂/♀ at 168 h after a single high dose. The excretion pattern was similar between the

Study type / Animal / PMRA No.	Study results
	sexes. Bile was not a major route of elimination (13/11% in ♂/♀ after single low dose and 6/5% in ♂/♀ after single high dose). The half-life of elimination from plasma was 34–39 h following a single low or single high dose. The half-life of elimination from tissues was generally between 30 and 90 h after a single dose and between 60 and 140 h after repeat doses. The longest half-life was observed in the fat after repeat dosing (3338 h). **Biliary recirculation:** Following single intraduodenal infusion of pooled bile to bile duct-cannulated rats, the amount of radioactivity eliminated in the bile was approximately 8–10% of the AD, indicating that up to 10% of the radiolabelled dose material is biliary re-circulated following an oral dose administration of [phenyl-U-^{14}C]-acynonapyr. **Metabolism:** Unchanged acynonapyr was detected in fecal samples from all dose groups and was the main component detected in the intact 300 mg/kg bw rats of both sexes (approximately 10/19% of the AD in ♂/♀ at 3 mg/kg bw and 59% of the AD in both sexes at 300 mg/kg bw). AP was also detected in the feces of all dose groups and was the main component in all but the intact 300 mg/kg bw groups (approximately 48% of the AD at 3 mg/kg bw and 31% at 300 mg/kg bw). The main component detected in urine was a hydroxylated AP-1 conjugate, identified as AP-4-glucuronide. A minor urinary metabolite AP-1-OH-glucuronide was also identified in all dose groups. At least 13 metabolites were detected in the bile and were minor in nature, with no single component accounting for >2.3% of the AD. Six of the components were identified as glucuronides, five of which were hydroxylated, including AP-4-glucuronide. Unchanged acynonapyr was main component detected in all plasma samples. AP and AP-4-glucuronide were also detected. In liver and kidney, AP was one of the main components detected. AP-1 was also detected at >5% of the TRR, and AP-4-glucuronide, AP-1-sulphate isomers, and AP-OH were detected at <5% of the TRR. Unchanged acynonapyr was the main component in all fat samples, except 300 mg/kg bw males, for which AP was the main component. AP and AP-2 were detected in fat at >5% of the TRR, with NA-89-OH also detected at <5% of the TRR. A higher proportion of unchanged acynonapyr was found in fat of ♀ (34% of the TRR versus 26% of the TRR in ♂ at a single dose of 3 mg/kg bw; 55% of the TRR versus 12% of the TRR in ♂ at a single dose of 300 mg/kg bw). The proportion of unchanged acynonapyr was higher after repeated doses, compared to a single dose.

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	[Phenyl-U-^{14}C]-acynonapyr is metabolized by cleavage of the trifluoromethyl pyridinol moiety to give AP. AP is further metabolized by cleavage of the propane group to give AP-1, which is further metabolized by sulphate or glucuronide conjugation. AP and AP-1 are metabolized by hydroxylation to give AP-OH and AP-1-OH, which are further metabolized by glucuronide conjugation. AP-1-OH may also occur through cleavage of propane from AP-OH. Hydroxylation of acynonapyr to give NA-89-OH and carbonylation of AP to give AP-2 are minor routes. Cleavage of the trifluoromethyl pyridinol moiety on NA-89-OH may also result in the formation of AP-OH.
Acute toxicity studies	
Acute oral toxicity (Fixed Dose Procedure) Sprague Dawley rat PMRA No. 3328833	LD_{50} > 2000 mg/kg bw (♂/♀) Clinical signs of toxicity included loss of hair on forelimbs and hindlimbs. **Low acute toxicity**
Acute dermal toxicity Sprague Dawley rat PMRA No. 3328835	LD_{50} > 2000 mg/kg bw (♂/♀) Clinical signs of toxicity included redness around the nose and near the application site. **Low acute toxicity**
Acute inhalation toxicity (nose-only) Sprague Dawley rat PMRA No. 3328839	LC_{50} > 4.79 mg/L Clinical signs of toxicity included fur staining, subdued behaviour and abnormal respiration. **Low acute toxicity**
Eye irritation New Zealand White rabbit PMRA No. 3328841	MIS = 2.0 at 1 h MAS = 0.44 **Minimally irritating**
Skin irritation New Zealand White rabbit	MIS and MAS = 0 **Non irritating**

Study type / Animal / PMRA No.	Study results
PMRA No. 3328843	
Dermal sensitization (maximization) Hartley guinea pig PMRA No. 3328845	**Acceptable with limitations** Results suggested a negative response; however, due to issues noted with the conduct of the study, and the fact that the formulated product produced a positive response in the Buehler assay, acynonapyr will be considered a potential dermal sensitizer. **Potential dermal sensitizer** **Limitations:** Difficulty in preparing homogeneous and injectable solutions, insufficient evidence that dose levels tested were adequate.
Short-term toxicity studies	
28-d oral toxicity (diet) CD-1 mouse PMRA No. 3328849	NOAEL = 113/137 mg/kg bw/day (♂/♀) LOAEL = 1172/1384 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ bilirubin, ↓ HGB, ↑ reticulocytes, ↑ liver wt, ↑ adrenal wt, ↑ spleen wt, ↑ hepatocellular hypertrophy, ↑ erythropoiesis in spleen (♂/♀); ↓ RBC, ↓ HCT, ↓ albumin, ↓ A/G ratio, ↑ ALT, ↓ thymus wt (♂) Toxicokinetics: AP was below the limit of detection at all dose levels. At the LOAEL, acynonapyr and AY were detected. The ratio of AY to acynonapyr was 55/41% in ♂/♀.
90-d oral toxicity (diet) CD-1 mouse PMRA No. 3328853	NOAEL = 216/256 mg/kg bw/day (♂/♀) LOAEL = 1128/1270 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg, ↓ RBC, ↓ HGB, ↓ HCT, ↑ RBC distribution width, ↑ reticulocytes, ↑ ALT, ↑ AST, ↑ LDH, ↑ K, ↑ liver wt, ↑cortical hypertrophy in adrenals, ↑ hemopoiesis in spleen (♂/♀); ↑ bilirubin, ↑ rel. liver wt, ↑ spleen wt, ↑ hemopoiesis in the sternum, ↑ centrilobular hypertrophy in liver (♂); clinical signs in 2 ♀ (piloerection, dark/pale eyes, pale skin on extremities, limping, walking on tip toes, hunched body posture), ↑ WBC, ↑ bilirubin, ↓ triglycerides, ↓ albumin, ↑ rel. adrenal wt, ↑ centrilobular hypertrophy, ↑ prominent lobular architecture in liver (♀)
28-d oral toxicity (diet) Sprague Dawley rat PMRA No. 3328851	NOAEL = 48/53 mg/kg bw/day (♂/♀) LOAEL = 233/260 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ HGB, ↓ HCT, ↑ reticulocytes, ↑ total cholesterol, ↑ K, ↑ GPT, ↑ phospholipids, ↑ urinary pH, ↑ rel. liver wt, ↑ adrenal wt, ↑ rel. spleen wt, ↑ rel. thyroid wt, ↑ hepatocellular hypertrophy, ↑ erythropoiesis in spleen, ↑ follicular cell hypertrophy in thyroid, vacuolar change in adrenals (♂/♀); ↓ MCV, ↓ MCH, ↑ platelet, ↑ prothrombin time, ↑ abs. spleen wt, (♂); ↓ bwg, ↓ RBC, ↑ rel. kidney wt,

Study type / Animal / PMRA No.	Study results
	accumulation of foamy cells in lungs and lymph nodes, vacuolar change in thyroid and pancreas (♀) Toxicokinetics: AP was below the limit of detection at all dose levels. At the LOAEL, blood levels of acynonapyr in ♀ at were nearly twofold higher than that of ♂, and the concentration of AY was 47/38% lower than that of acynonapyr in ♂/♀.
90-d oral toxicity (diet) Wistar rat PMRA No. 3328855	NOAEL = 17/21 mg/kg bw/day (♂/♀) LOAEL = 69/84 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bwg, ↓ RBC, ↑ MCV, ↑ reticulocytes,↑ rel. liver wt, histopathological findings in kidney (basophilic tubules, brown pigment) (♂/♀); ↑ phosphorus, ↑ rel. kidney wt, inflammatory cell infiltration of the kidney (♂); ↑ abs. liver wt, ↑ kidney wt, ↑ spleen wt (♀)
90-d oral toxicity (diet) Sprague Dawley rat PMRA No. 3328857	NOAEL = 15/18 mg/kg bw/day (♂/♀) LOAEL = 61/73 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ rel. liver wt, ↑ hepatocellular hypertrophy (♂/♀); ↑ urine pH (♂); ↓ bw, ↓ bwg, ↓ RBC, ↓ HGB, ↓ HCT, ↑ reticulocytes, ↑ rel. spleen wt, ↑ rel. kidney wt, ↑ follicular cell hypertrophy in thyroid (♀)
28-d oral toxicity (capsule) (dose range-finding) Beagle dog PMRA No. 3328860	**Acceptable with limitations** NOAEL and LOAEL not established ≥200 mg/kg bw/day: ↑ MCV, ↑ reticulocytes, ↑ hemopoiesis/extramedullary hemopoiesis in the sternum and spleen (♂/♀); loose/liquid feces (♂); ↓ bwg, ↓ fc, ↑ rel. liver wt, ↓ thymus wt, scattered foamy alveolar macrophages in lung, adrenal cortical vacuolation of zona fasciculata (this dose only), germinal center vacuolation in the mandibular and mesenteric lymph nodes (this dose only) (♀) 1000 mg/kg bw/day: ↓ RBC, ↓ HGB, ↓ HCT, ↑ MCV, ↑ reticulocytes, ↑ ALP (♂/ ♀); ↓ bwg, ↓ fc, ↑ ALT, bilirubin (♂); ↓ thyroid wt (♀) Toxicokinetics: Systemic exposure to acynonapyr, AP, and AY increased with dose; however, the increase was not proportional to the dose. T_{max} was reached within 4–8 h, 4–12 h, and 4–10 h for acynonapyr, AP, and AY, respectively. Systemic exposure to acynonapyr and AY following repeat dosing was generally similar to Day 1. Systemic exposure to AP increased slightly following repeat dosing. Acynonapyr was more prevalent than its metabolites. AP was more abundant than AY. There was no major sex difference. **Limitations:** Dose-range finding study with small group sizes.

Study type / Animal / PMRA No.	Study results
90-d oral toxicity (capsule) Beagle dog PMRA No. 3328862	NOAEL = 10 mg/kg bw/day (♂/♀) LOAEL = 50 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bwg, ↑ platelets, ↑ reticulocytes, ↑ ALP, ↑ liver wt, ↑ hemopoiesis in femur and sternum (♂/♀); ↓ lymphocytes, ↑ neutrophils, ↑ adrenal wt, ↑ spleen wt, lymphocytolysis and vacuolation (in the mandibular lymph node, mesenteric lymph node, and gut; associated lymphoid tissue), spleen white pulp vacuolation and capsular fibrosis (♂); ↓ bw, ↓ fc, ↑ bilirubin (♀)
52-wk oral toxicity (capsule) Beagle dog PMRA No. 3328864	NOAEL = 4 mg/kg bw/day (♂/♀) LOAEL = 20 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg, ↓ RBC, ↓ HGB, ↓ HCT, ↑ MCV, ↓ RBC distribution width, ↑ ALP, ↑ cellularity of the hemopoietic tissue in the sternal bone marrow, ↑ numbers of brown-pigmented macrophages in mandibular lymph node (♂/♀); thinness (1♂), ↓ fc, ↑ number of tingible body macrophages and vacuolated macrophages in mandibular lymph node (♂)
3-d dermal toxicity (dose range-finding) Sprague Dawley rat PMRA No. 3324373	**Acceptable with limitations** NOAEL and LOAEL not established No treatment-related clinical signs or effects on bw were observed. Toxicokinetics: The most abundant circulating compound in blood was acynonapyr, followed by metabolite AY and then small amounts of metabolite AP. The amount of circulating compounds increased with dose level, but only about twofold as opposed to 10-fold as per the dose progression. **Limitations:** Dose-range finding study with only two dose levels, small group sizes and limited assessments.
28-d dermal toxicity (with 14-d recovery period) Sprague Dawley rat PMRA No. 3324372	NOAEL = 1000 mg/kg bw/day (♂/♀) LOAEL not established No adverse treatment-related findings at any dose level. Toxicokinetics: Plasma levels of acynonapyr and metabolites AP and AY increased in a dose-proportional manner. The most abundant circulating compound was acynonapyr, followed by metabolite AY and then small amounts of metabolite AP.
90-d dermal toxicity – waiver request PMRA No. 3324374	**The waiver was accepted based on the following:** Low toxicity was observed in the 28-d dermal toxicity study, and conduct of a 90-d dermal study would not likely yield critical findings, given that effects on reproduction and the developing young were identified as the critical endpoints for human health risk assessment in oral toxicity studies.

Study type / Animal / PMRA No.	Study results
90-d inhalation toxicity – waiver request PMRA No. 3324368	**The waiver was accepted based on the following:** Acynonapyr exhibits low volatility and low acute inhalation toxicity. Conduct of a 90-d inhalation study would not likely yield critical findings, given that effects on reproduction and the developing young were identified as the critical endpoints for human health risk assessment in oral toxicity studies.
Chronic toxicity and oncogenicity studies	
78-wk oral toxicity (diet) CD-1 mouse PMRA No. 3328703	NOAEL = not established/13 mg/kg bw/day (♂/♀) LOAEL = 79/342 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ incidence of hemolymphoreticular tissue lymphoma (♂); ↑ incidence of nephropathy in kidney, ↑ uterine weight, ↑ incidence of necrosis of liver, enlarged uterus (♀) Effects of note at a dose level above the LOAEL: ↑ incidence of hepatocellular adenoma (♂) **Evidence of tumourigenicity in males** Hemolymphoreticular tissue lymphoma (♂): 0%, 10%, 12%, 18% (HC range: 2–8%, HC mean: 5%) Hepatocellular adenomas (♂): 8%, 4%, 6%, 20% (HC range: 8–28%, HC mean: 16%)
2-yr oral toxicity (diet) Wistar rat PMRA No. 3328713	NOAEL = 12/16 mg/kg bw/day (♂/♀) LOAEL = 45/61 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ chronic progressive nephropathy (♂/♀); ↑ abnormal breathing sounds, ↑ thyroid wt, ↑ erythrophagocytosis in the mandibular lymph node, ↑ dark focus in the liver and liver congestion, ↑ hyperplasia of islet of Langerhans, ↑ incidence of angiomatous hyperplasia and hemangioma in mesenteric lymph node, ↑ dark focus in the thymus associated with thymus congestion, ↑ incidence of follicular cell adenoma in thyroid gland (♂); ↓ bw, ↓ bwg, ↑ thymus congestion, ↑ incidence of focal hyperplasia of follicular cells in thyroid gland, ↑ kidney wt, ↑ renal tubular basophilia (♀) **Evidence of tumourigenicity in males** Thyroid follicular cell adenoma (♂): 1.9%, 7.7%, 9.6%, 13.5% (HC range: 1.9–11.1%, HC mean: 6.6%) Mesenteric lymph node hemangioma (♂): 7.7%, 5.8%, 13.5%, 23.1% (HC range: 3.8–19.2%, HC mean: 7.0%) Mesenteric lymph node hemangiosarcoma (♂): 9.6%, 5.8%, 1.9%, 5.5% (HC range: 0–7.7%, HC mean: 2.8%) Mesenteric lymph node hemangioma and hemangiosarcoma combined (♂): 17.3%, 11.5%, 15.4%, 28.8%

Study type / Animal / PMRA No.	Study results
	Skin fibroma (♂): 0%, 4.3%, 0%, 3.8% (HC range: 0–7%) Skin fibrosarcoma (♂): 0%, 0%, 0%, 3.8% (HC range: 0–1%) Skin fibroma and fibrosarcoma combined: 0%, 4.3%, 0%, 7.7% Astrocytoma of the brain (♂): 0%, 0%, 0%, 3.8% (HC range: 0–3.8%, HC mean: 1.5%)
Developmental and reproductive toxicity studies	
Developmental/ reproduction toxicity (diet) (dose range-finding) Sprague Dawley rat PMRA No. 3328872	**Acceptable with limitations** NOAEL and LOAEL not established **Parental toxicity** ≥38/51 mg/kg bw/day (♂/♀): adverse clinical observations during lactation (hunched posture, urine-stained abdominal fur, thin body condition in 1–2 rats), ↓ RBC, ↓ HGB, ↓ HCT, ↓ platelets, ↑ adrenal wt, degeneration of the adrenal gland and alveolar histiocytic infiltration (P ♀), ↑ adrenal wt, ↑ liver wt, ↑ spleen wt, hematopoiesis of the liver (F1 ♀); ↓ terminal bw, lymphoid depletion and histiocytic infiltration in mesenteric lymph node, lymphoid depletion in spleen (F1 ♂) ≥141/179 mg/kg bw/day (♂/♀): adverse clinical observations during precohabitation (dehydration, thin body condition, hunched posture) and gestation (dehydration, thin body, hunched posture, chromorhinorrhea, pale, ungroomed coat), 2 rats found dead on GD 17 and 25 (during gestation), ↓ bw, ↓ bwg, ↓ fc, (in 2 rats found dead; incidences of sinusoid histiocytic infiltration of the mesenteric lymph node, cardiomyopathy, lymphoid depletion of the mesenteric lymph node and spleen) (P ♀); clinical observations (dehydration, hunched posture, thin body condition), ↓ bw, ↓ bwg, ↓ fc, ↓ abs. liver wt, ↓ abs. kidney wt, ↓ abs. spleen wt, ↑ rel. liver wt, ↑ rel. kidney wt, ↑ rel. adrenal wt, cardiomyopathy, alveolar histiocytic infiltration, sinusoid histiocytic infiltration and lymphoid depletion of the mesenteric lymph node, necrosis of the skeletal muscle, histiocytic infiltration of the marginal zone and lymphoid depletion of the spleen, and centrilobular hypertrophy (P ♂) 232 mg/kg bw/day (P ♂): clinical observations (dehydration, hunched posture, thin body condition, scan/reduced feces, pale ears, ↓ motor activity, chromorhinorrhea, hyperpnea, tachypnea, ataxia, bradypnea, piloerection) resulted in early termination of this group after approximately 2 weeks of exposure (prior to mating), ↓ bw, bw loss, ↓ fc, increased incidence of degeneration of the adrenal gland, cardiomyopathy, alveolar histiocytic infiltration, sinusoid histiocytic infiltration of the mesenteric lymph node, necrosis of the skeletal muscle, histiocytic infiltration of the marginal zone of the spleen **Reproductive toxicity**

Study type / Animal / PMRA No.	Study results
	≥38/51 mg/kg bw/day (♂/♀): ↓ lactation index 141/179 mg/kg bw/day (P ♀): ↓ number of estrous cycles per 14 d, ↑ number of rats with six or more consecutive days of diestrus, ↑ number of days in cohabitation, ↓ fertility index, ↓ pregnancy rate, ↓ live fetuses (P ♀); ↓ abs. epididymides wt, ↓ abs. testes wt, ↑ rel. epididymides wt, ↑ rel. testes wt, ↑ number of days in cohabitation, ↓ number of rats mating, ↓ fertility index (P ♂) **Offspring toxicity** 51 mg/kg bw/day: delayed vaginal patency, ↑ bw at sexual maturity (♀) P generation rats in the highest dose group were either not pregnant, found dead, had a litter of all early resorptions, or had no surviving pups on the day of delivery. Therefore, no F1 generation pups were available for evaluation. **Limitations:** Dose range-finding study with small group sizes and limited assessments, no F1 pups available for evaluation at the highest dose.
2-generation reproductive toxicity (diet) Sprague Dawley rat PMRA No. 3328878	**Parental and F2 post-weaning toxicity** (select F2 animals dosed until 100 d old) NOAEL = 4.8/5.9 mg/kg bw/day (♂/♀) LOAEL = 24/30 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ pre-mating/post-weaning bw (F1, F2), ↓ post-weaning bwg (F2), ↑ rel. liver wt (P) (♂/♀); ↓ pre-mating bwg (P, F1) (♂); ↓ gestation and lactation bw (P), ↓ lactation bwg (P, F1), ↑ kidney wt (P), ↑ adrenal wt (P), ↓ abs. kidney wt (F1), ↑ incidence and severity of alveolar histiocytic infiltration in the lung (P), ↓ RBC, ↑ reticulocytes, ↓ HGB, ↓ HCT (♀) **Reproductive toxicity** NOAEL = 24/30 mg/kg bw/day (♂/♀) LOAEL = 62/74 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ duration of gestation (P), ↑ number of dams with stillborn pups (P), ↑ number of dams with all pups dying from PND 0–3 (P), ↑ days in cohabitation (F1), ↓ fertility index (F1), ↓ number of pregnant ♀ (F1), ↓ number of successful matings (F1), ↓ number of implantation sites/litter (F1 and F2 litters), ↓ number of pups delivered (F1 and F2 litters), ↓ live birth index (F1 and F2 litters), ↑ number of stillborn pups/litter (F1 and F2 litters), ↓ mean litter size (PND 0) (F1 and F2 litters), ↑ number of pups dying, missing, or cannibalized on PND 0 (F1 litters), ↓ anogenital distance in combined sexes (PND 0 and 21; F2) **Offspring toxicity** NOAEL = 5.9 mg/kg bw/day

Study type / Animal / PMRA No.	Study results
	LOAEL = 30 mg/kg bw/day Effects at the LOAEL: ↓ pup weight/litter (F1, PND 1–7), ↑ number of pups with dehydration and/or cold to touch (F1), ↓ abs. kidney wt (F1; ♂/♀), ↓ abs. uterus wt (with cervix and oviducts) (F2; ♀) Notable effects at HDT (74 mg/kg bw/day): ↓ viability index (F1/F2), ↑ number of pups dying, missing, or cannibalized (F1 PND 2-4; F2 PND 1-4 and 8-14), ↓ motor activity (F1), ↓ air righting reflex (F2), ↓ acoustic startle response (F2; PND 12), delayed sexual maturation (F1 ♂/♀; F2 ♂), ↓ anogenital distance in combined sexes (PND 0 and 21; F2) **No evidence of sensitivity of the young** **Evidence of serious effects in the young (reduced survival) in the presence of parental toxicity**
Developmental toxicity (gavage) – dose range-finding Sprague Dawley rat Full report not submitted; summary as reported by study author in main study under PMRA No. 3328866	**Acceptable with limitations** NOAEL and LOAEL not established **Maternal toxicity** 1000 mg/kg bw/day: ↓ bwg, ↑ early resorptions, ↑ post-implantation loss **Developmental toxicity** 1000 mg/kg bw/day: ↑ early resorptions, ↑ post-implantation loss, ↓ number of live fetuses **Limitations:** Dose range-finding study with limited assessments; full study report not provided.
Developmental toxicity (gavage) Sprague Dawley rat PMRA No. 3328866	**Maternal toxicity** NOAEL = 150 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Effects at the LOAEL: ↓ bw (GD 9–21) **Developmental toxicity** NOAEL = 150 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Effects at the LOAEL: ↓ fetal bw, reduced skeletal ossification site averages (per fetus per litter) for metatarsals and hindlimb phalanges **No evidence of sensitivity of the young** **No evidence of treatment-related malformations**
Developmental toxicity (gavage) – dose range-finding	**Acceptable with limitations** NOAEL and LOAEL not established **Maternal toxicity**

Study type / Animal / PMRA No.	Study results
New Zealand white rabbit PMRA No. 3328868	≥100 mg/kg bw/day: scant feces, ↓ bwg, ↓ fc 400 mg/kg bw/day: mortality of 1♀ (GD 16) and subsequent sacrifice of all surviving ♀ (GD 19 due to severely ↓ fc), thin body condition, no feces in cage pan, ↓ bw (GD 15–19), bw loss throughout the study. **Developmental toxicity** No observed effects up to 100 mg/kg bw/day (observations included sex, external abnormalities, early and late resorptions, live and dead fetuses, fetal bw). Examinations at the 400 mg/kg bw/day dose level were limited due to the early sacrifice of does. **Limitations:** Dose range-finding study with small group sizes and limited assessments of fetal development.
Developmental toxicity (gavage) New Zealand white rabbit PMRA No. 3328870	**Maternal toxicity** NOAEL = 15 mg/kg bw/day LOAEL = 50 mg/kg bw/day Effects at the LOAEL: Scant feces, early sacrifice of 1♀ on GD 20 (following abortion, bw loss, ↓ fc and clinical signs of toxicity including thin body condition, no feces in the cage pan, scant feces, abdominal distension, soft and liquid feces, dark red substance in the cage pan, mild dehydration, ungroomed coat, fecal-stained fur, and sparse hair coat on the limbs), bw loss when bwg corrected for gravid uterine wt, ↓ bwg (50 mg/kg bw/day: ↓ 9.1%, GD 6–29; 150 mg/kg bw/day: ↓ 27%, GD 6–29), ↓ fc (50 mg/kg bw/day: ↓ 6%, relative, GD 15–18, GD 24–29; 150 mg/kg bw/day: ↓ 17–28%, relative, GD 9–29) **Developmental toxicity** NOAEL = 15 mg/kg bw/day LOAEL = 50 mg/kg bw/day Effects at the LOAEL: ↓ bw (♀), ↓ ossification sites of the caudal vertebrae Effects at 50 mg/kg bw/day: spina bifida in one fetus (equivocal) **No evidence of sensitivity of the young** **Equivocal evidence of treatment-related malformations in the presence of maternal toxicity**
Genotoxicity studies	
Bacterial reverse mutation-preincubation method *S.* typhimurium (TA100, TA1535, TA98, TA1537),	**Negative ± metabolic activation** Treated up to a limit concentration Precipitation was observed at all concentrations in all strains in the first experiment and in the strains TA100, TA1535, and WP2 uvrA in the second experiment in the absence of metabolic activation. Precipitation was observed in strains TA98 and TA1537 in the presence of metabolic

Study type / Animal / PMRA No.	Study results
E. coli (WP2 uvrA) PMRA No. 3328723	activation in the first experiment. It was confirmed that the precipitate did not interfere with colony counting.
Mammalian cell gene mutation (in vitro) Thymidine kinase locus in mouse lymphoma L5178Y cells PMRA No. 3324371	**Negative ± metabolic activation** Tested up to an insoluble or cytotoxic concentration.
Mammalian chromosome aberration (in vitro) Human peripheral lymphocytes PMRA No. 3328737	**Negative ± metabolic activation** Tested up to cytotoxic concentrations.
Mouse bone marrow micronucleus test (in vivo) CD-1 mouse PMRA No. 3328739	**Negative** There were no signs of toxicity during the study.
Immunotoxicity studies	
Immunotoxicity – waiver request PMRA No. 3324366	**The waiver was accepted for this conditionally required study based on the following:** The lack of immunotoxicity present in the acynonapyr toxicity database.
Neurotoxicity studies	
Acute oral neurotoxicity (gavage)	NOAEL = 2000 mg/kg bw (HDT) LOAEL not established No adverse treatment-related effects. **No evidence of neurotoxicity**

Study type / Animal / PMRA No.	Study results
Sprague Dawley rat PMRA No. 3328847	
90-d neurotoxicity – waiver request PMRA No. 3324367	**The waiver was accepted for this conditionally required study based on the following:** There was no evidence of neurotoxicity in the acute neurotoxicity study in rats. In the 90-d and the 2-yr dietary studies in rats that included neurotoxicity assessments, limited effects suggestive of neurotoxicity were observed only at high doses that also resulted in overt systemic toxicity. Overall, the conduct of a 90-d neurotoxicity study in rats was not required as it is not likely to result in critical findings considering that effects on reproductive and the developing young were the most critical endpoints for human health risk assessment.
Special studies (non-guideline)	
Hepatocellular proliferation – time to peak effect Up to 21-d oral administration (diet) CD-1 mouse PMRA No. 3324369	**Acceptable with limitations** NOAEL not established Reportedly high AST and ALP after 4 and/or 8 d (consistent with hepatocellular hypertrophy) based on historical values; however, no concurrent control group was available for comparison and actual historical data were not provided. Hepatocellular hypertrophy, enlarged nuclei, and binucleation of hepatocytes were observed in all animals at all timepoints (mean severity grade increased with time). Nuclear membrane infolding/distortion (associated with hypertrophy) observed at sacrifice on Day 15 and 22. Number of Ki67 positive hepatocytes ↑ with time. No obvious difference between sacrifice on Day 8 and sacrifice on Day 22. In conclusion, the time of peak effect could not be established under the conditions of this study. **Limitations:** Only one dose level tested; no concurrent control group; historical control data not provided.
Hepatocellular proliferation – dose response study 14-d oral (diet) CD-1 mouse PMRA No. 3324364	**Acceptable with limitations** NOAEL not established (focus of study was assessment of liver weight and liver; liver samples were stained with Anti Ki67 to determine cell proliferation) ≥1000 ppm: ↑ hepatocellular hypertrophy 2500 ppm: ↑ single cell necrosis of hepatocytes No significant increase in hepatocellular proliferation (as measured by Ki67) was observed up to the top dose of the test item in this study.

Study type / Animal / PMRA No.	Study results
	Limitations: Test material intake not estimated; small group size; limited assessments.
Hepatic drug-metabolizing enzyme induction 7-d oral (diet) with 14-d recovery. Wistar rat (♀) PMRA No. 3328745	**Acceptable with limitations** NOAEL not established (focus of study was to evaluate expression of UDP-GT family genes in liver microsomes; assessments also included liver and thyroid wt, UDP-GT activity and T3, T4, and TSH levels). Non-recovery group ≥100 mg/kg bw/day: ↑ expression of Ugt1a6 and Ugt1a7 422 mg/kg bw/day: ↓ bwg, ↑ expression of Ugt1a1 There were no treatment-related changes in hepatic drug metabolizing enzyme (UDP-GT) activity or thyroid hormone levels. Increased expression of Ugt1 family genes not observed in recovery group, indicating reversibility. It was postulated that prolonged exposure to acynonapyr induces expression of Ugt1 family genes, followed by increased UDP-GT activity, leading to increased excretion of thyroid hormones, which results in thyroid lesions through a negative feedback mechanism. **Limitations:** Focused study with limited assessments and small group sizes.
Hepatic drug-metabolizing enzyme induction 7-d oral (diet) CD-1 mouse (♂) PMRA No. 3328747	**Acceptable with limitations** NOAEL not established (focus of study was to determine gene expression, and induction of major cytochrome P450s in the liver; liver microsomes were prepared, RNA extracted and stained with Ki-67) ≥17 mg/kg bw/day: ↑ expression of Cyp210 ≥388 mg/kg bw/day: ↑ P450 and PROD activity, ↑ hepatocellular hypertrophy, ↑ hepatocyte Ki-67 labeling index 1407 mg/kg bw/day: ↑ liver wt It was postulated that acynonapyr induces liver enzymes via CAR induction, similar to phenobarbital. **Limitations:** Focused study with limited assessments and small group sizes.
Evaluation of nephrotoxicity and hepatoxicity 7-d oral (diet) Sprague Dawley and Wistar rats	**Acceptable with limitations** NOAEL not established (focus of study was the assessment of kidney and liver toxicity; kidneys were stained with Ki-67 to assess cell proliferation and liver samples of ♀ Wistar rats were examined via electron microscopy to characterize hepatocellular vacuoles)

Study type / Animal / PMRA No.	Study results
PMRA No. 3328749 and 3328646	≥ approximately 350 mg/kg bw/day (both strains): brown urine, ↓ bw, ↓ bwg, ↓ fc, ↓reticulocytes, ↑ BUN, ↑ severity of single cell necrosis, ↑ accumulation of foamy cells in the lungs (♂/♀); ↓ spleen wt, decrease erythropoiesis in the spleen (♂); ↑ vacuolated lymphocytes, ↑ platelets (♀) ≥ 395/385 mg/kg bw/day (Wistar strain; ♂/♀): ↑ adrenal wt, vacuolation of acinar cells (♂/♀); ↑ platelets, ↑ vacuolated lymphocytes (♂); ↓ spleen wt, ↓ thymus wt, thyroid follicular cell hypertrophy (♀) ≥ 348/317 mg/kg bw/day (Sprague Dawley strain; ♂/♀): ↑ water intake, ↓ eosinophils, ↑ cholesterol (♂/♀); pale cloudy urine, ↓ triglycerides (♂); ↑ neutrophils (♀) Approximately 1300 mg/kg bw/day (both strains): clinical signs, ↓ protein, ↓ albumin, ↓ glucose, blood and leukocytes in the urine, vacuolar changes in adrenal glands, liver, and spleen, lymphoid hypoplasia in the spleen, Kupffer cell vacuolation, necrosis in the liver (♂); ↑ ALT and AST (♀) 1459/1420 mg/kg bw/day (Wistar strain, ♂/♀): Mortality (1♂, 2♀), ↓ HGB and HCT, ↑ neutrophils, ↑ GGT, ↓ ALP, ↑ urine protein concentration, ↑ liver wt, (♂/♀); ↓ lymphocyte, ↑ ALT and AST, ↓ thymus wt, follicular cell hypertrophy (♂); ↓ RBC, ↑ microgranuloma liver (♀) 1225/1260 mg/kg bw/day (Sprague Dawley strain; ♂/♀): ↓ lymphocytes, ↑ adrenal wt, vacuolation of acinar cells, microgranuloma of the heart (♂/♀); ↑ vacuolated lymphocytes, ↓ triglycerides, ↑ K, pale cloudy urine, ↑ ultimobranchial cyst in the thyroid (♀) There were no major sex or strain differences in the serum concentration of unchanged acynonapyr or metabolites. AP or AP-1 was the most prominent metabolite and the most prominent compound found in serum, depending on strain and dose. In the electron microscopic examination of liver samples from ♀ Wistar rats, no specific structures were observed in the vacuolation in the control group, suggesting lipid droplets. The vacuolation observed in the rats from the highest dose group contained spiral-shaped myelinoid bodies, in which lamellar membrane structures had accumulated, suggesting phospholipid deposition. **Limited evidence of increased susceptibility in females was observed.** Females were observed with increased incidences of follicular cell hypertrophy compared to males. ALT and AST activity and the increased liver weight observed in Wistar rats was more severe in females

Study type / Animal / PMRA No.	Study results
	compared to males. The effects on adrenal weight and vacuolar changes in the adrenal glands were more severe in females compared to males. **Limited evidence of increased susceptibility in the Wistar rats was also observed.** Effects only observed in Wistar rats include mortality, increased liver weights, higher GGT activity, anemia, and incidences of follicular cell hypertrophy. ALT and AST activity, and the severity of vacuolar changes in the adrenal glands were more severe in the Wistar rats. Vacuolation of acinar cells in the pancreas and increased adrenal weights were observed in Wistar rats but was not seen in Sprague Dawley rats. However, compound consumption was slightly higher in Wistar compared to Sprague Dawley rats, which may partially explain the difference in toxicity observed. **Limitations:** Focused study with limited assessments and small group sizes.
Determination of the need for a comparative thyroid assay (white paper) PMRA No. 3324365	Due to thyroid effects noted in high dose levels in the repeat dose studies in rats, the applicant assessed the need for a comparative thyroid assay (CTA) for acynonapyr using the criteria outlined in the USEPA's CTA Decision Framework (CLA briefing, 2018). These criteria include consideration of the dose levels causing effects on the thyroid in comparison to those selected as points of departure for human health risk assessment, and calculated margins of exposure. The lowest dose level causing effects on the thyroid was determined to be 12 mg/kg bw/day in Wistar male rats in the 2-yr dietary study, where non-adverse increases in thyroid weight were observed in the most sensitive strain. The proposed toxicology reference values provide margins of at least 2400 (for dermal and inhalation risk assessment) or 1200 (for chronic dietary assessment) to the dose levels at which effects on the thyroid were observed in the available studies.

Table 5 Toxicity profile of metabolites of acynonapyr

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study type / Animal / PMRA No.	Study results
Metabolite AP	
Acute oral toxicity (Acute Toxic Class) Sprague Dawley rat (♀)	LD_{50} > 300 mg/kg bw and ≤2000 mg/kg bw; cut-off of 500 mg/kg bw (♀)

Study type / Animal / PMRA No.	Study results
PMRA No. 3328628	Clinical signs of toxicity included salivation, bradypnea, decreased motor activity, incomplete eyelid opening, prone position, mucous feces, soiled wet fur around mouth, soiled perineal region. **High acute toxicity**
Bacterial reverse mutation – preincubaton method *S.* typhimurium (TA100, TA1535, TA98, TA1537), *E. coli* (WP2 uvrA) PMRA No. 3328725	**Negative ± metabolic activation** Tested up to cytotoxic concentrations
Metabolite AP-2	
Acute oral toxicity (Acute Toxic Class) Sprague Dawley rat (♀) PMRA No. 3328630	LD_{50} > 300 mg/kg bw and ≤2000 mg/kg bw; cut-off of 500 mg/kg bw (♀) Clinical signs of toxicity included decreased motor activity, staggering gait, decreased skin temperature, bradypnea, prone position, lateral position, mucous feces, soiled perineal region. **High acute toxicity**
28-d oral toxicity (diet) Sprague Dawley rat PMRA No. 3328640	NOAEL = 37/38 mg/kg bw/day (♂/♀) LOAEL = 122/127 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw, ↓ fc, ↓ creatinine, ↑ cholesterol, ↑ rel. adrenal wt, accumulation of foamy cells in the lung, hepatocellular hypertrophy, single cell necrosis in the kidney (♂/♀); mortality (1♂, Day 23), ↓ bwg, ↑ GGT activity, ↑ liver wt, ↑ rel. thyroid wt, ↓ abs. kidney wt, necropsy finding in ♂ found dead (large kidneys, dilated urinary bladder, dark red areas in thymus) (♂); ↓ bwg, ↓ ALP, ↑ BUN, ↑ inorganic phosphate, ↑ urinary leukocytes, ↑ urinary ketone bodies, ↑ liver wt, ↑ thyroid wt, follicular cell hypertrophy in thyroid (♀)
Bacterial reverse mutation *S.* typhimurium (TA100, TA1535, TA98, TA1537), *E. coli* (WP2 uvrA) PMRA No. 3328727	**Negative ± metabolic activation** Tested up to cytotoxic or insoluble concentrations

Study type / Animal / PMRA No.	Study results
Metabolite AY	
Acute oral toxicity (Acute Toxic Class) Sprague Dawley rat (♀) PMRA No. 3328632	LD_{50} > 300 mg/kg bw and ≤2000 mg/kg bw; cut-off of 500 mg/kg bw (♀) Clinical signs of toxicity included prone position, staggering gait, absent righting reflex, gait disturbance, incomplete eyelid opening, decreased skin temperature, lacrimation, lateral position, bradypnea. **High acute toxicity**
28-d oral toxicity (diet) Sprague Dawley rat PMRA No. 3328642	NOAEL = 318/320 mg/kg bw/day (♂/♀) LOAEL = 1152/1216 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw, ↓ bwg, bw loss (over first 2 days), ↓ fc, ↑ RBC, ↑ HCT, ↑ cholesterol, ↑ rel. liver wt., ↑ hepatocellular hypertrophy, ↑ nuclear inclusion bodies in proximal tubules (♂/♀); ↑ HGB (♂); ↓ ALP (♀)
90-d oral toxicity (diet) Sprague Dawley rat PMRA No. 3328644	NOAEL = 160/190 mg/kg bw/day (♂/♀) LOAEL = 464/524 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ rel. liver wt, nuclear inclusion bodies in proximal tubules of kidneys (♂/♀); ↓ bw, ↓ bwg (♀)
Bacterial reverse mutation *S.* typhimurium (TA100, TA1535, TA98, TA1537), *E. coli* (WP2 uvrA) PMRA No. 3328729	**Positive ± metabolic activation** Tested up to a limit concentration TA1535 positive at ≥2500 µg/plate with/without S9 WP2 uvrA positive at ≥185 µg/plate with S9 and at ≥313 µg/plate without S9
Mouse micronucleus test (in vivo) CD-1 mouse PMRA No. 3328741	**Negative** Clinical signs of toxicity included piloerection, ↓ spontaneous motor activity, crawling/prone position, stupor; bw loss was also observed.
Gene mutation assay in Muta Mouse (TG 488) Study assessed potential to induce gene mutation in the liver and glandular stomach PMRA No. 3328743	**Negative** Clinical signs of toxicity included prone position, piloerection, ↓ locomotor activity, irregular respiration. All mice dosed at 1000 mg/kg bw were euthanized on Day 6 due to severe toxicity.

Study type / Animal / PMRA No.	Study results
Metabolite AY-1-Glc	
Acute oral toxicity (Acute Toxic Class) Sprague Dawley rat (♀) PMRA No. 3328634	LD_{50} > 2000 mg/kg bw (♀) Clinical signs of toxicity included soft stool. **Low acute toxicity**
Bacterial reverse mutation *S.* typhimurium (TA100, TA1535, TA98, TA1537), *E. coli* (WP2 uvrA) PMRA No. 3328731	**Negative ± metabolic activation** Tested up to a limit concentration
Metabolite AY-5	
Acute oral toxicity (Acute Toxic Class) Sprague Dawley rat (♀) PMRA No. 3328636	LD_{50} > 2000 mg/kg bw (♀) Clinical signs of toxicity included watery stool. **Low acute toxicity**
Bacterial reverse mutation *S.* typhimurium (TA100, TA1535, TA98, TA1537), *E. coli* (WP2 uvrA) PMRA No. 3328733	**Negative ± metabolic activation** Tested up to a limit concentration
Metabolite AH	
Acute oral toxicity (Acute Toxic Class) Sprague Dawley rat (♀) PMRA No. 3328638	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity were noted. **Low acute toxicity**
Bacterial reverse mutation *S.* typhimurium (TA100, TA1535, TA98, TA1537), *E. coli* (WP2 uvrA) PMRA No. 3328735	**Negative ± metabolic activation** Tested up to a cytotoxic concentration

Table 6 Toxicity profile of Kodama Miticide containing acynonapyr

Effects are known or assumed to occur in both sexes unless otherwise noted.

Study type / Animal / PMRA No.	Study results
Acute oral toxicity (Acute Toxic Class) Sprague Dawley rat (♀) PMRA No. 3328925	LD_{50} > 2000 mg/kg bw (♀) Clinical signs of toxicity included soft stools. **Low acute toxicity**
Acute dermal toxicity Sprague Dawley rat PMRA No. 3328927	LD_{50} > 2000 mg/kg bw (♂/♀) Clinical signs of toxicity included redness near application site, perineal soiling, and loss of hair on forelimbs. **Low acute toxicity**
Acute inhalation toxicity (nose-only) Sprague Dawley rat PMRA No. 3324399	LC_{50} > 5.39 mg/L (♂/♀) Clinical signs of toxicity included irregular respiration. **Low acute toxicity**
Primary eye irritation New Zealand White rabbit PMRA No. 3328929	MIS = 0 MAS = 0 **Non-irritating**
Primary skin irritation New Zealand White rabbit PMRA No. 3328931	MIS = 0 MAS = 0 **Non-irritating**
Dermal sensitization (Buehler) Hartley guinea pig PMRA No. 3328933	Positive **Potential dermal sensitizer**

Table 7 AHETF/PHED unit exposure estimates for mixer/loaders and applicators handling Kodama Miticide (µg/kg a.i. handled)

Exposure scenario and PPE		Dermal	Inhalation[1]
Mixer/loader AHETF estimates			
A	Liquid, open mix/load PPE: Single layer, CR gloves	58.5	0.63
Applicator AHETF estimates			
B	Airblast, liquid, open cab PPE: Single layer, CR gloves	3769.3	9.08
C	Airblast, liquid, open cab PPE: Single layer, CR gloves, CR hat	414.93	9.08

Exposure scenario and PPE		Dermal	Inhalation[1]
D	Airblast, liquid, closed cab PPE: Single layer	20.98	0.32
Mixer/loader + applicator AHETF/PHED estimates			
A+B	Liquid, open mix/load, airblast, open cab PPE: Single layer, CR gloves (M/L/A)	3827.8	9.71
A+C	Liquid, open mix/load, airblast, open cab PPE: Single layer, CR gloves (M/L/A), CR hat (A)	473.43	9.71
A+D	Liquid, open mix/load, airblast closed cab PPE: Single layer (M/L/A), CR gloves (M/L)	79.48	0.95
E	Liquid, backpack, PHED PPE: Single layer, CR gloves (M/L/A)	5445.85	62.1
F	Liquid, MPHG, PHED PPE: Single layer, CR gloves (M/L/A)	5585.49	151
G	Liquid, MPHW, PHED PPE: Single layer, CR gloves (M/L/A)	943.37	45.2

A = applicator; CR = chemical-resistant; M/L = mixer/loader; M/L/A = mixer/loader/applicator; MPHG = mechanically-pressurized handgun; MPHW = manually-pressurized handwand; PPE = personal protective equipment

1 Light inhalation rate for all application equipment except for backpack sprayer, which is moderate.

Table 8 Mixer/loader/applicator exposure and risk assessment for acynonapyr

Exposure scenario	Application rate[1]	ATPD[2]	Exposure (µg/kg bw/day)		MOE		
			Dermal[3]	Inhalation[4]	Dermal[5]	Inhalation[5]	Combined[6]
A+B (AB open cab)	0.124 kg/ha	20 ha/day	11.87	0.301	126	4983	**123**
A+C (AB open cab, CR hat)	0.124 kg/ha	20 ha/day	1.468	0.301	1022	4983	848
A+D (AB closed cab)	0.124 kg/ha	20 ha/day	0.246	0.029	6088	50934	5438
E (Backpack)	0.248 g/L	150 L/day	0.25	0.03	5920	51900	5320
F1 (MPHG)	0.248 g/L	3800 L/day	6.58	1.78	228	843	**179**
F2 (MPHG)	0.124 kg/ha	2 ha/day	1.73	0.468	866	3204	682
G (MPHW)	0.248 g/L	150 L/day	0.04	0.02	34200	71400	23100

Bolded text indicates the target MOE was not exceeded.

AB = airblast; ATPD = area treated per day; CR = chemical-resistant; MOE = margin of exposure; MPHG = mechanically pressurized handgun; MPHW = manually pressurized handwand

1 For handheld equipment, the application rate (g/L) = 0.124 kg a.i./ha ÷ minimum spray volume (500 L/ha) × conversion (1000 g/kg) = 0.248 g a.i./L.

2 Default ATPD table (updated on 2023-01-18). For exposure scenario F2, the default amount handled per day value of 3800 L/day was refined to 2 ha/day.

[3] Dermal exposure (µg/kg bw/day) = (dermal unit exposure (µg/kg a.i. handled) × dermal absorption (10%) × ATPD × application rate) ÷ 80 kg bw.
[4] Inhalation exposure (µg/kg bw/day) = (inhalation unit exposure (µg/kg a.i. handled) × ATPD × application rate) ÷ 80 kg bw.
[5] Dermal or Inhalation MOE = NOAEL of 1.5 mg/kg bw/day ÷ (exposure (µg/kg bw/day) × conversion (mg/1000 µg)); Target MOE = 300.
[6] Combined MOE = 1 ÷ ((1/Dermal$_{MOE}$) + (1/Inhalation$_{MOE}$)).

Table 9 Cancer occupational mixer/loader/applicator exposure and risk assessment for acynonapyr

Application method	Application rate[1]	ATPD[2]	ADD (µg/kg bw/day)[3]		WD/Yr (days/year)[4]	Work years	LADD (mg/kg bw/day)[5]	Cancer risk[6]
			Dermal	Inhalation				
A+C (AB open, hat)	0.124 kg/ha	7 ha	0.51	0.11	5	40	0.0043	2.1E-7
A+D (AB closed)	0.124 kg/ha	7 ha	0.09	0.01	5	40	0.0007	3.3E-8
E (Backpack)	0.248 g/L	150 L	0.25	0.03	5	40	0.0020	9.7E-8
F2 (MPHG)	0.124 kg/ha	2 ha	1.73	0.468	5	40	0.0155	7.6E-7
G (MPHW)	0.248 g/L	150 L	0.04	0.02	5	40	0.0005	2.2E-8

AB = airblast; ADD = absorbed daily dose; ATPD = area treated per day; LADD = lifetime average daily dose; MPHG = mechanically pressurized handgun; MPHW = manually pressurized handwand; WD/Yr = work days per year
[1] For handheld equipment, the application rate (g/L) = 0.124 kg a.i./ha ÷ minimum spray volume (500 L/ha) × conversion (1000 g/kg) = 0.248 g a.i./L.
[2] Standard ATPD values.
[3] ADD = application rate × ATPD × dermal absorption (10%) or inhalation absorption (100%) × dermal or inhalation unit exposure (Appendix I, Table 7) ÷ 80 kg bw.
[4] WD/Yr = 5 based on professional judgement.
[5] LADD = ADD × conversion (mg/1000 µg) × career duration (40 years/lifetime) × exposure days (5 days/year) ÷ 365 (days/year) ÷ 78 years/lifetime. Career duration of 40 years/lifetime.
[6] Cancer risk = q_1* (4.910E-2 (mg/kg bw/day)$^{-1}$) × LADD.

Table 10 Postapplication worker exposure and risk estimate for acynonapyr on treated pome fruit

Postapplication activity	Peak DFR (µg/cm^2)[1]	TC (cm^2/hour)[2]	Dermal exposure (µg/kg bw/day)[3]	MOE[4]	REI[5] (days)
Thinning	0.31	3000	9.30	**161**	6
Hand Harvesting		1400	4.34	346	0.5

Bolded text indicates the target MOE was not exceeded.
DFR = dislodgeable foliar residue; MOE = margin of exposure; REI = restricted-entry interval; TC = transfer coefficient
[1] Calculated using the standard 25% dislodgeable on the day of application and 10% dissipation per day (outdoor scenario).
[2] TCs obtained from the PMRA Agricultural TCs (PRO2014-02). Exposure to only the 2 highest TC activities is presented, as calculated MOEs did not demonstrate risks of concern for those with TCs less than 1400 cm^2/hour.
[3] Exposure = (peak DFR × TC × 8 h × 10% dermal absorption) ÷ (80 kg bw × 1000 µg/mg).
[4] Based on a NOAEL of 1.5 mg/kg bw/day; Target MOE = 300.
[5] Minimum REI is 12 h (0.5 d) to allow residues to dry, suspended particles to settle, and vapours to dissipate.

Table 11 The estimated lifetime cancer risk to postapplication workers from exposure to acynonapyr after application to pome fruit

Postapplication activity	ADD (µg/kg bw/day)[1]	Cancer		
		WD/Yr (days/year)	LADD (mg/kg bw/day)[3]	Cancer risk[4]
Hand Thinning	9.30	15	0.1960	9.6E-6
Hand Harvesting	4.34	15	0.0915	4.5E-6

ADD = absorbed daily dose; LADD = lifetime average daily dose; TC = transfer coefficient; WD/Yr = work days per year

1 ADD (µg/kg bw/day) = dermal exposure (Appendix I, Table 10).

2 WD/Yr (days/year) = 15

3 LADD = ADD × conversion (mg/1000 µg) × career duration (40 years/lifetime) × exposure days (15 days/year) ÷ 365 (days/year) ÷ 78 years/lifetime. Career duration of 40 years/lifetime.

4 Cancer risk = q_1* (4.910E-2 (mg/kg bw/day)$^{-1}$) × LADD.

Table 12 Postapplication dermal exposure and risk estimates to residents on Day 0 from pome fruit trees treated commercially with acynonapyr

Crop (maximum application rate; number of applications)	Life stage	Peak DFR (µg/cm^2)[1]	TC (cm^2/hour)[2]	Exposure time (hours/day)	Dermal exposure (mg/kg bw/day)[3]	MOE[4]	REI
Pome fruit (0.124 kg a.i./ha; 1/season)	Adults (16+ yrs)	0.31	1700	1	6.59E-4	2300	Until sprays have dried
	Youth (11 < 16 yrs)		1400	0.5	3.81E-4	3900	
	Children (6 < 11 yrs)		930	0.5	4.50E-4	3330	

DFR = dislodgeable foliar residue; MOE = margin of exposure; REI = restricted-entry interval; TC = transfer coefficient

1 Calculated using the standard value of 25% of the application rate on Day 0 after the last application and 10% dissipation per day. The DFR value was calculated based on 1 application of the highest rate of all fruit trees (0.124 g a.i./ha).

2 A single TC is representative of all activities in residential fruit trees. TCs were obtained from the USEPA's *Residential Standard Operating Procedures for Residential Pesticide Exposure Assessment* (revised October 2012).

3 Dermal exposure = (peak DFR × TC × exposure time × 10% dermal absorption) ÷ (bw (80 kg for adults; 57 kg for youth; 32 kg for children) × 1000 µg/mg).

4 Based on a NOAEL of 1.5 mg/kg bw/day; Target MOE = 300.

Table 13 The estimated lifetime cancer risk to residents from exposure to acynonapyr after application to pome fruit

Life stage	TWA DFR (µg/cm²)[1]	TC (cm²/hour)[2]	Exposure time (hours/day)	ADD (mg/kg bw/day)[3]	Cancer			
					Exposure days/year[4]	LADD (mg/kg bw/day)[5]	Cancer risk[6]	Lifetime cancer risk[7]
Adults (16+ yrs)	0.158	1700	0.5	1.68E-4	15	5.57E-6	2.7E-7	3.0E-7
Youth (11 < 16 yrs)	0.158	1400	0.25	9.69E-5	15	2.55E-7	1.3E-8	
Children (6 < 11 yrs)	0.158	930	0.25	1.15E-4	15	3.02E-7	1.5E-8	

ADD = absorbed daily dose; d/yr = exposure days/year; DFR = dislodgeable foliar residue; LADD = lifetime average daily dose; TC = transfer coefficient; TWA = time-weighted average

1 Calculated using the standard value of 25% of the application rate on Day 0 after the last application and 10% dissipation per day. The DFR value was calculated based on 1 application at the highest rate of all fruit trees (0.124 g a.i./ha) and the time-weighted average was calculated over the course of the estimated 15-d 'exposure days' period.

2 A single TC is representative of all activities in residential fruit trees. TCs were obtained from the USEPA's *Residential Standard Operating Procedures for Residential Pesticide Exposure Assessment* (revised October 2012).

3 ADD = (TWA DFR × TC × exposure time × 10% dermal absorption) ÷ (bw (80 kg for adults; 57 kg for youths; 32 kg for children) × 1000 µg/mg).

4 Exposure d/yr (d/yr) = 15

5 LADD = (ADD × years of exposure (63 or 5 or 5 years/lifetime) × exposure days/year) ÷ (365 (days/year) × 78 years/lifetime).

6 Cancer risk = q_1* (4.910E-2 (mg/kg bw/d)$^{-1}$) × LADD.

7 Lifetime cancer risk = ∑ cancer risks (all life stages).

Table 14 Drinking water model input parameters

Parameter	Parent (acynonapyr)	Surface water		Groundwater	
		Daughter1[1]	Daughter2[2]	Daughter1[1]	Daughter2[2]
Photolysis at 40°N latitude (d)	0.11	Stable (0.973)	Stable (1.0)	NA	NA
Hydrolysis at pH 7 at 25°C (d)	12.6	Stable (1.0)	Stable (1.0)	Stable (1.0)	Stable (1.0)
Aerobic aquatic half-life at 20°C (d)	1.0[3]	516.4[4] (0.860)	57.8[5] (1.0)	NA	NA
Anaerobic aquatic half-life at 20°C (d)	0.15[3]	1336.8[4] (0.858)	81.6[5] (0.982)	NA	NA
Aerobic soil half-life at 20°C (d)	66.6[6]	152.4[7] (1.0)	332.2[8] (1.0)	152.4[7] (1.0)	332.2[8] (1.0)
K_{oc} (L/kg)	18288[9]	3615[10]	92.33[11]	3615[12]	632.6[13]

Parameter	Parent (acynonapyr)	Surface water		Groundwater	
		Daughter1[1]	Daughter2[2]	Daughter1[1]	Daughter2[2]
Molecular weight (g/mol)	504.47	504.47	504.47	504.47	504.47
Vapour pressure (torr)	8.47E-9	4.6E-7	2.5E-6	4.6E-7	2.5E-6
Solubility (mg/L)	0.00228	238	5740	238	5740
Henry's law Constant	1.01E-4	3.57E-8	3.82E-9	3.57E-8	3.82E-9
Air Diffusion Coefficient (cm^2/day)	3.00E+3	3.00E+3	3.00E+3	3.00E+3	3.00E+3
Heat of Henry (J/mol)	45782	45782	45782	45782	45782

1 Daughter1 as combined residues of AP+AP-suc+AP-fum+AP-mal; transformation fractions are in parentheses.
2 Daughter2 as combined residues of AY+AY-4; transformation fractions are in parentheses.
3 Longer of 2 half-life values for acynonapyr.
4 Longer of 2 half-life values for Daughter1 with higher fraction.
5 Longer of 2 half-life values for Daughter2 with higher fraction.
6 Upper bound 90th percentile confidence on the mean of 4 values for acynonapyr.
7 Upper bound 90th percentile confidence on the mean of 4 values for Daughter1.
8 Upper bound 90th percentile confidence bound on mean of 3 values for AY.
9 20th percentile of 4 K_{oc} values for acynonapyr.
10 Estimated K_{oc} for AP-mal (the lowest among AP, AP-suc, AP-fum and AP-mal).
11 Estimated K_{oc} for AY-4 (the lower between AY and AY-4).
12 Estimated K_{oc} for AP-mal.
13 Estimated K_{oc} for AY since AY-4 was not detected in hydrolysis and soil degradation from acynonapyr.
NA: not applicable

Table 15 Level 1 estimated environmental concentrations (EECs) of combined residues of acynonapyr, AP, AY, AP-suc, AP-fum, AP-mal, and AY-4 in potential sources of drinking water

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Acute[1]	Chronic[2]	Daily[3]	Yearly[4]	Overall[5]
1 × 127.6 g a.i./ha by ground foliar application	2.9	2.6	2.4	1.4	1.3

1 The highest (peak) simulated average concentration (µg a.i./L) in 1 m below the water table.
2 The temporal average concentration (µg a.i./L) in the 1 m below the water table over the post-breakthrough simulation period.
3 90th percentile of the highest 1-d average concentration from each year.
4 90th percentile of yearly average concentrations.
5 Average of all yearly average concentrations.

Table 16 Integrated food residue chemistry summary

Nature of the residue in apples		**PMRA No. 3328829**
Radiolabel position	[Phenyl-U-^{14}C]-label: 7.75 MBq/mg [Pyridine-2,6-^{14}C]-label: 8.54 MBq/mg [Azabicyclo-1,5-^{14}C]-label: 8.02 MBq/mg	
Treatment		
Test site	Cultivated in outdoor containers. Two trees per container, sized approximately 1 m^2 and 60 cm deep, filled with sandy loam soil.	
Treatment	A single foliar spray application at BBCH 72 (110 DBH); BBCH 77–79 (30 DBH); or BBCH 87/89 (7 DBH).	
Total rate	Phenyl: 91.7–96.4 Pyridine: 88.7–94.8 Azabicyclo: 85.9–104.1	
Formulation	Suspension concentrate (SC) formulation of acynonapyr (guarantee: 200 g/L)	
Harvest	Samples of apple fruits were harvested at maturity at 7 DAT, 30 DAT, and 110 DAT.	
Extraction solvents	Acetone (surface wash) and acetone:water (7:3, v/v)	

Overall TRRs and extractability of residues in apples

PHI (DAT)	**Matrices**	**[Phenyl-U-^{14}C]**		**[Pyridine-2,6-^{14}C]**		**[Azabicyclo-1,5-^{14}C]**	
		%TRR	**ppm[3]**	**%TRR**	**ppm[3]**	**%TRR**	**ppm[3]**
7 DAT	Surface wash[1]	96.1	0.980	96.5	0.862	92.7	1.049
	Extract[2]	3.7	0.038	3.4	0.030	6.9	0.078
	PES	0.2	0.002	0.1	0.001	0.4	0.005
	Total TRRs[5]	100	1.020	100	0.893	100	1.132
30 DAT	Surface wash[1]	73.5	0.610	75.7	0.637	79.4	0.496
	Extract[2]	24.8	0.205	22.6	0.190	18.2	0.114
	PES	1.7	0.014	1.7	0.014	2.4	0.015
	Total TRRs[5]	100	0.830	100	0.842	100	0.624
110 DAT	Surface wash[1]	50.7	0.067	30.0	0.034	35.5	0.075
	Extract[2]	39.8	0.053	62.5	0.071	51.2	0.107
	PES	9.5	0.013	7.5	0.009	13.3[4]	0.028[4]
	Total TRRs[5]	100	0.133	100	0.114	100	0.210

[1] Fruits were washed with acetone.
[2] Extraction with acetone:water (7:3, v/v).
[3] Expressed as mg parent equivalents/kg fresh weight.

[4] Further characterized by subsequent solubilization steps. Final PES was 0.0199 ppm and 9.5% TRR.
[5] Sum of TRRs in all fractions.

Summary of major identified metabolites in apples	
Radiolabel position	**[Phenyl-U-^{14}C] / [Pyridine-2,6-^{14}C] / [Azabicyclo-1,5-^{14}C]**
Mature apple (7 DAT)	Acynonapyr
Mature apple (30 DAT)	Acynonapyr, AP
Mature apple (110 DAT)	Acynonapyr, AP, AY

Nature of the residue in lettuce	**PMRA No. 3328827**
Radiolabel position	[Phenyl-U-^{14}C]-label: 7.75 MBq/mg [Pyridine-2,6-^{14}C]-label: 8.30 MBq/mg [Azabicyclo-1,5-^{14}C]-label: 8.02 MBq/mg
Treatment	
Test site	Seeded in starter trays and the seedlings were transferred to 3-inch pots containing sandy loam soil. Three plants per radiolabel were transplanted to individual 19-inch diameter pots located on separate benches in the greenhouse.
Treatment	Group 1: Two foliar applications made 30 DBH (1st application) and 23 DBH (2nd application). Group 2: Single foliar application made 30 DBH. Group 3: Two foliar applications made 14 DBH (1st application) and 7 DBH (2nd application).

Total rate

		Application rate (g a.i./ha)		**Total application rate (g a.i./ha)**
		1st	**2nd**	
Azabicyclo-label	Group 1	186	183	369
	Group 2	186	-	186
	Group 3	180	182	362
Phenyl-label	Group 1	188	197	385
	Group 2	188	-	188
	Group 3	187	192	379
Pyridine-label	Group 1	199	191	390
	Group 2	192	-	192
	Group 3	179	183	362

Formulation	SC formulation of acynonapyr (guarantee: 200 g/L)
Harvest	Group 1: 23 d after the 2nd application Group 2: 30 d after the 1st (only) application Group 3: 7 d after the 2nd application
Extraction solvents	Surfaced-washed lettuce: 2 × acetone (surface wash); and 3 × acetone:water (70:30, v/v) using a 1:4 ratio (w/v) with the lettuce sample

	Non-surface-washed lettuce: 3 × acetone:water (70:30, v/v) using a 1:4 ratio (w/v) with the lettuce sample

Overall TRRs and extractability of residues in lettuce

Matrix	Group	Matrices	[Phenyl-U-^{14}C]		[Pyridine-2,6-^{14}C]		[Azabicyclo-1,5-^{14}C]	
			%TRR	ppm[3]	%TRR	ppm[3]	%TRR	ppm[3]
Surface-washed lettuce	1[5]	Surface wash[1]	61.2	4.30	65.7	4.20	67.4	6.04
		Extract[2]	36.5	2.57	31.5	1.98	30.3	2.71
		PES	2.37	0.17	2.83	0.18	2.39	0.21
		Total TRRs[4]	100	7.04	100	6.39	100	8.97
	2[6]	Surface wash[1]	60.3	1.43	56.1	1.45	62.0	2.22
		Extract[2]	36.9	0.87	40.5	1.04	34.3	1.23
		PES	2.77	0.07	3.35	0.09	3.65	0.13
		Total TRRs[4]	100	2.37	100	2.58	100	3.58
	3[7]	Surface wash[1]	73.8	9.27	89.0	10.4	83.8	6.80
		Extract[2]	25.5	3.21	10.5	1.23	15.6	1.27
		PES	0.70	0.09	0.55	0.06	0.54	0.04
		Total TRRs[4]	100	12.6	100	11.7	100	8.12
Non-surface-washed lettuce	1[5]	Total extractables	97.2	6.36	96.2	8.24	96.3	8.26
		PES	2.78	0.18	3.77	0.33	3.66	0.31
		Total TRRs	100	6.54	100	8.57	100	8.58
	2[6]	Total extractables	96.0	3.02	95.9	2.09	95.5	4.62
		PES	3.98	0.13	4.09	0.089	4.55	0.22
		Total TRRs	100	3.14	100	2.18	100	4.84
	3[7]	Total extractables	98.7	9.45	98.8	9.88	99.0	7.22
		PES	1.35	0.13	1.22	0.12	1.09	0.080
		Total TRRs	100	9.58	100	10.0	100	7.30

[1] Lettuce was washed with acetone.
[2] Extraction with acetone/water (7/3, v/v).
[3] Expressed as mg acynonapyr/kg fresh weight.
[4] Sum of residues from all fractions
[5] Received 2 applications for a total of 369–390 g a.i./ha at growth stages BBCH 19 and BBCH 26 and harvested 23 d following the 2nd application.
[6] Received 1 application of 186–192 g a.i./ha at a growth stage BBCH 19 and harvested 30 d following the application.

[7] Received 2 applications for a total of 362–379 g a.i./ha at growth stages BBCH 35 and 42, and harvested 7 d following the 2nd application.

Summary of major identified metabolites in lettuce	
Matrix	**[Phenyl-U-^{14}C], [Pyridine-2,6-^{14}C], and [Azabicyclo-1,5-^{14}C]**
	Major metabolites
Surface-washed	
Group 1	Acynonapyr, AP
Group 2	Acynonapyr, AP
Group 3	Acynonapyr, AP
Non-surface-washed	
Group 1	Acynonapyr, AP
Group 2	Acynonapyr, AP, AY-1-Glc
Group 3	Acynonapyr, AP

Nature of the residue in cucumber	**PMRA No. 3328825**
Radiolabel position	[Phenyl-U-^{14}C]-label: 7.76 MBq/mg [Pyridine-2,6-^{14}C]-label: 8.54 MBq/mg
Treatment	
Test site	The treated plants for each radiolabelled experiment were grown in 15 L free-draining, plastic pots, which were kept in separate glasshouse compartments.
Treatment	1st application – After flowering with approximately 70% of fruit at maturity (BBCH 87) 2nd application – 7 d after first application (approximately BBCH 88)
Total rate	Phenyl-label: 395 g a.i./ha Pyridine-label: 396 g a.i./ha
Formulation	Suspension concentrate (SC) formulation of acynonapyr (guarantee: 200 g/L)
Harvest	Harvest 1: 1 d after 2nd application (1DAA2) Harvest 2: 3 d after 2nd application (3DAA2) Harvest 3: 7 d after 2nd application (7DAA2) Harvest 4: 14 d after 2nd application (14DAA2)
Extraction solvents	Surface wash with hexane prior to extraction with acetone:ultrapure water (7:3, v/v)

Overall TRRs and extractability of residues in cucumber					
Matrix	**Fraction**	**[Phenyl-U-^{14}C]**		**[Pyridine-2,6-^{14}C]**	
		%TRR	**ppm[3]**	**%TRR**	**ppm[3]**
Fruit					
1DAA2	Surface wash[1]	33.3	0.006	41.4	0.005
	Extracts[2]	63.4	0.011	57.8	0.008
	PES	3.3	0.001	0.8	0.001
	Total TRRs[4]	100	0.018	100	0.013
3DAA2	Surface wash[1]	37.3	0.015	44.1	0.018
	Extracts[2]	59.8	0.015	55.3	0.022
	PES	2.9	0.001	0.6	0.001
	Total TRRs[4]	100	0.026	100	0.040
7DAA2	Surface wash[1]	25.1	0.002	25.1	0.013
	Extracts[2]	66.5	0.005	73.9	0.037
	PES	8.4	0.001	1.0	0.001
	Total TRRs[4]	100	0.008	100	0.051
14DAA2	Surface wash[1]	27.3	0.002	15.4	0.008
	Extracts[2]	64.5	0.005	83.4	0.041
	PES	8.3	0.001	1.2	0.001
	Total TRRs[4]	100	0.007	100	0.050
Foliage					
1DAA2	Surface wash[1]	52.9	1.058	22.0	0.213
	Extracts[2]	44.8	0.896	75.9	0.736
	PES	2.3	0.046	2.1	0.020
	Total TRRs[4]	100	2.000	100	0.969
3DAA2	Surface wash[1]	45.7	0.948	38.3	0.483
	Extracts[2]	51.1	1.061	59.7	0.752
	PES	3.2	0.066	2.0	0.025
	Total TRRs[4]	100	2.075	100	1.260
7DAA2	Surface wash[1]	29.0	0.792	22.0	0.228
	Extracts[2]	63.8	1.741	71.9	0.744
	PES	7.2	0.197	6.1	0.063
	Total TRRs[4]	100	2.730	100	1.035
14DAA2	Surface wash[1]	17.7	0.307	17.7	0.181
	Extracts[2]	76.1	1.319	75.0	0.766

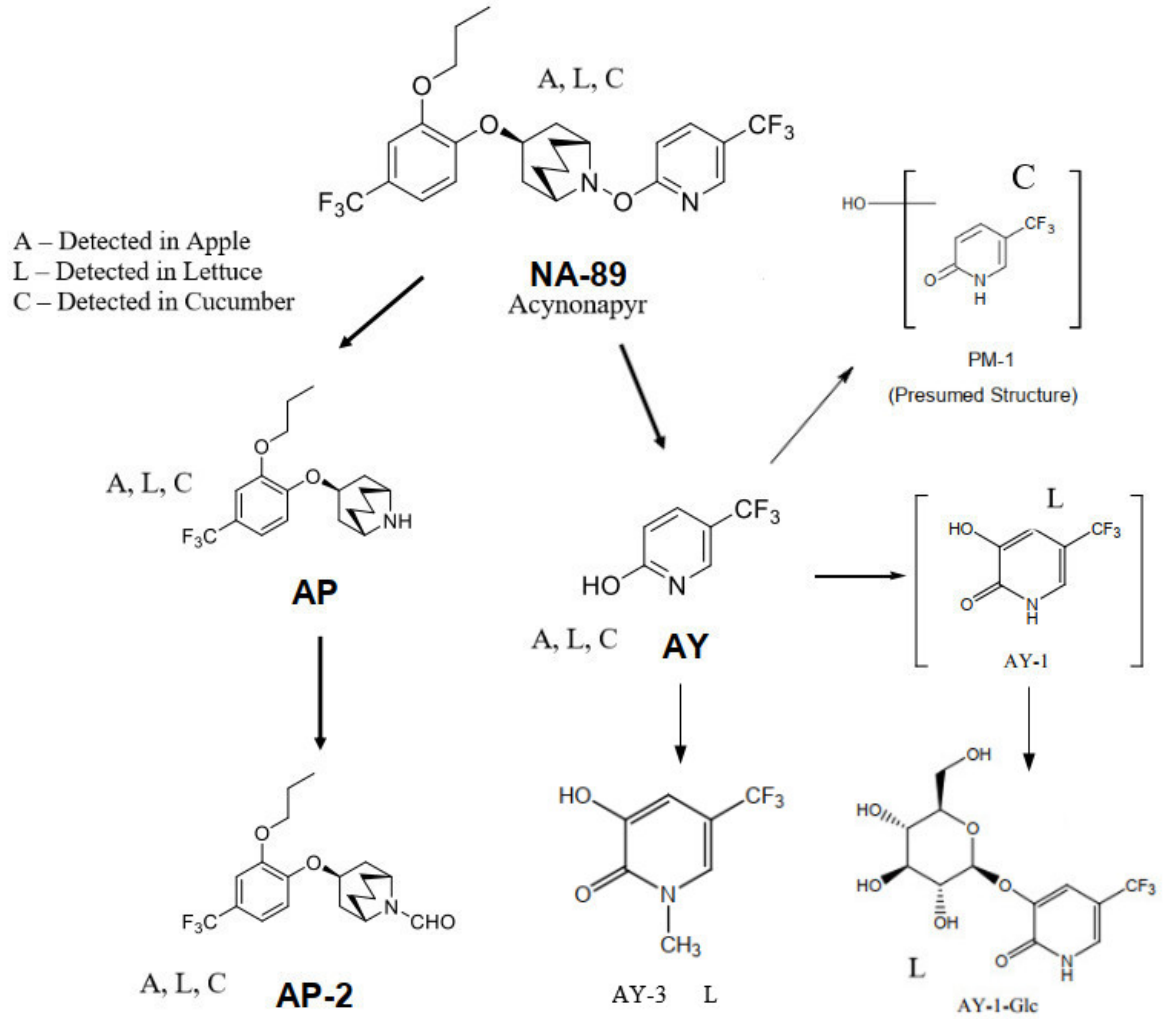
	PES	6.2	0.107	7.3	0.075
	Total TRRs[4]	100	1.733	100	1.022

[1] Washed with hexane.
[2] Sum of all acetone:water (7:3; v/v) extracts.
[3] Expressed as mg parent equivalents/kg fresh weight.
[4] Sum of TRRs in all fractions.

Summary of major identified metabolites in cucumber

Matrix	**Major metabolites (>10% of the TRR)**
	[Phenyl-U-^{14}C] / [Pyridine-U-^{14}C]
Fruit	
1DAA2	Acynonapyr, AY, PM-1
3DAA2	Acynonapyr, AP, AY
7DAA2	Acynonapyr, AY, PM-1
14DAA2	Acynonapyr, AY, PM-1
Foliage	
1DAA2	Acynonapyr, AP, AY
3DAA2	Acynonapyr, AP, AY, PM-1
7DAA2	Acynonapyr, AP, AY, PM-1
14DAA2	Acynonapyr, AP

Proposed metabolic scheme in plants



Freezer storage stability in plant matrices				**PMRA No. 3324404**
Tested matrices	**Analyte**	**Tested intervals**	**Temperature (°C)**	**Category**
Apple fruit	Acynonapyr, AP, and AP-2	0 d, 33 d (1 month), 182 d (6 months), and 299 d (9.8 months)	-10 to -25	High-water
Although residues of acynonapyr were observed to degrade during frozen storage, they were accounted for when analyzing for residues of AP, expressed in acynonapyr equivalents. Therefore, the combined residues of acynonapyr + AP were shown to be stable for up to 182 d.				

Crop field trials and residue decline on pome fruits	**PMRA No. 3324407**

Crop field trials were conducted on apples and pears in North American regions during the 2020 growing season using NA-89 SC (acynonapyr end-use product, guarantee: 20% by wt) at approved label rates and harvested according to label directions. Foliar applications were made with concentrated or dilute spray volumes. The number and geographic distribution of trials were generally in accordance with Health Canada's DIR2010-05. Independence of trials was assessed. Residue decline data showed that residues of acynonapyr decreased with increasing PHIs in both apples and pears; but no general trend could be determined for the AP metabolite in apples and pears. Residues of the metabolite AP-2 were too low (<LOQ) to determine a decline trend. Adequate storage stability data are available to support the storage intervals of the pome fruits. Samples were analyzed using a validated analytical method.

Crop	**Spray**	**Total application rate (g a.i./ha)**	**PHI (d)[1]**	**Analyte**	**Residue levels (ppm)[2,3]**					
					n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Whole apple fruit	Diluted	126–130	6–7, 14, 21	Acynonapyr	12	0.011	0.060	0.024	0.028	0.016
				AP		<0.01	0.023	0.014	0.015	0.005
				AP-2		<0.01	0.021	<0.01	0.011	0.004
				Enforcement[4]		<0.029	<0.070	<0.038	<0.042	0.012
				DEA[5]		<0.039	<0.080	<0.051	<0.055	0.012
	Concentrated		6–7, 14	Acynonapyr		0.011	0.054	0.037	0.037	0.015
				AP		<0.01	0.035	<0.01	0.015	0.009
				AP-2		<0.01	0.013	<0.01	0.010	0.001
				Enforcement[4]		<0.029	<0.071	<0.058	<0.052	0.015
				DEA[5]		<0.039	<0.081	<0.068	<0.063	0.015
Whole pear fruit	Diluted	127–130	6–7, 14, 20, 29	Acynonapyr	6	0.040	0.058	0.051	0.050	0.009
				AP		0.012	0.027	0.018	0.019	0.006
				AP-2		<0.01	<0.01	<0.01	<0.01	-
				Enforcement[4]		<0.050	<0.077	<0.070	<0.067	0.012

				DEA[5]		<0.060	<0.087	<0.080	<0.077	0.012
	Concentrated		7, 14	Acynonapyr		0.041	0.049	0.046	0.045	0.004
				AP		0.015	0.023	0.022	0.020	0.005
				AP-2		<0.01	<0.01	<0.01	<0.01	-
				Enforcement[4]		<0.061	<0.072	<0.063	0.065	0.006
				DEA[5]		<0.071	<0.082	<0.073	0.075	0.006

n = number of independent trials; HAFT = highest average field trial; LAFT = lowest average field trial; SDEV = standard deviation. For computation of the LAFT, HAFT, median, mean, and SDEV, values <LOQ are assumed to be LOQ.

1 Expressed as parent equivalents.

2 Values based on per trial averages.

3 Although the label PHI is 7 d, in some cases, residues were observed to increase with increasing PHIs. As such, the highest individual residues of each analyte and the highest combined residues of all analytes from the residue decline trials were considered in calculating the statistics.

4 The combined residues include acynonapyr and metabolite AP, expressed as parent equivalents.

5 The combined residues include acynonapyr and metabolites AP and AP-2, expressed as parent equivalents.

Processed food and feed – apples	**PMRA No. 3324407**

A processing study on apples was conducted in 1 distinctive North American growing region using NA-89 SC (acynonapyr end-use product) at 638 g a.i./ha (approximately fivefold approved rate). Adequate storage stability data are available on apples to support the storage intervals of the processed commodities. Samples were analyzed using a validated analytical method.

RAC	Processed fractions	Acynonapyr HAFT[RAC] (ppm)	AP HAFT[RAC] (ppm)	Median processing factor of acynonapyr[1]	Median processing factor of AP	Anticipated residues of acynonapyr + AP (ppm)
Apples	Apple juice	0.060	0.035	0.08	0.017	0.0054

1 Based on the enforcement residue definition, which includes acynonapyr and metabolite AP.

Table 17 Food residue chemistry overview of metabolism studies and risk assessment

Plant studies			
Residue definition for enforcement Primary fruit crops		Acynonapyr + AP, expressed as parent equivalents	
Residue definition for risk assessment Primary fruit crops		Acynonapyr + AP + AP-2, expressed as parent equivalents	
Metabolic profile in diverse crops		Similar in apple, lettuce, and cucumber	
Dietary risk from food and drinking water			
Basic acute dietary exposure analysis, 95th percentile **ARfD for females 13–49 yrs, infants, and children up to 12 yrs old = 0.03 mg/kg bw** **Estimated acute drinking water concentration = 21 µg a.i./L (Level 1; groundwater)**	**Population**	**Estimated risk % of ARfD**	
		Food alone	**Food and drinking water**
	All infants	21.1	26.3
	Children 1–2 yrs	31.1	33.3
	Children 3–5 yrs	19.2	20.2
	Children 6–12 yrs	7.75	9.48
	Females 13–49 yrs	2.41	4.99
Refined chronic non-cancer dietary exposure analysis **ADI = 0.01 mg/kg bw/day** **Estimated chronic drinking water concentration = 2.6 µg a.i./L (refined Level 1; groundwater)**	**Population**	**Estimated risk % of ADI**	
		Food alone	**Food and drinking water**
	General Population	0.0	0.6
	All Infants	0.1	2.1
	Children 1–2 yrs old	0.2	0.9
	Children 3–5 yrs old	0.1	0.7
	Children 6–12 yrs old	0.0	0.5
	Youth 13–19 yrs old	0.0	0.4
	Adults 20–49 yrs old	0.0	0.5
	Adults 50+ yrs old	0.0	0.5

Refined chronic cancer dietary exposure analysis q_1^* = 2.455E-2 $(mg/kg\ bw/day)^{-1}$ Estimated chronic drinking water concentration = 2.6 µg a.i./L (refined Level 1; groundwater)	Population	Estimated lifetime cancer risk	
		Food alone	Food and drinking water
	Total population	<1E-6	1E-6

Table 18 Aggregate non-cancer exposure and risk estimates for acynonapyr

Life Stage	Exposure (mg/kg bw/day)		MOE		
	Dermal[1]	Dietary[2]	Dermal[3]	Dietary[4]	Aggregate[5]
Adult (16+ yrs)	0.00066	0.000052	2280	113000	2200
Youth (11 < 16 yrs)	0.00038	0.000037	3900	160000	3800
Children (6 < 11 yrs)	0.00045	0.000053	3300	111000	3200

1 Refer to the postapplication dermal exposure and risk estimates to residents on Day 0 from pome fruit trees treated commercially with acynonapyr in Appendix I, Table 12.
2 Refer to the food residue chemistry overview of metabolism studies and risk assessment in Appendix I, Table 17.
3 Dermal MOE = aggregate dermal NOAEL of 1.5 mg/kg bw/day ÷ dermal exposure; Target MOE = 300.
4 Dietary MOE = aggregate dietary NOAEL of 5.9 mg/kg bw/day ÷ dietary exposure; Target MOE = 300.
5 Aggregate MOE = 1 ÷ ((1/dermal MOE)+(1/dietary MOE)); Target MOE = 300.

Table 19 Aggregate cancer exposure and risk estimates for acynonapyr

Life stage	Dermal cancer risk[1]	Lifetime dermal cancer risk[1]	Refined lifetime dietary cancer risk[2]	Aggregate lifetime cancer risk[3]
Adult (16+ yrs)	2.7E-7	3.0E-7	1.4E-6	1.7E-6
Youth (11 < 16 yrs)	1.3E-8			
Children (6 < 11 yrs)	1.5E-8			

1 Refer to the estimated lifetime cancer risk to residents from exposure to acynonapyr after application to pome fruit in Appendix I, Table 13.
2 Refer to the food residue chemistry overview of metabolism studies and risk assessment in Appendix I, Table 17.
3 Aggregate lifetime cancer risk = lifetime dermal cancer risk + lifetime dietary cancer risk.

Table 20 Fate and behaviour of acynonapyr and its transformation products (TPs) in the environment

Study type	Test material / test system	Value[1]	TPs	Comments	Study PMRA No.
Abiotic transformation					
Hydrolysis	25°C, pH 4, 7, and 9 phenyl- and pyridine-labelled acynonapyr	pH 4: DT_{50} = 1.15 d (SFO) pH 7: DT_{50} = 13.2 d (SFO) pH 9: DT_{50} = 6.56 d (SFO)	**Major:** AH, AP, AY, AY-5 **Minor:** none identified	Hydrolysis is an important route of dissipation for acynonapyr in the environment.	3328796
	25°C, pH 4 azabicyclo-labelled acynonapyr	pH 4: DT_{50} = 1.15 d (SFO)	**Major:** AP, UK-15 **Minor:** none identified Note: This study provides an inadequate understanding of the TPs		3328798
Phototransformation on soil	20°C, pH 6.0, silt loam soil, 1.6% OC phenyl-, pyridine-, and azabicyclo-labelled acynonapyr	DT_{50} = 20.3 d (SFO) summer sunlight, 30–50°N	**Major:** AP, AY **Minor:** none identified	Phototransformation in soil can be an important route of dissipation for acynonapyr in the environment.	3328802
Phototransformation in water	25°C, pH 7, buffered solution pyridine- and azabicyclo-labelled acynonapyr	DT_{50} = 0.124 d (SFO) summer sunlight, 30–50°N	**Major:** AP, AY, AY-4 **Minor:** none identified	Phototransformation in water is an important route of dissipation for acynonapyr in the environment.	3328800
Phototransformation in air	Acynonapyr is unlikely to undergo direct phototransformation based on its UV spectrum absorptions. The AOPWIN (version 1.92)-predicted half-life in the gas phase in the atmosphere is 0.113 d based on the hydroxyl (OH) radical reaction (1.5E+6 molecules OH/cm^3) during 12 h of daylight. Using acynonapyr's Henry's law Constant of 6.33E-6 atm·m^3/mol and log K_{ow} of 6.5 as data inputs for EPI Suite*, estimations of acynonapyr sorbed to				

Study type	Test material / test system	Value[1]	TPs	Comments	Study PMRA No.
	airborne particles range from 19 to 89% (AEROWIN, version 1.00). The half-life in air adjusted to account for the sorbed fraction ranges from 0.14–1.04 d. *EPI (Estimation Programs Interface) Suite is a suite of physical/chemical property and environmental fate estimation programs				
Biotransformation					
Biotransformation in aerobic soil	**Parent, acynonapyr**				
	E1 silt loam, UK, 20°C, pH 5.4, 5.2% OC phenyl-labelled acynonapyr	DT_{50} = 53.8 d (DFOP) t_R = 72.4 d	**Major:** AP, AY **Minor:** none identified	Acynonapyr is slightly to moderately persistent. Biotransformation in aerobic soil is an important route of dissipation for acynonapyr.	3328807
	J3 clay loam, UK, 20°C, pH 7.6, 1.8% OC phenyl-labelled acynonapyr	DT_{50} = 78.4 d (SFO)	**Major:** AP, AY **Minor:** AP-suc, AP-mal		
	New York silt loam, US, 20°C, pH 5.6, 1.6% OC phenyl-labelled acynonapyr	DT_{50} = 52.8 d (SFO)	**Major:** AP, AY **Minor:** none identified		
	California sandy loam, US, 20°C, pH 5.4, 0.48% OC phenyl-, pyridine-, and azabicyclo-labelled acynonapyr	DT_{50} = 41.5 d (SFO)	**Major:** AP, AY **Minor:** none identified		
	TP, AP				
	Hanford loam, US, 20°C, pH 6.4, 0.85% OC phenyl-labelled AP	DT_{50} = 892 d (SFO)	**Major:** none formed **Minor:** none identified	The TP, AP, is persistent. Biotransformation in aerobic soil is not an important	3324577

Study type	Test material / test system	Value[1]	TPs	Comments	Study PMRA No.
	Niagara silt loam, US, 20°C, pH 6.8, 1.6% OC phenyl-labelled AP	DT_{50} = 286 d (DFOP) t_R = 335 d		route of dissipation for AP.	
	Quincy loamy sand, US, 20°C, pH 7.2, 0.56% OC phenyl-labelled AP	DT_{50} = 616 d (DFOP) t_R = 826 d			
	TP, AY				
	PT102 loam, UK, 20°C, pH 6.3, 3.0% OC pyridine-labelled AY	DT_{50} = 92.5 d (SFO)	**Major:** none formed **Minor:** none identified	The TP, AY, is moderately persistent. Biotransformation in aerobic soil can be an important route of dissipation for AY.	3328898
	PT103 sandy loam, UK, 20°C, pH 3.9, 1.3% OC pyridine-labelled AY	DT_{50} = 52.6 d (DFOP) t_R = 93.3 d			
	SK920191 sandy clay loam, UK, 20°C, pH 7.4, 2.1% OC pyridine-labelled AY	DT_{50} = 53.3 d (IORE) t_R = 341.7 d			
Biotransformation in anaerobic soil	Hanford sandy loam, US, 20°C, pH 5.4, 5.2% OC phenyl-, pyridine-, and azabicyclo-labelled acynonapyr	DT_{50} = 18.1 d (SFO) total system	**Major:** AP, AY **Minor:** none identified	Acynonapyr is slightly persistent. Biotransformation in anaerobic soil is an important route of dissipation for acynonapyr.	3328809

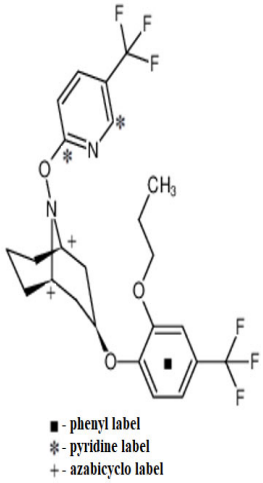
Study type	Test material / test system	Value[1]	TPs	Comments	Study PMRA No.
Biotransformation in aerobic water systems	LVP, US, 20°C, pH 8.4 phenyl-, pyridine-, and azabicyclo-labelled acynonapyr	DT_{50} = 1.05 d (SFO) total system	**Major:** AP, AY, AP-suc, AP-fum, AP-mal **Minor:** none identified	Acynonapyr is non-persistent. Transformation in aerobic water systems is an important route of dissipation for acynonapyr.	3328811
	JWP, US, 20°C, pH 6.3 phenyl-, pyridine-, and azabicyclo-labelled acynonapyr	DT_{50} = 0.85 d (SFO) total system	**Major:** AP, AY, AP-suc **Minor:** none identified		
Biotransformation in anaerobic water systems	BC, US, 20°C, pH 8.1 pyridine- and azabicyclo-labelled acynonapyr	DT_{50} = 0.11 d (SFO) total system	**Major:** AP, AY **Minor:** AP-suc (12% AR at end of incubation in excluded phenyl label)	Acynonapyr is non-persistent. Transformation in anaerobic water systems is an important route of dissipation for acynonapyr.	3328813
	JWP, US, 20°C, pH 6.4 phenyl-, pyridine-, and azabicyclo-labelled acynonapyr	DT_{50} = 0.33 d (SFO) total system	**Major:** AP, AY **Minor:** AP-suc		
Mobility					
Adsorption / desorption	**Parent, acynonapyr**				
	4 Japanese soils	K_{oc} ranging from 15,719 to 50,128	NA	Acynonapyr is classified as immobile in soil.	3328815
	OECD 121 estimate	K_{oc} approximately equal to 891,251	NA	Acynonapyr is classified as immobile in soil.	3328817
	TP, AP				

Study type	Test material / test system	Value[1]	TPs	Comments	Study PMRA No.
	3 US soils used in AP soil biotransformation study	K_{oc} ranging from 4,441 to 7,412	NA	AP is classified as slightly mobile to immobile in soil.	3324575
Soil leaching	No soil leaching study with acynonapyr was submitted and none is required.				
Volatilization	Acynonapyr is not expected to be volatile under field conditions based on its vapour pressure (1.1298E-6 Pa at 20°C). Its Henry's law Constant (1/H = 3.80E+3 at 20°C) suggests acynonapyr may be slightly volatile from water surfaces or moist soils. Based on overall low detection of volatile organics in all laboratory biotransformation studies, acynonapyr and its TPs are not expected to be volatile under field conditions.				
Field studies					
Terrestrial field dissipation	WC silt loam, US, pH 5.2, 4.2% OM End-use product, GWN-10409 (20.31% a.i.)	DT_{50} = 49.0 d (DFOP) t_R = 144 d	**Major:** AP, AY **Minor:** none identified	Acynonapyr is unlikely to accumulate in soil and carry over to the next growing season.	3324408
	GC loamy fine sand, US, pH 8.3, 1.4% OM End-use product, GWN-10409 (20.31% a.i.)	DT_{50} = 30.6 d (SFO)	**Major:** AP, AY **Minor:** none identified	At the sites tested, neither acynonapyr nor its residues appeared to be susceptible to leaching.	3324409
Aquatic field dissipation	No aquatic field dissipation study with acynonapyr was submitted and none was required.				
Field leaching	No field leaching study with acynonapyr was submitted and none was required.				
Bioconcentration / bioaccumulation / biomagnification					
Bioconcentration	Bluegill sunfish, *Lepomis macrochirus* Flow through, phenyl-labelled acynonapyr	Low exposure (0.05 µg/L) BCF_{KGL}: 8732 High exposure (0.5 µg/L)	AP	Acynonapyr can bioconcentrate in the tissues of fish.	3328784

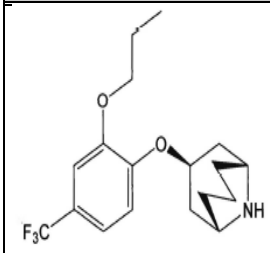
Study type	Test material / test system	Value[1]	TPs	Comments	Study PMRA No.
		BCF_{KGL}: 12257			
	Bluegill sunfish, *Lepomis macrochirus* Flow through, phenyl-labelled AP	Low exposure (6.3 µg/L) BCF_{KGL}: 117 High exposure (63 µg/L) BCF_{KGL}: 127	None identified	AP is not expected to bioconcentrate in the tissues of fish.	3325061
Bioaccumulation / biomagnification	Bluegill sunfish, *Lepomis macrochirus* Dietary exposure, flow through, phenyl-labelled acynonapyr	BMF_{Lg} = 0.0930	AP	Acynonapyr is not expected to bioaccumulate in fish tissue via dietary exposure.	3328786
	Benthic oligochaetes, *Lumbriculus variegatus* Static, sediment-applied, phenyl-labelled acynonapyr	BAF_K = 0.708	Polar metabolites (22.4–35.2%) and an unidentified metabolite (Met 1; 6.28–13.5%) were detected in the sediment. Metabolites detected in overlying water were below 1%.	Acynonapyr is not expected to bioaccumulate in oligochaetes via sediment ingestion.	3328788

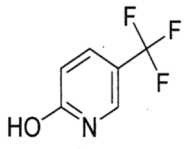
[1] Combined labels, where applicable.

Table 21 Transformation products (TPs) of acynonapyr detected in environmental fate studies

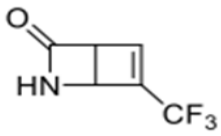
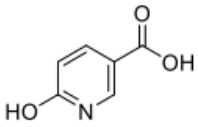
Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
Parent					
Parent, Acynonapyr 3-*endo*-[2-propoxy-4-(trifluoromethyl)phenoxy]-9-[5-(trifluoromethyl)-2-pyridyloxy]-9-azabicyclo[3.3.1]nonane  **CAS#:** 1332838-17-1 **Formula:** $C_{24}H_{26}F_6N_2O_3$ **MW:** 504.47 g/mol **SMILES:** C1(=CC(=CC=C1OC2CC3CCCC(C2)N3OC4=NC=C(C=C4)C(F)(F)F)C(F)(F)F)OCCC	Hydrolysis[1] (3328796)	pH 4, 25°C	phenyl	89.8 (0)	ND (30)
			pyridine	92.2 (0)	ND (30)
		pH 7, 25°C	phenyl	90.6 (0.1)	4.0 (30)
			pyridine	92.4 (0)	**37.3 (30)**
		pH 9, 25°C	phenyl	94.6 (0)	ND (30)
			pyridine	90.2 (0)	ND (30)
	Hydrolysis[1] (3328798)	pH 4, 25°C	azabicyclo	98.0 (0)	ND (30)
	Soil photodegradation (3328802)	Irradiated	phenyl	98.3 (0)	**35.0 (14)**
			pyridine	102.0 (0)	**36.0 (14)**
			azabicyclo	99.8 (0)	**35.2 (14)**
		Dark	phenyl	98.3 (0)	**70.6 (14)**
			pyridine	102.0 (0)	**77.0 (14)**
			azabicyclo	99.8 (0)	**73.6 (14)**
	Aqueous photodegradation (3328800)	Irradiated	pyridine	90.2 (0)	ND (22)
			azabicyclo	90.4 (0)	ND (22)
		Dark	pyridine	87.6 (3)	3.3 (22)
			azabicyclo	93.3 (3)	**25.0 (22)**
	Aerobic aquatic (3328811)	LV, US	phenyl	97.5 (0)	ND (102)
			pyridine	93.5 (0)	ND (102)
			azabicyclo	94.2 (0)	ND (102)
		JW, US	phenyl	91.2 (0)	ND (100)
			pyridine	81.2 (0)	ND (100)

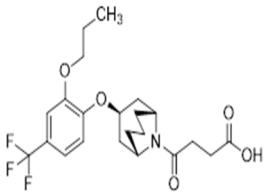
Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
			azabicyclo	88.9 (0)	ND (100)
	Anaerobic aquatic (3328813)	JW, US	phenyl	49.2 (0)	ND (100)
			pyridine	54.0 (0)	ND (100)
			azabicyclo	53.2 (0)	ND (100)
		BC, US	phenyl[2]	NA	ND (104)
			pyridine	44.4 (0)	ND (104)
			azabicyclo	70.8 (0)	ND (104)
	Aerobic soil (3328807)	E1 silt loam	phenyl	89.1 (0)	**22.5 (120)**
		J3 clay loam	phenyl	93.9 (0)	**29.9 (120)**
		NY silt loam	phenyl	96.7 (0)	**22.1 (120)**
		CA sandy loam	phenyl	88.3 (0)	**20.1 (120)**
			pyridine	105.6 (0)	**12.5 (120)**
			azabicyclo	95.6 (0)	**15.7 (120)**
	Anaerobic soil (3328809)	Hanford CA sandy loam	phenyl	91.9 (-30)	ND (119)
			pyridine	98.7 (-30)	ND (119)
			azabicyclo	90.6 (-30)	ND (119)
	K_{oc} >17 000 – classified as immobile in soil				
Major TPs					
AP 3-*endo*-[2-propoxy-4-(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonane	Hydrolysis[1] (3328796)	pH 4, 25°C	phenyl	**15.9 (7)**	**15.0 (30)**
			pyridine	NA	
		pH 7, 25°C	phenyl	**70.5 (30)**	**70.5 (30)**
			pyridine	NA	
		pH 9, 25°C	phenyl	**88.4 (30)**	**88.4 (30)**
			pyridine	NA	

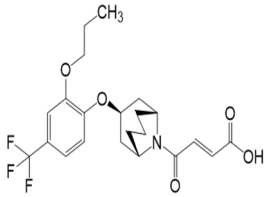
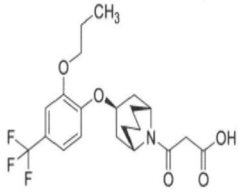
Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
 **Formula:** $C_{18}H_{24}F_3NO_2$ **MW:** 343.38 g/mol	Hydrolysis[1] (3328798)	pH 4, 25°C	azabicyclo	**21.4 (15)**	**19.7 (30)**
	Soil photodegradation (3328802)	Irradiated	phenyl	**61.5 (6)**	**55.8 (14)**
			pyridine	NA	
			azabicyclo	**55.6 (14)**	**55.6 (14)**
		Dark	phenyl	**20.2 (6)**	**19.1 (14)**
			pyridine	NA	
			azabicyclo	**29.7 (3)**	**22.2 (14)**
	Aqueous photodegradation (3328800)	Irradiated	pyridine	NA	
			azabicyclo	**94.3 (1)**	**92.9 (22)**
		Dark	pyridine	NA	
			azabicyclo	**61.8 (22)**	**61.8 (22)**
	Aerobic aquatic (3328811)	LV, US	phenyl	**56.9 (2)**	**13.1 (102)**
			pyridine	NA	
			azabicyclo	**48.1 (2)**	**23.9 (102)**
		JW, US	phenyl	**80.8 (14)**	**72.3 (100)**
			pyridine	NA	
			azabicyclo	**83.0 (14)**	**72.5 (100)**
	Anaerobic aquatic (3328813)	JW, US	phenyl	**89.0 (1)**	**78.0 100)**
			pyridine	NA	
			azabicyclo	**86.1 (30)**	**76.3 (100)**
		BC, US	phenyl[2]	NA	**69.2 (104)**
			pyridine	NA	
			azabicyclo	**89.1 (1)**	**78.6 (104)**
		E1 silt loam	phenyl	**48.2 (120)**	**48.2 (120)**

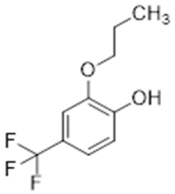
Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
	Aerobic soil (3328807)	J3 clay loam	phenyl	**26.0 (56)**	**19.7 (120)**
		NY silt loam	phenyl	**51.2 (120)**	**51.2 (120)**
		CA sandy loam	phenyl	**61.1 (90)**	**51.7 (120)**
			pyridine	NA	
			azabicyclo	**63.3 (120)**	**63.3 (120)**
	Anaerobic soil (3328809)	Hanford CA sandy loam	phenyl	**75.5 (60)**	**75.2 (119)**
			pyridine	NA	
			azabicyclo	**72.6 (60)**	**59.5 (119)**
AY or HTFP 2-hydroxy-5-(trifluoromethyl)pyridine  **CAS#:** 33252-63-0 **Formula:** $C_6H_4F_3NO$ **MW:** 163.10 g/mol	Hydrolysis[1] (3328796)	pH 4, 25°C	phenyl	NA	
			pyridine	**94.8 (30)**	**94.8 (30)**
		pH 7, 25°C	phenyl	NA	
			pyridine	**56.2 (30)**	**56.2 (30)**
		pH 9, 25°C	phenyl	NA	
			pyridine	**57.3 (11)**	**30.0 (30)**
	Hydrolysis[1] (3328798)	pH 4, 25°C	azabicyclo	NA	
	Soil photodegradation (3328802)	Irradiated	phenyl	NA	
			pyridine	**49.5 (9)**	**39.6 (14)**
			azabicyclo	NA	
		Dark	phenyl	NA	
			pyridine	**27.7 (9)**	**19.8 (14)**
			azabicyclo	NA	
	Aqueous photodegradation (3328800)	Irradiated	pyridine	**82.1 (0.2)**	ND (22)
			azabicyclo	NA	
		Dark	pyridine	**95.6 (22)**	**95.6 (22)**

Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
			azabicyclo	NA	
	Aerobic aquatic (3328811)	LV, US	phenyl	NA	
			pyridine	**88.4 (7)**	**11.8 (102)**
			azabicyclo	NA	
		JW, US	phenyl	NA	
			pyridine	**92.4 (7)**	**33.7 (100)**
			azabicyclo	NA	
	Anaerobic aquatic (3328813)	JW, US	phenyl	NA	
			pyridine	**96.5 (2)**	**41.2 (100)**
			azabicyclo	NA	
		BC, US	phenyl[2]	NA	
			pyridine	**99.9 (1)**	**37.7 (104)**
			azabicyclo	NA	
	Aerobic soil (3328807)	E1 silt loam	phenyl	NA	
		J3 clay loam	phenyl	NA	
		NY silt loam	phenyl	NA	
		CA sandy loam	phenyl	NA	
			pyridine	**16.2 (90)**	**15.4 (120)**
			azabicyclo	NA	
	Anaerobic soil (3328809)	Hanford CA sandy loam	phenyl	NA	
			pyridine	**73.0 (60)**	**72.0 (119)**
			azabicyclo	NA	
AY-4	Hydrolysis[1] (3328796)			NA	
	Hydrolysis[1] (3328798)			NA	

Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
6-(trifluoromethyl)-2-azabicyclo-[2.2.0]hex-5-en-3-one  **Formula:** $C_6H_4F_3NO$ **MW:** 163.10 g/mol	Soil photodegradation (3328802)			NA	
	Aqueous photodegradation (3328800)	Irradiated	pyridine	**93.8 (7)**	**93.6 (22)**
			azabicyclo	NA	
		Dark	pyridine	ND	
			azabicyclo	NA	
	Aerobic aquatic (3328811)			NA	
	Anaerobic aquatic (3328813)			NA	
	Aerobic soil (3328807)			NA	
	Anaerobic soil (3328809)			NA	
AY-5 6-hydroxynicotinic acid  **CAS#:** 5006-66-6 **Formula:** $C_6H_5NO_3$ **MW:** 139.11 g/mol	Hydrolysis[1] (3328796)	pH 4, 25°C	phenyl	NA	NA
			pyridine	ND	ND
		pH 7, 25°C	phenyl	NA	NA
			pyridine	ND	ND
		pH 9, 25°C	phenyl	NA	NA
			pyridine	**55.3 (30)**	**55.3 (30)**
	Hydrolysis[1] (3328798)	pH 4, 25°C	azabicyclo	NA	
	Soil photodegradation (3328802)			NA	
	Aqueous photodegradation (3328800)			NA	
	Aerobic aquatic (3328811)			NA	
	Anaerobic aquatic (3328813)			NA	
	Aerobic soil (3328807)			NA	
	Anaerobic soil (3328809)			NA	
AP-suc 4-oxo-3-{3-*endo*[2-propoxy-4-(trifluoromethyl)ph	Hydrolysis[1] (3328796)			NA	
	Hydrolysis[1] (3328798)			NA	
	Soil photodegradation (3328802)			NA	

Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
enoxy]-9-azabicyclo[3.3.1]nonan-9-yl}butyric acid  **Formula:** $C_{22}H_{28}F_3NO_5$ **MW:** 443.46 g/mol	Aqueous photodegradation (3328800)			NA	
	Aerobic aquatic (3328811)	LV, US	phenyl	**43.6 (32)**	**27.5 (102)**
			pyridine	NA	
			azabicyclo	**54.4 (32)**	**29.1 (102)**
		JW, US	phenyl	7.7 (1)	ND (102)
			pyridine	NA	
			azabicyclo	7.9 (1)	ND (100)
	Anaerobic aquatic (3328813)	JW, US	phenyl	0.3 (7, 14)	ND (100)
			pyridine	NA	
			azabicyclo	0.2 (0)	ND (100)
		BC, US	phenyl[2]	NA	**12.1 (104)**
			pyridine	NA	
			azabicyclo	7.0 (62)	4.3 (104)
	Aerobic soil (3328807)	E1 silt loam	phenyl	ND	
		J3 clay loam	phenyl	7.1 (120)	7.1 (120)
		NY silt loam	phenyl	ND	
		CA sandy loam	phenyl	ND	
			pyridine	NA	
			azabicyclo	ND	
	Anaerobic soil (3328809)			NA	
	Hydrolysis[1] (3328796)			NA	
	Hydrolysis[1] (3328798)			NA	
	Soil photodegradation (3328802)			NA	
	Aqueous photodegradation (3328800)			NA	

Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
AP-fum 4-oxo-4-{3-*endo*-[2-propoxy-4-(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonan-9-yl}crotonic acid  **Formula:** $C_{22}H_{26}F_3NO_5$ **MW:** 441.44 g/mol	Aerobic aquatic (3328811)	LV, US	phenyl	**16.1 (102)**	**16.1 (102)**
			pyridine	NA	
			azabicyclo	9.1 (60)	8.8 (102)
		JW, US	phenyl	ND	
			pyridine	NA	
			azabicyclo	ND	
	Anaerobic aquatic (3328813)			NA	
	Aerobic soil (3328807)			NA	
	Anaerobic soil (3328809)			NA	
AP-mal 3-oxo-3-{3-*endo*[2-propoxy-4-(trifluoromethyl)phenoxy]-9-azabicyclo[3.3.1]nonan-9-yl}propionic acid  **Formula:** $C_{21}H_{26}F_3NO_5$ **MW:** 429.43 g/mol	Hydrolysis[1] (3328796)			NA	
	Hydrolysis[1] (3328798)			NA	
	Soil photodegradation (3328802)			NA	
	Aqueous photodegradation (3328800)			NA	
	Aerobic aquatic (3328811)	LV, US	phenyl	**9.9 (102)**	**9.9 (102)**
			pyridine	NA	
			azabicyclo	4.4 (102)	4.4 (102)
		JW, US	phenyl	ND	
			pyridine	NA	
			azabicyclo	ND	
	Anaerobic aquatic (3328813)			NA	
	Aerobic soil (3328807)	E1 silt loam	phenyl	ND	
		J3 clay loam	phenyl	7.1 (120)	7.1 (120)
		NY silt loam	phenyl	ND	

Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
		CA sandy loam	phenyl	ND	
			pyridine	NA	
			azabicyclo	ND	
	Anaerobic soil (3328809)			NA	
AH 2-propoxy-4-(trifluoromethyl)phenol  **CAS#:** 866615-48-7 **Formula:** $C_{10}H_{11}F_3O_2$ **MW:** 220.19 g/mol	Hydrolysis[1] (3328796)	pH 4, 25°C	phenyl	**88.6 (7)**	**79.5 (30)**
			pyridine	NA	
		pH 7, 25°C		ND	
		pH 9, 25°C		ND	
	Hydrolysis[1] (3328798)			NA	
	Soil photodegradation (3328802)			NA	
	Aqueous photodegradation (3328800)			NA	
	Aerobic aquatic (3328811)			NA	
	Anaerobic aquatic (3328813)			NA	
	Aerobic soil (3328807)			NA	
	Anaerobic soil (3328809)			NA	
UK-15  *m/z* 122.1 *m/z* 154.1 (proposed structure)	Hydrolysis[1] (3328796)			NA	
	Hydrolysis[1] (3328798)	pH 4, 25°C	azabicyclo	**70.7 (15)**	**68.4 (30)**
	Soil photodegradation (3328802)			NA	
	Aqueous photodegradation (3328800)			NA	
	Aerobic aquatic (3328811)			NA	
	Anaerobic aquatic (3328813)			NA	
	Aerobic soil (3328807)			NA	
	Anaerobic soil (3328809)			NA	
Other					
	Hydrolysis[1] (3328796)			NA	

Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
Carbon dioxide, CO_2	Hydrolysis[1] (3328798)			NA	
	Soil photodegradation (3328802)	Irradiated	phenyl	0.6 (14)	0.6 (14)
			pyridine	6.4 (14)	6.4 (14)
			azabicyclo	0.0	
		Dark	phenyl	0.1 (14)	0.1 (14)
			pyridine	0.6 (8)	0.2 (14)
			azabicyclo	0.0	
	Aqueous photodegradation (3328800)			≤2.1	
	Aerobic aquatic (3328811)	LV, US	phenyl	2.0 (102)	2.0 (102)
			pyridine	**48.2 (102)**	**48.2 (102)**
			azabicyclo	1.0 (102)	1.0 (102)
		JW, US	phenyl	1.2 (100)	1.2 (100)
			pyridine	**26.0 (100)**	**26.0 (100)**
			azabicyclo	0.8 (100)	0.8 (100)
	Anaerobic aquatic (3328813)	JW, US	phenyl	0.6 (100)	0.6 (100)
			pyridine	**18.6 (100)**	**18.6 (100)**
			azabicyclo	0.2 (100)	0.2 (100)
		BC, US	phenyl[2]	0.8 (104)	0.8 (104)
			pyridine	**20.1 (104)**	**20.1 (104)**
			azabicyclo	0.1 (104)	0.1 (104)
	Aerobic soil (3328807)	E1 silt loam	phenyl	6.1 (120)	6.1 (120)
		J3 clay loam	phenyl	3.6 (120)	3.6 (120)
		NY silt loam	phenyl	6.8 (120)	6.8 (120)
			phenyl	7.3 (120)	7.3 (120)

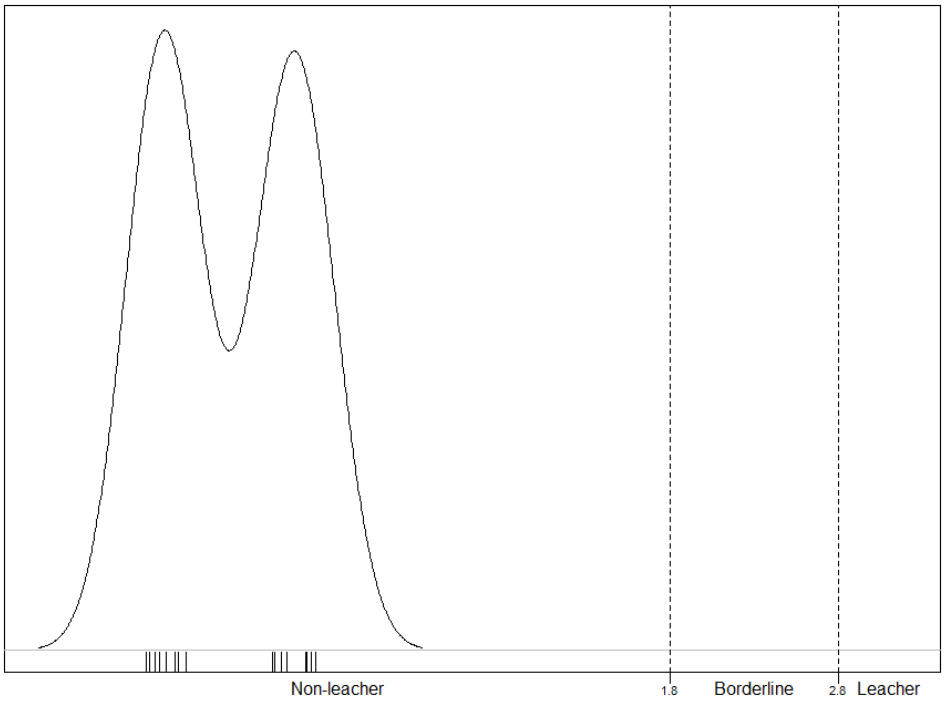
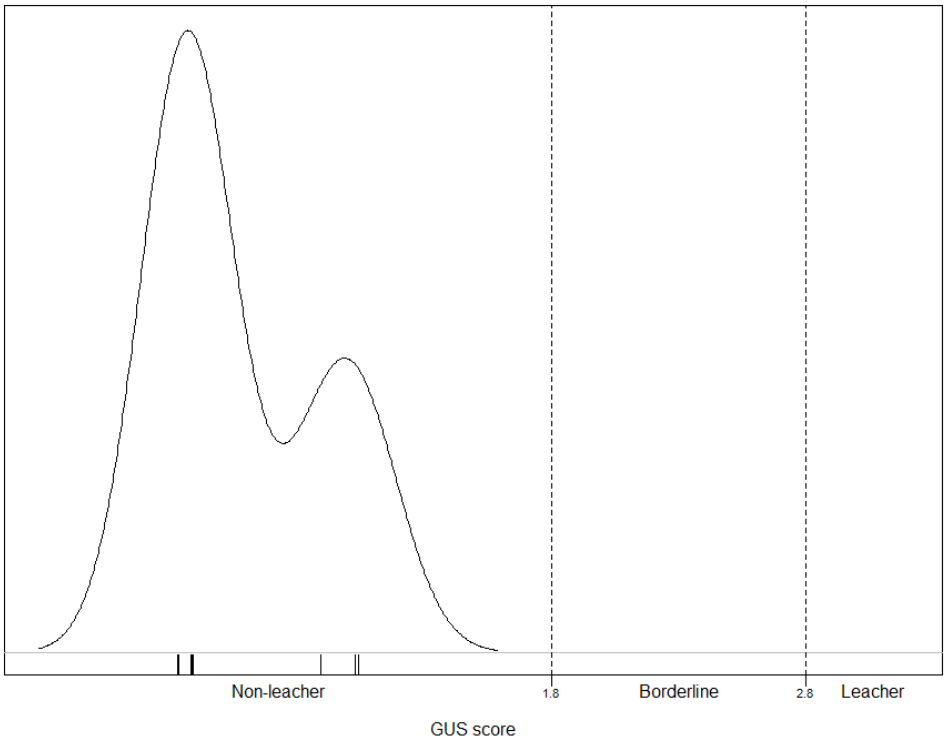
Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
		CA sandy loam	pyridine	**41.8 (120)**	**41.8 (120)**
			azabicyclo	9.5 (120)	9.5 (120)
	Anaerobic soil (3328809)	Hanford CA sandy loam	phenyl	2.6 (119)	2.6 (119)
			pyridine	9.7 (119)	9.7 (119)
			azabicyclo	8.1 (119)	8.1 (119)
Non-extractable residues (NER)	Hydrolysis[1] (3328796)			NA	
	Hydrolysis[1] (3328798)			NA	
	Soil photodegradation (3328802)	Irradiated	phenyl	4.0 (14)	4.0 (14)
			pyridine	**13.8 (14)**	**13.8 (14)**
			azabicyclo	4.0 (14)	4.0 (14)
		Dark	phenyl	2.4 (14)	2.4 (14)
			pyridine	2.0 (9)	1.7 (14)
			azabicyclo	2.4 (14)	2.4 (14)
	Aqueous photodegradation (3328800)			NA	
	Aerobic aquatic (3328811)	LV, US	phenyl	**18.5 (102)**	**18.5 (102)**
			pyridine	**13.3 (60)**	**11.5 (102)**
			azabicyclo	**12.9 (102)**	**12.9 (102)**
		JW, US	phenyl	**23.9 (100)**	**23.9 (100)**
			pyridine	**23.3 (100)**	**23.3 (100)**
			azabicyclo	**23.2 (100)**	**23.2 (100)**
	Anaerobic aquatic (3328813)	JW, US	phenyl	**9.7 (100)**	**9.7 (100)**
			pyridine	**14.8 (100)**	**14.8 (100)**
			azabicyclo	**9.8 (100)**	**9.8 (100)**
		BC, US	phenyl[2]	7.8 (104)	7.8 (104)
			pyridine	**10.9 (104)**	**10.9 (104)**

Compound	Study (PMRA No.)			Max %AR (d)	%AR at study end (study length, d)
			azabicyclo	7.6 (104)	7.6 (104)
	Aerobic soil (3328807)	E1 silt loam	phenyl	8.8 (120)	8.8 (120)
		J3 clay loam	phenyl	**19.3 (120)**	**19.3 (120)**
		NY silt loam	phenyl	**10.9 (120)**	**10.9 (120)**
		CA sandy loam	phenyl	**14.1 (120)**	**14.1 (120)**
			pyridine	**23.5 (120)**	**23.5 (120)**
			azabicyclo	**10.3 (120)**	**10.3 (120)**
	Anaerobic soil (3328809)	Hanford CA sandy loam	phenyl	**15.0 (119)**	**15.0 (119)**
			pyridine	8.0 (119)	8.0 (119)
			azabicyclo	**26.5 (119)**	**26.5 (119)**

Bolded when appearing at >10%. All values reported are means of replicates, where applicable.
NA: not applicable; ND: not detected
[1] Hydrolysis half-lives for the parent can be used; however, quantitative levels for the TPs may be underestimated. The azabicyclo-labelled hydrolysis study also did not provide an adequate understanding of the nature of hydrolysis products.
[2] The BC, US system dosed with phenyl-labelled acynonapyr was only analyzed at the 104 d interval.

Table 22 Leaching assessment of acynonapyr

Leaching criteria of Cohen et al. (1984)[1]		
Criteria	**Value (parent acynonapyr)**	**Meets criterion for leaching?**
Solubility in water: >30 mg/L	0.00228 mg/L	No
K_d (mL/g): <5 and usually <1 or 2	>90 mL/g	No
K_{oc}: <300	>5000	No
Henry's law constant (atm·m^3/mol): <10^{-2}	6.33E-6 atm·m^3/mol	Yes
pK_a: Negatively charged (either fully or partially) at ambient pH	Does not dissociate. Acynonapyr is a nonionic substance.	No
Hydrolysis half-life: >20 wks (>140 d)	13.2 d	No
Soil phototransformation half-life: >1 wk (>7 d)	20.3 d	Yes
Half-life in soil: >2 to 3 wks (>14 to 21 d)	41.5–78.4 d	Yes
Groundwater ubiquity score (GUS) assessment[1]		
GUS distribution plot		**Notes**

Acynonapyr  	The GUS distributions indicate that acynonapyr and its TP, AP, are unlikely to be leachers.
TP: AP  	

[1] Sufficient information on the properties of the major TPs of acynonapyr were not available to assess their leaching potential using the criteria of Cohen et al. (1984) and GUS.

Table 23 Estimated environmental concentrations (EECs) used in the risk assessment for acynonapyr

Environmental matrices	EEC[1]	Calculation details	Notes
Soil	0.057 mg a.i./kg soil dw	Assumes evenly distributed in the top 0–15 cm of soil with bulk density of 1.5 g/cm^3.	Used in the earthworm risk assessment.
Soil surfaces	127.6 g a.i./ha	Maximum single application rate.	Used for the terrestrial plant seedling emergence risk assessment.
Plant surfaces	In-field: 127.6 g a.i./ha Off-field: 94.4 g a.i./ha	In-field EECs were calculated based on a direct spray of acynonapyr to foliage. Off-field EECs are calculated by adjusting the in-field EECs by assuming 74% spray drift deposition at one metre downwind of the point of application (early airblast application).	Used for the terrestrial plant vegetative vigour and foliar dwelling beneficial arthropods risk assessment.
Adult bee diet	3.65 µg a.i./bee/day	Estimated oral exposure for bees = application rate (0.1276 kg a.i./ha) × adjustment factor • Adult adjustment factor of 28.62 µg a.i./bee per kg a.i./ha was calculated as the fc of 0.292 g/bee per d × 98 µg a.i./g per kg a.i./ha (default tall grass residues). • Larvae adjustment factor of 12.15 µg a.i./bee per kg a.i./ha was calculated as the fc of 0.124 g/bee per d × 98 µg a.i./g per kg a.i./ha (default tall grass residues).	Used to evaluate risks to bees (pollinators).
Bee larvae diet	1.55 µg a.i./bee/day		
Adult bee contact	0.306 µg a.i./bee	Estimated contact exposure (µg a.i./bee) = 2.4 µg a.i./bee/day per kg a.i./ha × maximum single application rate (0.1276 kg a.i./ha).	
Water	**Screening level**		
	Acynonapyr 80 cm depth: 0.016 mg a.i./L	Concentrations of acynonapyr in water were calculated based on a direct overspray of	Assumes instantaneous and homogeneous mixing.

<table>
<tr><th>Environmental matrices</th><th>EEC[1]</th><th>Calculation details</th><th>Notes</th></tr>
<tr><td></td><td>15 cm depth:
0.085 mg a.i./L

AP
80 cm depth:
0.011 mg AP/L
15 cm depth:
0.058 mg AP/L

AY
80 cm depth:
0.005 mg AY/L</td><td>acynonapyr to a one-hectare wetland with depths of 15 and 80 cm.

EECs for the major TPs were calculated considering 100% transformation of the parent on a molar basis. The conversion factor was calculated as the molecular weight of the TP divided by the molecular weight of the parent.</td><td>The EECs in surface water at 15-cm depth were used to evaluate risk to amphibians while the 80-cm depth EECs were used to evaluate risks to all other aquatic organisms.</td></tr>
<tr><td></td><td colspan="3">Refined runoff</td></tr>
<tr><td></td><td>Combined residues (acynonapyr, AP, and AY)

80 cm, 96 h:
0.00142 mg/L

80 cm, 21 d:
0.00115 mg/L

15 cm, 96 h:
0.00362 mg/L

15 cm, 21 d:
0.00195 mg/L

Pore water peak:
0.00075 mg/L</td><td colspan="2">For the ecological risk assessment, EECs in water are calculated by modelling a 10 ha field adjacent to 1 ha water bodies of two different depths, 80 cm and 15 cm, using the Pesticide in Water Calculator (PWC; version 2.0). The residue definition for ecological modelling was determined as the combined residue of acynonapyr, AP, and AY. The PWC model calculates the amount of pesticide entering the water body and the subsequent degradation of the pesticide in the water and sediment. In ecological modelling, pesticide enters the water by runoff only, and deposition of pesticide on the water body due to spray drift is not included. The model is run for 50 years.

For each year of the simulation, the PWC calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the peak concentrations over different time periods (24-h, 96-h, 21-d, 60-d, and 90-d). The highest value of these averages for each calendar year is then calculated. The 90th percentiles of these yearly maxima are reported as the EECs for that period. In addition, the peak and 21-d average EECs in sediment pore water are generated by the model. Ecological water model input parameters are presented below:
<table>
<tr><th>Parameter</th><th>Parent (acynonapyr)</th><th>Daughter1 (AP)</th><th>Daughter2 (AY)</th></tr>
<tr><td>Photolysis at 40°N latitude (d)</td><td>0.11</td><td>Stable (0.973)</td><td>2.28 (1.0)</td></tr>
</table>
</td></tr>
</table>

Environmental matrices	EEC[1]	Calculation details		Notes	
		Hydrolysis at pH 7 at 25°C (d)	12.6	Stable (1.0)	Stable (1.0)
		Aerobic aquatic half-life at 20°C (d)	1.0[1]	736.6[2] (0.829)	57.8[3] (1.0)
		Anaerobic aquatic half-life at 20°C (d)	0.15[1]	733.1[2] (0.857)	81.6[3] (0.982)
		Aerobic soil half-life at 20°C (d)	66.6[4]	158.5[5] (1.0)	332.2[6] (1.0)
		K_{oc} (L/kg)	18288[7]	5615[8]	632.6[9]
		Molecular weight (g/mol)	504.47	504.47	504.47
		Vapour pressure (torr)	8.47E-9	4.6E-7	2.5E-6
		Solubility (mg/L)	0.00228	238	5740
		Henry's law Constant	1.01E-4	3.57E-8	3.82E-9
		Air Diffusion Coefficient (cm^2/d)	3.00E+3	3.00E+3	3.00E+3
		Heat of Henry (J/mol)	45782	45782	45792

1 Longer of 2 values for acynonapyr.
2 Longer of 2 half-life values for Daughter1 with higher transformation fraction.
3 Longer of 2 half-life values for Daughter2 with higher transformation fraction.
4 Upper bound 90th percentile confidence on the mean of 4 values for acynonapyr.
5 Upper bound 90th percentile confidence on the mean of 4 values for Daughter1.
6 Upper bound 90th percentile confidence on mean of 3 values for AY.
7 20th percentile of 4 values for acynonapyr.
8 20th percentile of 3 values for AP.
9 Estimated K_{oc} for AY.

Environmental matrices	EEC[1]	Calculation details	Notes
		The aquatic refined risk assessments (spray drift and runoff) are captured in Appendix I, Tables 32 and 33, respectively.	
Birds and mammals	See Appendix I, Tables 28 and 30 for the EECs for food items for birds and mammals.		

[1] All EECs were based on the maximum application rate for pome fruit: A single foliar application of 127.6 g a.i./ha.

Table 24 Toxicity of acynonapyr, its transformation products (TPs), and end-use product to non-target terrestrial species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
Invertebrates					
Earthworm, *Eisenia fetida*	14-d Acute	Acynonapyr (technical grade active ingredient, purity 99.0%)	NOEC ≥ 1000 mg a.i./kg soil dw LC_{50}/EC_{50} > 1000 mg a.i./kg soil dw No significant effects on survival or growth up to the highest tested concentration.	NA	3328792
Earthworm, *Eisenia andrei*	56-d Chronic	Acynonapyr (technical grade active ingredient, purity 99.4%)	NOEC ≥ 1000 mg a.i./kg soil dw LOEC > 1000 mg a.i./kg soil dw No significant effects on survival, growth, and reproduction up to the highest tested concentration.	NA	3328794
Honey bee, *Apis mellifera*	48-h Acute oral, adults	Acynonapyr (technical grade active ingredient, purity 99%)	NOED ≥ 98.8 µg a.i./bee LD_{50} > 98.8 µg a.i./bee No significant mortality or sublethal effects up to the highest tested concentration.	Practically nontoxic	3328790
	48-h Acute contact, adults		NOED ≥ 100 µg a.i./bee LD_{50} > 100 µg a.i./bee No significant mortality or sublethal effects up		

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			to the highest tested concentration.		
	72-h Acute oral, larvae	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOED ≥ 100 µg a.i./bee LD_{50} > 100 µg a.i./bee No significant mortality or sublethal effects up to the highest tested concentration.	Practically nontoxic	3324625
	10-d Chronic oral, adults	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOED ≥ 92 µg a.i./bee/day LOED > 92 µg a.i./bee/day No significant mortality or sublethal effects up to the highest tested concentration.	No classification	3324627
	4-d Chronic oral, larvae	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOED = 12.2 µg a.i./bee/day LOED = 23.8 µg a.i./bee/day Significant effects on pupal mortality and adult emergence were observed at the highest treatment level.	No classification	3324626
Predatory arthropod (mite), *Typhlodromus pyri*	7-d Contact, glass plates	Acynonapyr (technical grade active ingredient, purity 99.0%)	NOER = 5 g a.i./ha (survival) LR_{50} = 13 g a.i./ha Significant mortality was observed at the two highest treatment levels.	No classification	3324632
	14-d Contact, spray residue leaf discs	End-use product, GWN-10409 (20.31% a.i.)	NOER ≥ 268.6 g a.i./ha ER/LR_{50} > 268.6 g a.i./ha No significant effects on survival or reproduction up to the highest treatment level.	No classification	3426852
Parasitic arthropod (wasp),	48-h Contact, glass plates	Acynonapyr (technical grade active	NOER ≥ 100 g a.i./ha LR_{50} > 100 g a.i./ha	No classification	3324633

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
Aphidius rhopalosiphi		ingredient, purity 99.2%)	No significant mortality up to the highest treatment level.		
	48-h Contact, glass plates	End-use product, GWN-10409 (20.31% a.i.)	NOER ≥ 268.6 g a.i./ha ER/LR_{50} > 268.6 g a.i./ha No significant effects on survival or reproduction up to the highest treatment level.	No classification	3426853
Predatory bug, *Orius laevigatus*	10-d Contact, spray residue leaf discs	End-use product, GWN-10409 (20.31% a.i.)	NOER ≥ 268.6 g a.i./ha (survival and fecundity) ER/LR_{50} > 268.6 g a.i./ha NOER = 2.15 g a.i./ha (fertility) ER_{50} > 53.7 g a.i./ha No significant effects on survival or fecundity up to the highest treatment level. Significant effects on fertility were observed at the three highest treatment levels; however, a definitive ER_{50} could not be determined due to an insufficient dose-response.	No classification	3426854
Ladybird beetle, *Coccinella septempunctata*	21-d Contact, spray residue leaf discs	End-use product, GWN-10409 (20.31% a.i.)	NOER ≥ 268.6 g a.i./ha LR_{50} > 268.6 g a.i./ha No significant mortality up to the highest treatment level.	No classification	3426855
Lacewing, *Chrysoperla carnea*	27-d Contact, spray residue leaf discs	End-use product, GWN-10409 (20.31% a.i.)	NOER ≥ 268.6 g a.i./ha (survival and fertility) ER/LR_{50} > 268.6 g a.i./ha No significant effects on survival or fertility	No classification	3426856

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			up to the highest treatment level. Effects on fecundity were observed at all but the lowest treatment level, but remained <50%, and were not analyzed.		
Rove beetle, *Aleochara bilineata*	75-d Contact, spray residue on soil	End-use product, GWN-10409 (20.31% a.i.)	NOER ≥ 269 g a.i./ha ER_{50} > 269 g a.i./ha No significant effects on reproduction up to the highest treatment level.	No classification	3426857
Birds					
Bobwhite quail, *Colinus virginianus*	Acute oral	Acynonapyr (technical grade active ingredient, purity 99.0%)	NOEL = 500 mg a.i./kg bw (body weight) LD_{50} > 2000 mg a.i./kg bw No significant mortality up to the highest tested concentration. Transient effects on body weight were observed at 1000 mg a.i./kg bw and higher.	Practically nontoxic	3328764
	5-d Dietary	Acynonapyr (technical grade active ingredient, purity 99.0%)	NOEL = 84 mg a.i./kg bw/day (body weight) LD_{50} > 1230 mg a.i./kg bw/day Significant effects on body weight were observed at all but the lowest tested concentration, and mortality was observed in the two highest tested concentrations.	Practically nontoxic	3328766
	25-wk Reproduction	Acynonapyr (technical grade active ingredient,	NOEL = 4.01 mg a.i./kg bw/day LOEL = 43.0 mg a.i./kg bw/day	No classification	3325065

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
		purity 98.8%)	Significant effects on adult female body weight gain, number of hatchlings, number of offspring survivors, hatchling weight, and offspring survivor weight were observed at the highest tested concentration.		
Mallard duck, *Anas platyrhynchos*	5-d Dietary	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEL < 64 mg a.i./kg bw/day (body weight) LD_{50} = 347.8 mg a.i./kg bw/day Significant effects on body weight were observed in all treatment groups, and significant mortality was observed at the highest tested concentration.	Slightly toxic	3328768
	25-wk Reproduction	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEL = 4.48 mg a.i./kg bw/day LOEL = 56.1 mg a.i./kg bw/day Significant effects on adult mortality, adult male and female body weight gain, adult feed consumption, and number of eggs per hen were observed at the highest tested concentration.	No classification	3325066
Zebra finch, *Taeniopygia guttata*	Acute oral	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEL ≥ 2000 mg a.i./kg bw LD_{50} > 2000 mg a.i./kg bw No significant mortality or effects up to the highest tested concentration.	Practically nontoxic	3325063

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
Mammals					
Rat (Sprague Dawley)	Acute oral	Acynonapyr (technical grade active ingredient, purity 99.4%)	LD_{50} > 2000 mg a.i./kg bw	Practically nontoxic	3328833
	Acute oral	End-use product, GWN-10409 (19.9% a.i.)	LD_{50} > 2000 mg EP/kg bw (> 398 mg a.i./kg bw)	Practically nontoxic	3328925
	Acute oral	TP, AP (purity 99.4%)	LD_{50} = 500 mg a.i./kg bw	Moderately toxic	3328628
	Acute oral	TP, AY (purity 99.9%)	LD_{50} = 500 mg a.i./kg bw	Moderately toxic	3328632
	Acute oral	TP, AY-5 (purity 97.6%)	LD_{50} > 2000 mg a.i./kg bw	Practically nontoxic	3328636
	Acute oral	TP, AH (purity >99.9%)	LD_{50} > 2000 mg a.i./kg bw	Practically nontoxic	3328638
	2-Generation reproduction	Acynonapyr (technical grade active ingredient, purity 99.2%)	NOEC = 400 mg a.i./kg diet NOEL = 24 mg a.i./kg bw/day Significant effects on parents, offspring, and other parameters describing reproductive performance.	No classification	3328878
Vascular plants					
4 Monocot and 6 dicot crop species (Monocots: corn, oat,	14-d Seedling emergence	End-use product, GWN-10409 (20.31% a.i.)	NOER = 100 g a.i./ha (cucumber, shoot length and dry weight) ER_{25} > 200 g a.i./ha (all species)	No classification	3324608

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
onion, and ryegrass; Dicots: cabbage, tomato, radish, soybean, sunflower, and cucumber)	21-d Vegetative vigour	End-use product, GWN-10409 (20.31% a.i.)	NOER ≥ 200 g a.i./ha ER_{25} > 200 g a.i./ha (all species)	No classification	3324606

[1] Atkins et al. (1981) for bees and USEPA classification for others, where applicable.

Table 25 Toxicity of acynonapyr, its transformation products (TPs), and end-use product to non-target aquatic species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
Freshwater species					
Daphnia magna	48-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0092 mg a.i./L LC_{50}/EC_{50} > 0.0092 mg a.i./L (immobilization) No significant immobilization up to the highest tested concentration. Sublethal effects (lethargy) observed at the two highest tested concentrations.	No immobilization observed up to the functional solubility limit	3324628
	48-h Acute, static-renewal	End-use product, GWN-10409 (20.31% a.i.)	NOEC ≥ 1.9 mg a.i./L (≥ 15 mg end-use product/L nominal) LC_{50}/EC_{50} > 1.9 mg a.i./L (> 15 mg end-use product/L nominal) (immobilization) No significant immobilization up to the highest tested concentration. Sublethal effects (lethargy) observed at the two	No immobilization observed up to the functional solubility limit	3324622

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			highest tested concentrations.		
	48-h Acute, static-renewal	TP, AP (purity 98.9%)	NOEC = 1.5 mg AP/L LC_{50}/EC_{50} = 3.2 mg AP/L (immobilization) Significant immobilization was observed at the three highest tested concentrations.	Moderately toxic	3324624
	48-h Acute, static	TP, AY (purity 98.0%)	NOEC ≥ 96 mg AY/L LC_{50}/EC_{50} > 96 mg AY/L (immobilization) No significant immobilization or sublethal effects at the tested concentration.	Practically nontoxic	3328897
	21-d Chronic, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC = 0.00083 mg a.i./L LOEC = 0.0018 mg a.i./L (body length) Significant effects on body length and reproduction were observed at the two highest tested concentrations.	No classification	3324614
Amphipod, *Hyalella azteca*	10-d Spiked sediment, static-renewal	Acynonapyr (technical grade active ingredient), purity 98.8%)	Mean measured pore water (estimated freely dissolved pore water): NOEC ≥ 0.042 mg a.i./L (≥ 0.10 mg a.i./L) LOEC > 0.042 mg a.i./L (> 0.10 mg a.i./L) LC_{50}/EC_{50} > 0.042 mg a.i./L (> 0.10 mg a.i./L) (mortality and larval weight)	No classification	3324616

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			The mean overlying water concentration of the parent was 0.15 mg a.i./L for the highest treatment concentration. No significant effects on mortality or amphipod dry weight up to the highest tested concentration.		
Midge, *Chironomus dilutus*	10-d Spiked sediment, static-renewal	Acynonapyr (technical grade active ingredient, purity 98.8%)	Mean measured pore water (estimated freely dissolved pore water): NOEC = 0.038 mg a.i./L (0.013 mg a.i./L) LOEC = 0.083 mg a.i./L (0.025 mg a.i./L) (larval weight) LC_{50}/EC_{50} > 0.12 mg a.i./L (> 0.055 mg a.i./L) (mortality and larval weight) The mean overlying water concentration of the parent was 0.050 mg a.i./L for the highest treatment concentration. No significant effects on mortality up to the highest tested concentration. Significant effects on larval dry weight were observed at the two highest tested concentrations.	No classification	3324615
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 99.0%)	NOEC ≥ 0.02051 mg a.i./L (unfiltered) OR ≥ 0.00125 mg a.i./L (filtered) LC_{50} > 0.02051 mg a.i./L (unfiltered) OR	Nontoxic up to the functional solubility limit	3328776

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			> 0.00125 mg a.i./L (filtered) (mortality) No significant mortality or sublethal effects at the tested concentration.		
	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.012 mg a.i./L LC_{50} > 0.012 mg a.i./L (mortality) No significant mortality or sublethal effects at the tested concentration.	Nontoxic up to the functional solubility limit	3325053
	96-h Acute, static-renewal	End-use product, GWN-10409 (20.31% a.i.)	NOEC ≥ 4.5 mg a.i./L (≥ 30 mg end-use product/L nominal) LC_{50} > 4.5 mg a.i./L (> 30 mg end-use product/L nominal) (mortality) No significant mortality or sublethal effects up to the highest tested concentration.	Nontoxic up to the highest tested concentration	3325060
	96-h Acute, static-renewal	TP, AP (purity 98.9%)	NOEC = 2.8 mg AP/L LC_{50} = 3.7 mg AP/L (mortality) Significant mortality was observed at the three highest tested concentrations.	Moderately toxic	3325054
Bluegill, *Lepomis macrochirus*	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 99.4%)	NOEC ≥ 0.04185 mg a.i./L LC_{50} > 0.04185 mg a.i./L (mortality) No significant mortality or sublethal effects at the tested concentration.	Nontoxic up to the functional solubility limit	3328778
	96-h Acute, flow-through	TP, AP (purity 98.9%)	NOEC = 4.0 mg AP/L LC_{50} = 6.3 mg AP/L (mortality)	Moderately toxic	3325055

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			Significant mortality was observed at the highest tested concentration.		
Carp, *Cyprinus carpio*	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 99.0%)	NOEC ≥ 0.02323 mg a.i./L (unfiltered) OR ≥ 0.00087 mg a.i./L (filtered) LC_{50} > 0.02323 mg a.i./L (unfiltered) OR > 0.00087 mg a.i./L (filtered) (mortality) No significant mortality or sublethal effects at the tested concentration.	Nontoxic up to the functional solubility limit	3328780
Fathead minnow, *Pimephales promelas*	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0055 mg a.i./L LC_{50} > 0.0055 mg a.i./L (mortality) No significant mortality or sublethal effects at the tested concentration.	Nontoxic up to the functional solubility limit	3325056
	32-d ELS, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0057 mg a.i./L LOEC > 0.0057 mg a.i./L No significant effects on any endpoint up to the highest tested concentration.	No classification	3325059
Diatom, *Navicula pelliculosa*	96-h Acute, static	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0024 mg a.i./L EC_{50} > 0.0024 mg a.i./L No significant inhibition of yield, growth rate, and AUGC at the tested concentration. A stimulatory effect was observed.	Nontoxic up to the functional solubility limit	3324600
	96-h Acute, static	End-use product,	NOEC ≥ 0.11 mg a.i./L (≥ 15 mg end-use product/L nominal)	Nontoxic up to the highest	3324602

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
		GWN-10409 (20.31% a.i.)	EC_{50} > 0.11 mg a.i./L (> 15 mg end-use product/L nominal) No significant inhibition of yield, growth rate, and AUGC up to the highest tested concentration.	tested concentration	
Green algae, *Raphidocelis subcapitata*	96-h Acute, static	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0024 mg a.i./L EC_{50} > 0.0024 mg a.i./L No significant inhibition of yield, growth rate, and AUGC at the tested concentration. A stimulatory effect was observed.	Nontoxic up to the functional solubility limit	3324605
	96-h Acute, static	End-use product, GWN-10409 (20.31% a.i.)	NOEC ≥ 0.60 mg a.i./L (≥ 15 mg end-use product/L nominal) EC_{50} > 0.60 mg a.i./L (> 15 mg end-use product/L nominal) No significant inhibition of yield, growth rate, and AUGC up to the highest tested concentration. A stimulatory effect was observed.	Nontoxic up to the highest tested concentration	3324601
	96-h Acute, static	TP, AP (purity 98.9%)	NOEC = 0.011 mg AP/L EC_{50} = 0.025 mg AP/L (AUGC) Significant inhibition of yield, growth rate, and AUGC were observed at the four highest tested concentrations.	Very highly toxic	3324604
Blue-green algae, *Anabaena flos-aquae*	96-h Acute, static	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0034 mg a.i./L EC_{50} > 0.0034 mg a.i./L No significant inhibition of yield, growth rate, and	Nontoxic up to the functional solubility limit	3324599

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			AUGC at the tested concentration.		
	96-h Acute, static	End-use product, GWN-10409 (20.31% a.i.)	NOEC ≥ 0.24 mg a.i./L (≥ 15 mg end-use product/L nominal) EC_{50} > 0.24 mg a.i./L (> 15 mg end-use product/L nominal) No significant inhibition of yield, growth rate, and AUGC up to the highest tested concentration.	Nontoxic up to the highest tested concentration	3324603
Vascular plant, duckweed, *Lemna gibba*	7-d Static renewal	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.006 mg a.i./L EC_{50} > 0.006 mg a.i./L No significant effects at the tested concentration.	No classification	3324610
	7-d Static renewal	End-use product, GWN-10409 (20.31% a.i.)	NOEC = 1.4 mg a.i./L (7.5 mg end-use product/L nominal) EC_{50} > 2.9 mg a.i./L (> 15 mg end-use product/L nominal) Significant effects on yield and growth rate were observed at the highest tested concentration.	No classification	3324609
Marine species					
Amphipod, *Leptocheirus plumulosus*	10-d Spiked sediment, static	Acynonapyr (technical grade active ingredient, purity 98.8%)	Mean measured pore water (estimated freely dissolved pore water): NOEC ≥ 0.054 mg a.i./L (≥ 0.015 mg a.i./L) LOEC > 0.054 mg a.i./L (> 0.015 mg a.i./L) LC_{50}/EC_{50} > 0.054 mg a.i./L (> 0.015 mg a.i./L) (mortality and sublethal effects)	No classification	3324623

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
			The mean overlying water concentration of the parent was 0.0018 mg a.i./L for the highest treatment concentration. No significant mortality or sublethal effects up to the highest tested concentration.		
Crustacean, mysid shrimp, *Americamysis bahia*	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0044 mg a.i./L LC_{50}/EC_{50} > 0.0044 mg a.i./L No significant mortality or sublethal effects up to the highest tested concentration.	Nontoxic up to the functional solubility limit	3324631
	28-d Chronic, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC = 0.0036 mg a.i./L LOEC = 0.0077 mg a.i./L (female body length) Significant effects on female body length were observed at the highest tested concentration.	No classification	3324629
Mollusk, Eastern oyster, *Crassostrea virginica*	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0049 mg a.i./L LC_{50}/EC_{50} > 0.0049 mg a.i./L No significant effects on mortality and shell deposition at the tested concentration.	Nontoxic up to the functional solubility limit	3324630
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0071 mg a.i./L LC_{50} > 0.0071 mg a.i./L (mortality) No significant mortality or sublethal effects at the tested concentration.	Nontoxic up to the functional solubility limit	3325057

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Study PMRA No.
	34-d ELS, flow-through	Acynonapyr (technical grade active ingredient, purity 98.8%)	NOEC ≥ 0.0067 mg a.i./L LOEC > 0.0067 mg a.i./L No significant effects on any endpoint up to the highest tested concentration.	No classification	3325058
Diatom, *Skeletonema costatum*	96-h Acute, static	Acynonapyr (technical grade active ingredient, purity 98.8%)	EC_{50} > 0.0027 mg a.i./L Effects were noted at all treatment levels; however, a clear dose response was not determined.	Nontoxic up to the functional solubility limit	3324607
	96-h Acute, static	End-use product, GWN-10409 (20.31% a.i.)	NOEC = 0.064 mg a.i./L (3.8 mg end-use product/L nominal) EC_{50} = 0.16 mg a.i./L (9.9 mg end-use product/L nominal) (AUGC) Significant inhibition of yield, growth rate, and AUGC were observed at the two highest tested concentrations.	Highly toxic	3324611

[1] USEPA classification, where applicable. Because of the low solubility, even when using solvents, acute toxicity classifications remain uncertain for many of the studies. These are indicated in the table as "nontoxic up to the functional solubility limit", that is, the apparent solubility under test conditions, when no lethal or sublethal effects were observed at the tested concentrations.

Table 26 Endpoints and uncertainty factors (UFs) used to establish effects metrics as well as the level of concern (LOC) used for the risk assessment

Organism	Exposure – test substance	Endpoint	Value	UF	LOC
Terrestrial species					
Earthworm, *Eisenia fetida* or *Eisenia andrei*	14-d Acute – a.i.	LC_{50}	>1000 mg a.i./kg soil dw	2	1
	56-d Reproduction – a.i.	NOEC	≥1000 mg a.i./kg soil dw	1	1
Honey bee,	48-h Acute oral, adults – a.i.	LD_{50}	>98.8 µg a.i./bee	1	0.4

Organism	Exposure – test substance	Endpoint	Value	UF	LOC
Apis mellifera	48-h Acute contact, adults – a.i.	LD_{50}	>100 µg a.i./bee	1	0.4
	72-h Acute oral, larvae – a.i.	LD_{50}	>100 µg a.i./bee	1	0.4
	10-d Chronic oral, adults – a.i.	NOED	≥92 µg a.i./bee/d	1	1
	4-d Chronic oral, larvae – a.i.	NOED	12.2 µg a.i./bee/d	1	1
Predatory arthropod, *Typhlodromus pyri*	7-d Contact, glass plates – a.i.	LR_{50}	13 g a.i./ha	1	2
	14-d Contact, spray residue leaves – end-use product	ER/LR_{50}	>268.6 g a.i./ha	1	1
Parasitic arthropod, *Aphidius rhopalosiphi*	48-h Contact, glass plates – a.i.	LR_{50}	>100 g a.i./ha	1	2
	48-h Contact, glass plates – end-use product	ER/LR_{50}	>268.6 g a.i./ha	1	2
Predatory bug, *Orius laevigatus*	10-d Contact, spray residue leaves – end-use product	ER_{50}	>53.7 g a.i./ha	1	1
		LR_{50}	>268.6 g a.i./ha	1	1
Ladybird beetle, *Coccinella septempunctata*	21-d Contact, spray residue leaves – end-use product	LR_{50}	>268.6 g a.i./ha	1	1
Lacewing, *Chrysoperla carnea*	27-d Contact, spray residue leaves – end-use product	ER/LR_{50}	>268.6 g a.i./ha	1	1
Rove beetle, *Aleochara bilineata*	75-d Contact, spray residue soil – end-use product	ER_{50}	>269 g a.i./ha	1	1
Bobwhite quail, *Colinus virginianus*	Acute oral – a.i.	LD_{50}	>2000 mg a.i./kg bw	10	1
	5-d Acute dietary – a.i.	LD_{50}	>1230 mg a.i./kg bw/d	10	1
	25 wk Reproduction – a.i.	NOEL	4.01 mg a.i./kg bw/d	1	1
Mallard duck, *Anas platyrhynchos*	5-d Acute dietary – a.i.	LD_{50}	347.8 mg a.i./kg bw/d	10	1
	25-wk Reproduction – a.i.	NOEL	4.48 mg a.i./kg bw/d	1	1
Zebra finch, *Taeniopygia guttata*	Acute oral – a.i.	LD_{50}	>2000 mg a.i./kg bw	10	1
Rat (Sprague Dawley)	Acute oral – a.i.	LD_{50}	>2000 mg a.i./kg bw	10	1
	Acute oral – end-use product	LD_{50}	>398 mg a.i./kg bw	10	1

Organism	Exposure – test substance	Endpoint	Value	UF	LOC
	Acute oral – TP, AP	LD_{50}	500 mg a.i./kg bw	10	1
	Acute oral – TP, AY	LD_{50}	500 mg a.i./kg bw	10	1
	Acute oral – TP, AY-5	LD_{50}	>2000 mg a.i./kg bw	10	1
	Acute oral – TP, AH	LD_{50}	>2000 mg a.i./kg bw	10	1
	Reproduction – a.i.	NOEL	24 mg a.i./kg bw/d	1	1
Terrestrial vascular plants	14-d Seedling emergence	ER_{25}	>200 g a.i./ha	1	1
	21-d Vegetative vigour	ER_{25}	>200 g a.i./ha	1	1
Freshwater species					
Invertebrate, *Daphnia magna*	48-h Acute – a.i.	EC_{50}	>0.0092 mg a.i./L	2	1
	48-h Acute – end-use product	EC_{50}	>1.9 mg a.i./L	2	1
	48-h Acute – TP, AP	EC_{50}	3.2 mg AP/L	2	1
	48-h Acute – TP, AY	EC_{50}	>96 mg AY/L	2	1
	21-d Chronic – a.i.	NOEC	0.00083 mg a.i./L	1	1
Amphipod, *Hyalella azteca*	10-d Acute – a.i. (spiked sediment)	EC_{50}	>0.042 mg a.i./L (pore water) >0.15 mg a.i./L (overlying water)	2	1
Midge, *Chironomus dilutus*	10-d Acute – a.i. (spiked sediment)	EC_{50}	>0.12 mg a.i./L (pore water) >0.050 mg a.i./L (overlying water)	2	1
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute – a.i.	LC_{50}	>0.02051 mg a.i./L	10	1
	96-h Acute – a.i.	LC_{50}	>0.012 mg a.i./L	10	1
	96-h Acute – end-use product	LC_{50}	>4.5 mg a.i./L	10	1
	96-h Acute – TP, AP	LC_{50}	3.7 mg AP/L	10	1
Bluegill, *Lepomis macrochirus*	96-h Acute – a.i.	LC_{50}	>0.04185 mg a.i./L	10	1
	96-h Acute – TP, AP	LC_{50}	6.3 mg AP/L	10	1
Carp, *Cyprinus carpio*	96-h Acute – a.i.	LC_{50}	>0.02323 mg a.i./L	10	1

Organism	Exposure – test substance	Endpoint	Value	UF	LOC
Fathead minnow, *Pimephales promelas*	96-h Acute – a.i.	LC_{50}	>0.0055 mg a.i./L	10	1
	32-d ELS – a.i.	NOEC	≥0.0057 mg a.i./L	1	1
Amphibians (using fish data as a surrogate) [2]	96-h Acute – a.i.	LC_{50}	>0.04185 mg a.i./L	10	1
	96-h Acute – TP, AP	LC_{50}	3.7 mg AP/L	10	1
	32-d Chronic – a.i.	NOEC	≥0.0057 mg a.i./L	1	1
Aquatic vascular plants, *Lemna gibba*	7-d Acute – a.i.	EC_{50}	>0.006 mg a.i./L	2	1
	7-d Acute – end-use product	EC_{50}	>2.9 mg a.i./L	2	1
Diatom, *Navicula pelliculosa*	96-h Acute – a.i.	EC_{50}	>0.0024 mg a.i./L	2	1
	96-h Acute – end-use product	EC_{50}	>0.11 mg a.i./L	2	1
Green algae, *Raphidocelis subcapitata*	96-h Acute – a.i.	EC_{50}	>0.0024 mg a.i./L	2	1
	96-h Acute – end-use product	EC_{50}	>0.60 mg a.i./L	2	1
	96-h Acute – TP, AP	EC_{50}	0.025 mg AP/L	2	1
Blue-green algae, *Anabaena flos-aquae*	96-h Acute – a.i.	EC_{50}	>0.0034 mg a.i./L	2	1
	96-h Acute – end-use product	EC_{50}	>0.24 mg a.i./L	2	1
Marine species					
Amphipod, *Leptocheirus plumulosus*	10-d Acute – a.i. (spiked sediment)	EC_{50}	>0.054 mg a.i./L (pore water) >0.0018 mg a.i./L (overlying water)	2	1
Crustacean, mysid shrimp, *Americamysis bahia*	96-h Acute – a.i.	LC_{50}	>0.0044 mg a.i./L	2	1
	28-d Chronic – a.i.	NOEC	0.0036 mg a.i./L	1	1
Mollusk, Eastern oyster, *Crassostrea virginica*	96-h Acute – a.i.	EC_{50}	>0.0049 mg a.i./L	2	1
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute – a.i.	LC_{50}	>0.0071 mg a.i./L	10	1
	34-d ELS – a.i.	NOEC	≥0.0067 mg a.i./L	1	1
Diatom,	96-h Acute – a.i.	EC_{50}	>0.0027 mg a.i./L	2	1

Organism	Exposure – test substance	Endpoint	Value	UF	LOC
Skeletonema costatum	96-h Acute – end-use product	EC_{50}	0.16 mg a.i./L	2	1

[1] As no significant mortality or effects were observed in any of the acute or chronic fish studies with the technical grade active ingredient up to the highest tested concentration (functional solubility of the compound), the highest technical grade active ingredient endpoint of all the fish studies was used as the surrogate for amphibians.

Table 27 Screening-level risk assessment of acynonapyr for non-target terrestrial species other than birds and mammals

Organism	Exposure – test substance	Effect metric (endpoint/UF)	EEC[1]	RQ[2]	LOC
Invertebrates					
Earthworm, *Eisenia fetida* or *Eisenia andrei*	Acute – a.i.	LC_{50}/2: >500 mg a.i./kg soil dw	0.057 mg a.i./kg soil dw	<0.1	Not exceeded
	Reproduction – a.i.	NOEC: ≥1000 mg a.i./kg soil dw	0.057 mg a.i./kg soil dw	<0.1	Not exceeded
Honey bee, *Apis mellifera*	Acute oral, adults – a.i.	LD_{50}: >98.8 µg a.i./bee	3.65 µg a.i./bee/day	<0.1	Not exceeded
	Acute contact, adults – a.i.	LD_{50}: >100 µg a.i./bee	0.306 µg a.i./bee	<0.1	Not exceeded
	Acute oral, larvae – a.i.	LD_{50}: >100 µg a.i./bee	1.55 µg a.i./bee/day	<0.1	Not exceeded
	Chronic oral, adults – a.i.	NOED: ≥92 µg a.i./bee/day	3.65 µg a.i./bee/day	<0.1	Not exceeded
	Chronic oral, larvae – a.i.	NOED: 12.2 µg a.i./bee/day	1.55 µg a.i./bee/day	0.1	Not exceeded
Predatory arthropod, *Typhlodromus pyri*	Contact, glass plates – a.i.	LR_{50}: 13 g a.i./ha	In-field: 127.6 g a.i./ha	**9.8**	Exceeded
			Off-field: 94.4 g a.i./ha[3]	**7.3**	Exceeded
Parasitic arthropod, *Aphidius rhopalosiphi*	Contact, glass plates – a.i.	LR_{50}: >100 g a.i./ha	In-field: 127.6 g a.i./ha	<1.3	Not exceeded
			Off-field: 94.4 g a.i./ha[3]	<1.0	Not exceeded
	Contact, glass plates – end-use product	ER/LR_{50}: >268.6 g a.i./ha	In-field: 127.6 g a.i./ha	<0.5	Not exceeded
Vascular plants					
Vascular plant	Seedling emergence	ER_{25}: >200 g a.i./ha	127.6 g a.i./ha	<0.7	Not exceeded
	Vegetative vigour	ER_{25}: >200 g a.i./ha	127.6 g a.i./ha	<0.7	Not exceeded

[1] Estimated environmental concentration (EEC) and estimated environmental rate (EER) calculated based on the proposed use pattern for pome fruit of a single application of 127.6 g a.i./ha. The EEC is calculated for a soil depth of 15 cm, and density equal to 1.5 g/cm^3.

Exposure estimates for bees (µg a.i./bee) were calculated the following way:

Contact exposure route: maximum single application rate (kg a.i./ha) × 2.4 µg a.i./bee per kg a.i./ha;
Oral exposure route following foliar application: maximum single application rate (kg a.i./ha) × 98 µg a.i./bee × consumption rate;
Where: The maximum single application rate is 0.1276 kg a.i./ha, and the consumption rate is 0.292 g/day for adult bees and 0.124 g/day for larvae.

[2] **Bolded** when exceeding the LOC (LOC = 1 for most species; 0.4 for acute risk to pollinators; 1 for chronic risk to pollinators; and 2 for glass plate studies using the standard beneficial arthropod test species, *Typhlodromus pyri* and *Aphidius rhopalosiphi*).

[3] Off-field EEC using a maximum percent drift deposition at one metre downwind (74% for early airblast) from the point of application and the proposed use on outdoor pome fruit of a single application of 127.6 g a.i./ha.

Table 28 Screening-level risk assessment of acynonapyr and its transformation products (TPs) for birds and mammals

	Effect metric (mg a.i./kg bw/day)	Food guild (food item)	EDE (mg a.i./kg bw)[1]	RQ[2]	LOC
Small bird (0.02 kg)					
Acute	>200	Insectivore	10.3	<0.1	Not exceeded
Reproduction	4.01	Insectivore	10.3	**2.6**	Exceeded
Medium-sized bird (0.1 kg)					
Acute	>200	Insectivore	8.12	<0.1	Not exceeded
Reproduction	4.01	Insectivore	8.12	**2.0**	Exceeded
Large-sized bird (1 kg)					
Acute	>200	Herbivore (short grass)	5.24	<0.1	Not exceeded
Reproduction	4.01	Herbivore (short grass)	5.24	**1.3**	Exceeded
Small mammal (0.015 kg)					
Acute – technical grade active ingredient	>200[3]	Insectivore	5.91	<0.1	Not exceeded
Acute – TP, AP	50	Insectivore	4.02	<0.1	Not exceeded
Acute – TP, AY	50	Insectivore	1.91	<0.1	Not exceeded
Acute – TP, AY-5	>200	Insectivore	1.63	<0.1	Not exceeded
Acute – TP, AH	>200	Insectivore	2.58	<0.1	Not exceeded
Reproduction	24	Insectivore	5.91	0.2	Not exceeded

	Effect metric (mg a.i./kg bw/day)	Food guild (food item)	EDE (mg a.i./kg bw)[1]	RQ[2]	LOC
Medium-sized mammal (0.035 kg)					
Acute – technical grade active ingredient	>200[3]	Herbivore (short grass)	11.2	<0.1	Not exceeded
Acute – TP, AP	50	Herbivore (short grass)	7.66	0.2	Not exceeded
Acute – TP, AY	50	Herbivore (short grass)	3.64	<0.1	Not exceeded
Acute – TP, AY-5	>200	Herbivore (short grass)	3.1	<0.1	Not exceeded
Acute – TP, AH	>200	Herbivore (short grass)	4.91	<0.1	Not exceeded
Reproduction	24	Herbivore (short grass)	11.2	0.5	Not exceeded
Large-sized mammal (1 kg)					
Acute – technical grade active ingredient	>200[3]	Herbivore (short grass)	6.19	<0.1	Not exceeded
Acute – TP, AP	50	Herbivore (short grass)	4.21	<0.1	Not exceeded
Acute – TP, AY	50	Herbivore (short grass)	2.0	<0.1	Not exceeded
Acute – TP, AY-5	>200	Herbivore (short grass)	1.71	<0.1	Not exceeded
Acute – TP, AH	>200	Herbivore (short grass)	2.7	<0.1	Not exceeded
Reproduction	24	Herbivore (short grass)	6.19	0.3	Not exceeded

[1] EDE = estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR = food ingestion rate (Nagy, 1987);
For generic birds with bw less than or equal to 200 g, the "passerine" equation was used; for generic birds with bw greater than 200 g, the "all birds" equation was used:
Passerine equation (bw < or = 200 g): FIR (g dw/day) = 0.398(bw in g)$^{0.850}$
All birds equation (bw > 200 g): FIR (g dw/day) = 0.648(bw in g)$^{0.651}$
For mammals, the "all mammals" equation was used: FIR (g dw/day) = 0.235(bw in g)$^{0.822}$
bw = generic body weight;
EEC = Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

[2] **Bolded** when exceeding the LOC (LOC = 1 for birds and mammals).

[3] The acute LD_{50} value of >2000 mg a.i./kg bw obtained from the study with the technical grade active ingredient was used in the screening level risk assessment. Technical grade acynonapyr and its end-use product were both practically nontoxic to rats on an acute oral basis, with oral LD_{50} values >2000 mg product/kg bw. There were only minor clinical signs of toxicity at the highest tested concentration for both acute oral studies (that is, soft stools and loss of hair). When accounting for the active ingredient content of the test substance, the endpoint from the study with the end-use product is more

conservative than the one from the study with acynonapyr; however, this is more a result of the test compound being a formulated product than an indication of higher toxicity.

Table 29 Further characterization of risk to non-target beneficial arthropods considering vegetation distribution factors, deposition fractions, and results from extended laboratory studies

Organism	Exposure – test substance	Effect metric (g a.i./ha)	EEC (g a.i./ha)[1]	RQ[2]	LOC
On-field assessment:					
Tier I – Laboratory studies					
Predatory mite, *Typhlodromus pyri*	Contact, glass plates – a.i.	LR_{50}: 13	102	**7.8**	Exceeded
Parasitic wasp, *Aphidius rhopalosiphi*	Contact, glass plates – a.i.	LR_{50}: >100	102	<1.1	Not exceeded
	Contact, glass plates – end-use product	ER/LR_{50}: >268.6	102	<0.4	Not exceeded
Tier II – Extended laboratory studies					
Predatory mite, *Typhlodromus pyri*	Contact, spray residue leaves – end-use product	ER/LR_{50}: >268.6	102	<0.4	Not exceeded
Predatory bug, *Orius laevigatus*	Contact, spray residue leaves – end-use product	ER_{50}: >53.7	102	**<1.9**	Exceeded
		LR_{50}: >268.6	102	<0.4	Not exceeded
Ladybird beetle, *Coccinella septempunctata*	Contact, spray residue leaves – end-use product	LR_{50}: >268.6	102	<0.4	Not exceeded
Lacewing, *Chrysoperla carnea*	Contact, spray residue leaves – end-use product	ER/LR_{50}: >268.6	102	<0.4	Not exceeded
Rove beetle, *Aleochara bilineata*	Contact, spray residue soil – end-use product	ER_{50}: >269	76.6	<0.3	Not exceeded
Off-field assessment:					
Tier I – Laboratory studies					
Predatory mite, *Typhlodromus pyri*	Contact, glass plates – a.i.	LR_{50}: 13	9.4	0.7	Not exceeded
Parasitic wasp,	Contact, glass plates – a.i.	LR_{50}: >100	9.4	<0.1	Not exceeded

Organism	Exposure – test substance	Effect metric (g a.i./ha)	EEC (g a.i./ha)[1]	RQ[2]	LOC
Aphidius rhopalosiphi	Contact, glass plates – end-use product	ER/LR_{50}: >268.6	9.4	<0.1	Not exceeded
Tier II – Extended laboratory studies					
Predatory mite, *Typhlodromus pyri*	Contact, spray residue leaves – end-use product	ER/LR_{50}: >268.6	9.4	<0.1	Not exceeded
Predatory bug, *Orius laevigatus*	Contact, spray residue leaves – end-use product	ER_{50}: >53.7	9.4	<0.2	Not exceeded
		LR_{50}: >268.6	9.4	<0.1	Not exceeded
Ladybird beetle, *Coccinella septempunctata*	Contact, spray residue leaves – end-use product	LR_{50}: >268.6	9.4	<0.1	Not exceeded
Lacewing, *Chrysoperla carnea*	Contact, spray residue leaves – end-use product	ER/LR_{50}: >268.6	9.4	<0.1	Not exceeded
Rove beetle, *Aleochara bilineata*	Contact, spray residue soil – end-use product	ER_{50}: >269	9.4	<0.1	Not exceeded

[1] EECs based on the proposed use pattern for pome fruit of a single application of 127.6 g a.i./ha.
On-field EEC based on × foliar interception factor of 0.80 for full foliage pome fruit OR × soil interception factor of 0.6, as per proposed application instructions on the Kodama Miticide label.
Off-field EEC based on × 0.74 (74% for early airblast) × 0.1 (off-field foliar interception).
[2] **Bolded** when exceeding the LOC (LOC = 2 for glass plate studies, 1 for extended laboratory studies).

Table 30 Refined risk assessment of acynonapyr for birds

	Effect metric (mg a.i./kg bw/d)	Food guild (food item)	Maximum residues				Mean residues			
			On-field		Off-field[2]		On-field		Off-field[2]	
			EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ
Small bird (0.02 kg)										
Acute	>200	Insectivore	10.30	<0.05	7.65	<0.04	7.14	<0.04	5.28	<0.03
	>200	Granivore (grain and seeds)	1.60	<0.01	1.18	<0.01	0.76	<0.01	0.56	<0.01
	>200	Frugivore (fruit)	3.20	<0.02	2.37	<0.01	1.53	<0.01	1.13	<0.01

	Effect metric (mg a.i./kg bw/d)	Food guild (food item)	Maximum residues				Mean residues			
			On-field		Off-field[2]		On-field		Off-field[2]	
			EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ
Dietary[3]	34.78	Insectivore	10.30	0.3	7.65	0.22	7.14	0.21	5.28	0.15
	34.78	Granivore (grain and seeds)	1.60	0.05	1.18	0.03	0.76	0.02	0.56	0.02
	34.78	Frugivore (fruit)	3.20	0.09	2.37	0.07	1.53	0.04	1.13	0.03
Reproduction	4.01	Insectivore	10.30	**2.6**	7.65	**1.9**	7.14	**1.8**	5.28	**1.3**
	4.01	Granivore (grain and seeds)	1.60	0.4	1.18	0.3	0.76	0.19	0.56	0.14
	4.01	Frugivore (fruit)	3.20	0.8	2.37	0.59	1.53	0.38	1.13	0.28
Medium-sized bird (0.1 kg)										
Acute	>200	Insectivore	8.12	<0.04	6.01	<0.03	5.61	<0.03	4.15	<0.02
	>200	Granivore (grain and seeds)	1.26	<0.01	0.93	<0.01	0.60	<0.01	0.44	<0.01
	>200	Frugivore (fruit)	2.51	<0.01	1.86	<0.01	1.20	<0.01	0.89	<0.01
Dietary[3]	34.78	Insectivore	8.12	0.23	6.01	0.17	5.61	0.16	4.15	0.12
	34.78	Granivore (grain and seeds)	1.26	0.04	0.93	0.03	0.60	0.02	0.44	0.01
	34.78	Frugivore (fruit)	2.51	0.07	1.86	0.05	1.20	0.03	0.89	0.03
Reproduction	4.01	Insectivore	8.12	**2.0**	6.01	**1.5**	5.61	**1.4**	4.15	**1.0**
	4.01	Granivore (grain and seeds)	1.26	0.31	0.93	0.23	0.60	0.15	0.44	0.11
	4.01	Frugivore (fruit)	2.51	0.63	1.86	0.46	1.20	0.30	0.89	0.22
Large-sized bird (1 kg)										
Acute	>200	Insectivore	2.37	<0.01	1.75	<0.01	1.64	<0.01	1.21	<0.01
	>200	Granivore (grain and seeds)	0.37	<0.01	0.27	<0.01	0.17	<0.01	0.13	<0.01
	>200	Frugivore (fruit)	0.73	<0.01	0.54	<0.01	0.35	<0.01	0.26	<0.01

	Effect metric (mg a.i./kg bw/d)	Food guild (food item)	Maximum residues				Mean residues			
			On-field		Off-field[2]		On-field		Off-field[2]	
			EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ
	>200	Herbivore (short grass)	5.24	<0.03	3.88	<0.02	1.86	<0.01	1.38	<0.01
	>200	Herbivore (long grass)	3.20	<0.02	2.37	<0.01	1.04	<0.01	0.77	<0.01
	>200	Herbivore (broadleaf plants)	4.85	<0.02	3.59	<0.02	1.60	<0.01	1.19	<0.01
Dietary[3]	34.78	Insectivore	2.37	0.07	1.75	0.05	1.64	0.05	1.21	0.03
	34.78	Granivore (grain and seeds)	0.37	0.01	0.27	<0.01	0.17	<0.01	0.13	<0.01
	34.78	Frugivore (fruit)	0.73	0.02	0.54	0.02	0.35	0.01	0.26	<0.01
	34.78	Herbivore (short grass)	5.24	0.15	3.88	0.11	1.86	0.05	1.38	0.04
	34.78	Herbivore (long grass)	3.20	0.09	2.37	0.07	1.04	0.03	0.77	0.02
	34.78	Herbivore (broadleaf plants)	4.85	0.14	3.59	0.1	1.60	0.05	1.19	0.03
Reproduction	4.01	Insectivore	2.37	0.59	1.75	0.44	1.64	0.41	1.21	0.30
	4.01	Granivore (grain and seeds)	0.37	0.09	0.27	0.07	0.17	0.04	0.13	0.03
	4.01	Frugivore (fruit)	0.73	0.18	0.54	0.14	0.35	0.09	0.26	0.06
	4.01	Herbivore (short grass)	5.24	**1.3**	3.88	0.97	1.86	0.46	1.38	0.34
	4.01	Herbivore (long grass)	3.20	0.8	2.37	0.59	1.04	0.26	0.77	0.19
	4.01	Herbivore (broadleaf plants)	4.85	**1.2**	3.59	0.89	1.60	0.40	1.19	0.30

[1] EDE = estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:

FIR: food ingestion rate (Nagy, 1987). For generic birds with bw less than or equal to 200 g, the "passerine" equation was used; for generic birds with bw greater than 200 g, the "all birds" equation was used:

Passerine equation (bw < or = 200 g): FIR (g dw/day) = 0.398(bw in g) $^{0.850}$

All birds equation (body weight > 200 g): FIR (g dw/day) = 0.648(bw in g) $^{0.651}$

bw = generic body weight

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

[2] Off-field drift calculated assuming 74% drift resulting from an early season airblast application.

[3] It is noted that in both available acute dietary studies, significant reductions in bw compared to the controls were observed in most treatment groups. Feed consumption decreased with increasing dietary concentration which correlated to the pattern of reduced bwg with increasing dietary concentration. Despite the observed food avoidance in the acute dietary studies,

considering the overall results of both the acute dietary and oral studies, the acute risk to birds from the use of acynonapyr is considered acceptable (all acute RQs ≤ 0.3).

* **Bolded** when exceeding the LOC (LOC = 1 for birds).

Table 31 Screening-level risk assessment of acynonapyr for aquatic organisms

Organism	Exposure – test substance	Effect metric (endpoint/UF) (mg a.i./L)	EEC (mg a.i./L)	RQ[1]	LOC
Freshwater species					
Invertebrates					
Invertebrate, *Daphnia magna*	Acute – a.i.	EC_{50}/2: >0.0046	0.016	**<3.5**	Exceeded
	Acute – end-use product	EC_{50}/2: >0.95	0.016	<0.1	Not exceeded
	Acute – TP, AP	EC_{50}/2: 1.6	0.011	<0.1	Not exceeded
	Acute – TP, AY	EC_{50}/2: >48	0.005	<0.1	Not exceeded
	Chronic – a.i.	NOEC: 0.00083	0.016	**19**	Exceeded
Amphipod, *Hyalella azteca*	Spiked sediment – a.i.	EC_{50}/2: >0.075 (overlying water)	0.016	<0.3	Not exceeded
Midge, *Chironomus dilutus*	Spiked sediment – a.i.	EC_{50}/2: >0.025 (overlying water)	0.016	<0.7	Not exceeded
Fish					
Rainbow trout, *Oncorhynchus mykiss*	Acute – a.i.	LC_{50}/10: >0.002051	0.016	**<7.8**	Exceeded
	Acute – a.i.	LC_{50}/10: >0.0012	0.016	**<13**	Exceeded
	Acute – end-use product	LC_{50}/10: >0.45	0.016	<0.1	Not exceeded
	Acute – TP, AP	LC_{50}/10: 0.37	0.011	<0.1	Not exceeded
Bluegill, *Lepomis macrochirus*	Acute – a.i.	LC_{50}/10: >0.004185	0.016	**<3.8**	Exceeded
	Acute – TP, AP	LC_{50}/10: 0.63	0.011	<0.1	Not exceeded
Carp, *Cyprinus carpio*	Acute – a.i.	LC_{50}/10: >0.002323	0.016	**<6.9**	Exceeded
Fathead minnow, *Pimephales promelas*	Acute – a.i.	LC_{50}/10: >0.00055	0.016	**<29**	Exceeded
	ELS – a.i.	NOEC: ≥0.0057	0.016	**<2.8**	Exceeded

Organism	Exposure – test substance	Effect metric (endpoint/UF) (mg a.i./L)	EEC (mg a.i./L)	RQ[1]	LOC
Amphibians					
Amphibians (using fish data as a surrogate)[2]	Acute – a.i.	LC_{50}/10: >0.004185	0.085	**<20**	Exceeded
	Acute – TP, AP	LC_{50}/10: 0.37	0.058	<0.2	Not exceeded
	ELS – a.i.	NOEC: ≥0.0057	0.085	**<15**	Exceeded
Plants					
Aquatic vascular plants, *Lemna gibba*	Acute – a.i.	EC_{50}/2: >0.003	0.016	**<5.3**	Exceeded
	Acute – end-use product	EC_{50}/2: >1.45	0.016	<0.1	Not exceeded
Algae					
Diatom, *Navicula pelliculosa*	Acute – a.i.	EC_{50}/2: >0.0012	0.016	**<13**	Exceeded
	Acute – end-use product	EC_{50}/2: >0.055	0.016	<0.3	Not exceeded
Green algae, *Raphidocelis subcapitata*	Acute – a.i.	EC_{50}/2: >0.0012	0.016	**<13**	Exceeded
	Acute – end-use product	EC_{50}/2: >0.3	0.016	<0.1	Not exceeded
	Acute – TP, AP	EC_{50}/2: 0.0125	0.011	0.9	Not exceeded
Blue-green algae, *Anabaena flos-aquae*	Acute – a.i.	EC_{50}/2: >0.0017	0.016	**<9.4**	Exceeded
	Acute – end-use product	EC_{50}/2: >0.12	0.016	<0.2	Not exceeded
Marine species					
Invertebrates					
Amphipod, *Leptocheirus plumulosus*	Spiked sediment – a.i.	EC_{50}/2: >0.0009 (overlying water)	0.016	**<18**	Exceeded
Crustacean, mysid shrimp, *Americamysis bahia*	Acute – a.i.	LC_{50}/2: >0.0022	0.016	**<7.3**	Exceeded
	Chronic – a.i.	NOEC: 0.0036	0.016	**4.4**	Exceeded
Mollusk, Eastern oyster, *Crassostrea virginica*	Acute – a.i.	LC_{50}/2: >0.00245	0.016	**<6.5**	Exceeded

Organism	Exposure – test substance	Effect metric (endpoint/UF) (mg a.i./L)	EEC (mg a.i./L)	RQ[1]	LOC
Fish					
Sheepshead minnow, *Cyprinodon variegatus*	Acute – a.i.	LC_{50}/10: >0.00071	0.016	**<22**	Exceeded
	ELS – a.i.	NOEC: ≥0.0067	0.016	**<2.4**	Exceeded
Algae					
Marine diatom, *Skeletonema costatum*	Acute – a.i.	EC_{50}/2: >0.00135	0.016	**<12**	Exceeded
	Acute – end-use product	EC_{50}/2: 0.08	0.016	0.2	Not exceeded

[1] **Bolded** when exceeding the LOC (LOC = 1). It is noted that endpoints resulting from the exposure of many of the non-target aquatic organisms to the technical grade active ingredient were non-definitive (greater than values, >), limited by the low solubility of the active ingredient, with no effects observed at the highest tested concentration. The available acute studies with the 20 SC end-use product formulation indicate that the true toxicity endpoints are much higher than those resulting from the solubility-restricted studies conducted using the technical grade active ingredient. Therefore, where available for the same species and study duration, studies conducted using the end-use product were used to better characterize the risk.

[2] As no significant mortality or effects were observed in any of the acute or chronic fish studies with the technical grade active ingredient up to the highest tested concentration (functional solubility of the compound), the highest technical grade active ingredient endpoint of all the fish studies was used as the surrogate for amphibians.

Table 32 Risk quotients (RQs) for aquatic organisms determined for spray drift of acynonapyr

Organism (exposure – test substance)	Effect metric (endpoint/UF) (mg a.i./L)	Refined EEC (mg a.i./L)[1]	RQ[2]	LOC
Freshwater species				
Invertebrate, *Daphnia magna* (21-d Chronic – technical grade active ingredient)	NOEC: 0.00083	0.012	**14**	Exceeded
Fish, *Lepomis macrochirus* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.004185	0.012	**<2.8**	Exceeded
Fish, *Cyprinus carpio* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.002323	0.012	**<5.1**	Exceeded
Fish, *Pimephales promelas* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.00055	0.012	**<21**	Exceeded
Fish, *Pimephales promelas* (32-d Chronic – technical grade active ingredient)	NOEC: ≥0.0057	0.012	**<2.1**	Exceeded

Organism (exposure – test substance)	Effect metric (endpoint/UF) (mg a.i./L)	Refined EEC (mg a.i./L)[1]	RQ[2]	LOC
Amphibians (96-h Acute – technical grade active ingredient)[3]	LC_{50}/10: >0.004185	0.063	**<15**	Exceeded
Amphibians (32-d Chronic – technical grade active ingredient)[3]	NOEC: ≥0.0057	0.063	**<11**	Exceeded
Marine species				
Invertebrate, *Americamysis bahia* (96-h Acute – technical grade active ingredient)	LC_{50}/2: >0.0022	0.012	**<5.4**	Exceeded
Invertebrate, *Americamysis bahia* (28-d Chronic – technical grade active ingredient)	NOEC: 0.0036	0.012	**3.3**	Exceeded
Invertebrate, *Crassostrea virginica* (96-h Acute – technical grade active ingredient)	LC_{50}/2: >0.00245	0.012	**<4.8**	Exceeded
Fish, *Cyprinodon variegatus* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.00071	0.012	**<17**	Exceeded
Fish, *Cyprinodon variegatus* (34-d Chronic – technical grade active ingredient)	NOEC: ≥0.0067	0.012	**<1.8**	Exceeded

[1] Refined EECs were calculated using a maximum percent drift deposition at one metre downwind (74% for early airblast) from the point of application and the proposed use on outdoor pome fruit of a single application of 127.6 g a.i./ha.

[2] **Bolded** when exceeding the LOC (LOC = 1).

[3] As no significant mortality or effects were observed in any of the acute or chronic fish studies with the technical grade active ingredient up to the highest tested concentration (functional solubility of the compound), the highest technical grade active ingredient endpoint of all the fish studies was used as the surrogate for amphibians.

Table 33 Risk quotients (RQs) for aquatic organisms determined for runoff of acynonapyr

Organism (exposure – test substance)	Effect metric (endpoint/UF) (mg a.i./L)	Refined EEC (mg a.i./L)	RQ[1]	LOC
Freshwater species				
Invertebrate, *Daphnia magna* (21-d Chronic – technical grade active ingredient)	NOEC: 0.00083	0.00115	**1.4**	Exceeded
Invertebrate, *Hyalella azteca* (10-d Acute – technical grade active ingredient)	EC_{50}/2: >0.021 (pore water)	0.00075	<0.04	Not exceeded

Organism (exposure – test substance)	Effect metric (endpoint/UF) (mg a.i./L)	Refined EEC (mg a.i./L)	RQ[1]	LOC
Invertebrate, *Chironomus dilutus* (10-d Acute – technical grade active ingredient)	EC_{50}/2: >0.06 (pore water)	0.00075	<0.02	Not exceeded
Fish, *Lepomis macrochirus* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.004185	0.00142	<0.4	Not exceeded
Fish, *Cyprinus carpio* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.002323	0.00142	<0.7	Not exceeded
Fish, *Pimephales promelas* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.00055	0.00142	**<2.6**	Exceeded
Fish, *Pimephales promelas* (32-d Chronic – technical grade active ingredient)	NOEC: ≥0.0057	0.00115	<0.3	Not exceeded
Amphibians (96-h Acute – technical grade active ingredient)[2]	LC_{50}/10: >0.004185	0.00362	<0.9	Not exceeded
Amphibians (32-d Chronic – technical grade active ingredient)[2]	NOEC: ≥0.0057	0.00195	<0.4	Not exceeded
Marine species				
Invertebrate, *Leptocheirus plumulosus* (10-d Acute – technical grade active ingredient)	EC_{50}/2: >0.027 (pore water)	0.00075	<0.03	Not exceeded
Invertebrate, *Americamysis bahia* (96-h Acute – technical grade active ingredient)	LC_{50}/2: >0.0022	0.00142	<0.7	Not exceeded
Invertebrate, *Americamysis bahia* (28-d Chronic – technical grade active ingredient)	NOEC: 0.0036	0.00115	0.3	Not exceeded
Invertebrate, *Crassostrea virginica* (96-h Acute – technical grade active ingredient)	LC_{50}/2: >0.00245	0.00142	<0.6	Not exceeded
Fish, *Cyprinodon variegatus* (96-h Acute – technical grade active ingredient)	LC_{50}/10: >0.00071	0.00142	**<2.0**	Exceeded
Fish, *Cyprinodon variegatus* (34-d Chronic – technical grade active ingredient)	NOEC: ≥0.0067	0.00115	<0.2	Not exceeded

[1] **Bolded** when exceeding the LOC (LOC = 1).

[2] As no significant mortality or effects were observed in any of the acute or chronic fish studies with the technical grade active ingredient up to the highest tested concentration (functional solubility of the compound), the highest technical grade active ingredient endpoint of all the fish studies was used as the surrogate for amphibians.

Table 34 List of supported uses

Proposed label claim	Supported use claim
Crop group 11-09: Pome Fruits (apple; azarole; crabapple; loquat; mayhaw; medlar; pear; pear, Asian; quince; quince, Chinese; quince, Japanese; tejocote; cultivars, varieties, and/or hybrids of these): For control of Tetranychid mites such as twospotted spider mite, European red mite, red spider mite and pear rust mite, apply Kodama Miticide at an application rate of 0.58 L product per ha by ground application. Do not apply more than one application per year or more than a total of 0.58 L product per hectare per year.	Crop group 11-09: Pome Fruits (apple; azarole; crabapple; loquat; mayhaw; medlar; pear; pear, Asian; quince; quince, Chinese; quince, Japanese; tejocote; cultivars, varieties, and/or hybrids of these): For control of Tetranychid mites such as twospotted spider mite, European red mite, McDaniel spider mite and Pacific spider mite, apply Kodama Miticide at an application rate of 0.58 L product per ha by ground application. Do not apply more than one application per year or more than a total of 0.58 L product per hectare per year.

Table 35 Toxic Substances Management Policy (TSMP) considerations – Comparison to TSMP Track 1 criteria

TSMP Track 1 criteria	TSMP Track 1 criterion value		Active ingredient endpoints [acynonapyr]	TP endpoints [AP]	TP endpoints [AY]
CEPA-toxic or CEPA-toxic equivalent[1]	Yes		Yes	Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 d	No – DT_{50}: 18–78 d (aerobic and anaerobic soils)	Yes – DT_{50}: 286–892 d (aerobic soil only)	No – DT_{50}: 53–92 d (aerobic soil only)
	Water	Half-life ≥ 182 d	No – Total system DT_{50} ≤1 d in aerobic and anaerobic water sediment systems.	Yes – Not available, but possible based on observed degradation profile in study with parent.	No – Not available, but unlikely based on observed degradation profile in study with parent.
	Sediment	Half-life ≥ 365 d			
	Air	Half-life ≥ 2 d, or	No – AOPWIN (version 1.92)	No – AOPWIN (version 1.92)	Yes – AOPWIN (version 1.92)

TSMP Track 1 criteria	TSMP Track 1 criterion value		Active ingredient endpoints [acynonapyr]	TP endpoints [AP]	TP endpoints [AY]
		evidence of atmospheric transport to remote regions such as the Arctic	predicted half-life in the gas phase in the atmosphere is 0.113 d. The half-life in air adjusted to account for the sorbed fraction ranges from 0.14–1.04 d.[4]	predicted half-life in the gas phase in the atmosphere is 0.114 d based on the hydroxyl (OH) radical reaction during 12 hrs of daylight.	predicted half-life in the gas phase in the atmosphere is 7.58 d based on the hydroxyl (OH) radical reaction during 12 hrs of daylight.
Bioaccumulation[5]	Log $K_{ow} \geq 5$		Yes – 6.6	No – 4.7 (KOWWIN version 1.68)	No – 2.0 (KOWWIN version 1.68)
	BCF ≥ 5000		Yes – BCF_{KGL}: 8732 (low exposure) and 12257 (high exposure)	No – BCF_{KGL}: 117 (low exposure) and 127 (high exposure)	Not required
	BAF ≥ 5000		BMF_{Lg}: 0.0930 (fish dietary exposure) BAF_K: 0.708 (oligochaetes study)	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet all of the TSMP Track 1 criteria.	No, does not meet all of the TSMP Track 1 criteria.	No, does not meet all of the TSMP Track 1 criteria.

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

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

3 The pesticide and/or the TP(s) is considered persistent when the criterion is met in any one medium.

4 The AOPWIN (version 1.92) predicted half-life in the gas phase in the atmosphere is 0.113 d based on the hydroxyl (OH) radical reaction (1.5E+6 molecules OH/cm^3) during 12 h of daylight. Using acynonapyr's Henry's law constant of 6.33E-6 atm·m^3/mol and log K_{ow} of 6.5 as data inputs for EPI Suite*, estimations of acynonapyr sorbed to airborne particles range from 19 to 89% (AEROWIN, version 1.00). The half-life in air adjusted to account for the sorbed fraction ranges from 0.14–1.04 d.

5 Bioaccumulation describes the process by which a substance accumulates in a living organism – either from the surrounding medium or through food containing the substance. A substance's potential to bioaccumulate can be expressed by the bioaccumulation factor (BAF), the bioconcentration factor (BCF), or the octanol-water partition coefficient (log K_{ow}). The BAF and the BCF measure the concentration of a substance in a living organism relative to its concentration in the surrounding medium. The BAF accounts for substance intake from both food and the surrounding medium, while the BCF accounts for intake from the surrounding medium only. The log K_{ow} estimates a substance's tendency to partition from

water to organic media, such as lipids present in living organisms. In the absence of BAF or BCF data, the log K_{ow} may be used.

* EPI (Estimation Programs Interface) Suite is a suite of physical/chemical property and environmental fate estimation programs.

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

Table 1 compares the MRLs proposed for acynonapyr in Canada with corresponding American tolerances and Codex MRLs.[11] American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Index webpage, by pesticide or commodity.

Table 1 Comparison of proposed Canadian MRL, American tolerances, and Codex MRLs

Food commodity	Canadian MRL (ppm)	American tolerance (ppm)	Codex MRL (ppm)
Crop Group 11-09: Pome Fruits	0.2	Not established	Not established

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

References

A. List of studies/information submitted by registrant

1.0 Chemistry

PMRA Document Number	Reference
3324356	2022, Solvent Solubility and pH, DACO: 2.14.15,2.14.8 CBI
3324357	2020, NA89: Accelerated Storage Stability and Corrosion Characteristics, DACO: 2.14.14 CBI
3324360	2021, NA89: Physical and Chemical Characteristics: Color, Physical State, Odor, UV/Visible Absorption, Melting Point, Bulk Density, and Vapor Pressure, DACO: 2.14.1,2.14.12,2.14.2,2.14.3,2.14.4,2.14.6,2.14.9 CBI
3324388	2022, Chemistry Requirements for the Registration of a End-Use Product (EP), DACO: 3.1.1,3.1.2,3.1.3,3.1.4,3.5.4,3.5.5 CBI
3324389	2021, GWN-10409: Product Identity and Disclosure of Ingredients, Description of Materials Used to Produce the Product and Formulation Process, Discussion of Formation of Impurities, Certified Limits, and Submittal of Samples, DACO: 3.2.1,3.2.2,3.2.3,3.3.1 CBI
3324393	2021, GWN-10409: Dielectric Breakdown Voltage, DACO: 3.5.15 CBI
3324394	2021, GWN-10409: Miscibility, DACO: 3.5.13 CBI
3324398	2020, GWN-10409: Enforcement Analytical Method for the Determination of NA-89 by High Performance Liquid Chromatography, DACO: 3.4.1 CBI
3324401	2019, GWN-10409: Physical and Chemical Characteristics: Color, Physical State, Odor, Oxidation/Reduction, Flammability, pH, Viscosity, and Density/Relative Density, DACO: 3.5.1,3.5.11,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8, 3.5.9 CBI
3324402	2020, GWN-10409: Accelerated Storage Stability and Corrosion Characteristics, DACO: 3.5.10,3.5.14 CBI
3324580	2020, Environmental Chemistry Method: Validation of the Analytical Method for the Determination of NA-89, AP, & AY in Aqueous Matrices by LC-MS/MS, DACO: 8.2.2.3
3324581	2020, NA-89 - Validation of the Analytical Method for the Determination of a Test Substance in Sediment, DACO: 8.2.2.2
3324582	2020, Environmental Chemistry Method: Validation of the Analytical Method for the Determination of NA-89, AP, & AY in Soil Matrices by LC-MS/MS, DACO: 8.2.2.1
3324584	2020, Independent Laboratory Validation of the Analytical Method for the Determination of NA-89, AP & AY in Soil Matrices by LC-MS/MS, DACO: 8.2.2.1
3324585	2021, Independent Laboratory Validation of Analytical Method 12791.6382 for the Determination of GWN-8086 and Metabolites in Ground Water and Surface Water by LC-MS/MS, DACO: 8.2.2.3

3328600	2018, Analysis of Representative 5 Lots of NA-89 Technical Grade, DACO: 2.13.1,2.13.2,2.13.3 CBI
3328601	2018, Validation of Analytical Method for Active Ingredient (NA-89) in Technical Grade NA-89, DACO: 2.13.3 CBI
3328602	2018, Validation of Analytical Method for Residual Solvents [CBI removed] in Technical Grade NA-89, DACO: 2.13.3 CBI
3328603	2019, Validation of Analytical Method for Residual Solvent [CBI removed] in Technical Grade NA-89, DACO: 2.13.3 CBI
3328605	2018, Validation of Analytical Method for [CBI removed] Impurities, DACO: 2.13.3 CBI
3328606	2018, Validation of Analytical Method for [CBI removed] Impurity, DACO: 2.13.3 CBI
3328607	2018, Validation of Analytical Method for One Residual Solvent, DACO: 2.13.3 CBI
3328608	2019, Complimentary Validation of Analytical Method for One Residual Solvent, DACO: 2.13.3 CBI
3328609	2017, NA-89: Determination of General Physico-Chemical Properties, DACO: 2.14.10,2.14.12,2.14.15,2.16,8.2.3.2
3328610	2018, Dissociation Constant of NA-89, DACO: 2.14.10,8.2.3.2
3328613	2013, Partition Coefficient (n-Octanol/Water) of NA-89, DACO: 2.14.11
3328623	2018, Water Solubility of Acynonapyr (25 C), DACO: 2.14.7
3328624	2011, Water Solubility of 74-2793, DACO: 2.14.7
3328625	2015, Water Solubility of AP, DACO: 2.14.7
3328627	2016, Vapour Pressure of AP, DACO: 2.14.9
3345229	2022, Response to PMRA Letter Dated 6 April 2022 Supporting the Registration of the Following Submissions: Acynonapyr Technical Submission No. 2022-1017, DACO: 2.13.1,2.13.2,2.2

2.0 Human and animal health

PMRA Document Number	Reference
3324361	2021, Acynonapyr (NA-89) Mammalian Toxicology Summary, DACO: 4.1
3324362	2021, NA-89: Time of Peak Effect Hepatocellular Proliferation Study in the Male Mouse, DACO: 4.8
3324363	2021, GWN-8086: Dose Response Hepatocellular Proliferation Study in the Male Mouse, DACO: 4.8
3324364	2021, GWN-8086: Dose Response Hepatocellular Proliferation Study in the Male Mouse, DACO: 4.8
3324365	2021, Acynonapyr: Assessment to Determine the Need for a Comparative Thyroid Assay, DACO: 4.8
3324366	2021, Weight of the Evidence Based Rationale for Waiving the Immunotoxicity Study Requirement for Acynonapyr, DACO: 4.5.15
3324367	2021, Weight of the Evidence-Based Rationale for Waiving the Subchronic Neurotoxicity Study Requirements for Acynonapyr, DACO: 4.5.13

3324368	2020, Weight of the Evidence Based Rationale for Waiving the 90-day Inhalation Study Requirement for Acynonapyr, DACO: 4.3.6
3324369	2021, NA-89: Time of Peak Effect Hepatocellular Proliferation Study in the Male Mouse, DACO: 4.8
3324370	2021, Acynonapyr: The Metabolism of [azabicyclo-1,5-^{14}C] Acynonapyr in the Rat Following Oral Administration, DACO: 4.5.9
3324371	2020, NA-89 Tech.: Cell Mutation Assay at the Thymidine Kinase Locus ($TK^{+/-}$) in Mouse Lymphoma L5178Y Cells, DACO: 4.5.5
3324372	2020, NA-89: 28-Day Repeated Dermal Dose Toxicity and Toxicokinetics Study in Rats with a 14-Day Recovery Period, DACO: 4.3.5
3324373	2020, NA-89: 3-Day Repeated Dermal Dose Range Finding Toxicity Study in Rats, DACO: 4.3.5
3324374	2021, Acynonapyr Waiver Request for the 90-Day Rat Dermal Toxicity Study (OCSPP 870.3250), DACO: 4.3.4
3324399	2020, GWN-10409: Acute Inhalation Toxicity (Acute Toxic Class Method) in Rats, DACO: 4.6.3
3324404	2021, Validation of the Analytical Method for the Determination of NA-89 and its Metabolites (AP, AP-2, AY, AY-1-Glc, and AY-3) in Pome Fruit Raw Agricultural Commodities and Processed Fractions, DACO: 7.2.2,7.3
3324407	2021, Magnitude and Decline of the Residues of NA-89 and its Metabolites in or on Pome Fruit Raw Agricultural and Processed Commodities Following One Foliar Airblast Application of NA-89 SC (2020), DACO: 7.4.1,7.4.2, 7.4.5
3328628	2014, Acute Oral Toxicity Study of AP in Rats, DACO: 4.2.1
3328630	2014, Acute Oral Toxicity Study of AP-2 in Rats, DACO: 4.2.1
3328632	2015, Acute Oral Toxicity Study of AY in Rats, DACO: 4.2.1
3328634	2020, AY-1-Glc: Acute Oral Toxicity Study in Rats, DACO: 4.2.1
3328636	2013, Acute Oral Toxicity Study of AY-5 in Rats, DACO: 4.2.1
3328638	2013, Acute Oral Toxicity Study of AH in Rats, DACO: 4.2.1
3328640	2016, AP-2 - 28-Day Repeated Dose Oral Toxicity Study in Rats, DACO: 4.3.3
3328642	2020, AY - 28-Day Repeated Dose Oral Toxicity Study in Rats, DACO: 4.3.3
3328644	2019, AY - 90-Day Repeated Dose Oral Toxicity Study in Rats, DACO: 4.3.1
3328646	2015, Electron-Microscopic Observation of Hepatic Vacuolation in Rats Treated with NA-89, DACO: 4.8,8.6.2
3328703	2016, A 78 Week Carcinogenicity Dietary Study of NA-89 in Mice, DACO: 4.4.3
3328705	2019, Sub-Classification of Lymphoma in Mouse Carcinogenicity Study, DACO: 4.4.3,8.6
3328707	2022, Historical Control Data Report -Lymphoma in Carcinogenicity Study, DACO: 4.4.3,8.6
3328709	2022, Historical Control Data of Lymphoma in Carcinogenicity Study for Male Mice, DACO: 4.4.3,8.6

3328711	2022, NA-89 (ISO Name: Acynonapyr): Comprehensive Explanation of Lymphomas Occurring in a Carcinogenicity Study in Mice, DACO: 4.4.3,8.6
3328713	2017, A 2 Year Combined Toxicity and Carcinogenicity Dietary Study of NA-89 in Rats, DACO: 4.4.4
3328715	2018, Validation of Methodologies for the Formulation and Analysis of NA-89 in Dietary Formulations, DACO: 4.2.9,4.3.8,4.4.5
3328717	2018, Validation of Methodologies for the Formulation and Analysis of NA-89 in DMF Dosing Solutions, DACO: 4.2.9,4.3.8,4.4.5
3328719	2018, Validation of an Analytical Method for the Determination of 74-2793 (NA-89), 31-3564 (AP), Pyridinol (AY) and 7-Dehydrocholesterol (7-DHC) in Dog Plasma by HPLC with Ultraviolet Detection, DACO: 4.2.9,4.3.8,4.4.5
3328721	2018, Stability Test and Method Validation of the AY Concentration in the Diet, DACO: 4.2.9
3328723	2014, NA-89 - Bacterial Reverse Mutation Test, DACO: 4.5.4
3328725	2014, AP - Bacterial Reverse Mutation Test, DACO: 4.5.4
3328727	2014, AP-2 - Bacterial Reverse Mutation Test, DACO: 4.5.4
3328729	2015, AY - Bacterial Reverse Mutation Test, DACO: 4.5.4
3328731	2020, AY-1-Glc: Bacterial Reverse Mutation Test, DACO: 4.5.4
3328733	2014, Bacterial Reverse Mutation Test of AY-5, DACO: 4.5.4
3328735	2014, Bacterial Reverse Mutation Test of AH, DACO: 4.5.4
3328737	2014, NA-89: In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Lymphocyte Cultures, DACO: 4.5.6
3328739	2014, NA-89: Mammalian Erythrocyte Micronucleus Test in Mouse Bone Marrow, DACO: 4.5.7
3328741	2015, AY: Micronucleus Test in Mice, DACO: 4.5.7
3328743	2018, Gene Mutation Assay of AY in Muta Mouse, DACO: 4.5.8
3328745	2016, NA-89 - Hepatic Drug-Metabolizing Enzyme Induction Study in Rats, DACO: 4.8
3328747	2016, NA-89 - Hepatic Drug-Metabolizing Enzyme Induction Study in Mice, DACO: 4.8
3328749	2016, Evaluation of the Nephrotoxicity of 74-2793 (Series 28-2031) in Rats, DACO: 4.8,8.6
3328751	2015, Isolation of AP-4 from Rat Urine Obtained Following Administration of [Phenyl-U-^{14}C]-NA-89 in Rats, DACO: 4.8,8.6
3328825	2016, The Metabolism of [^{14}C]NA-89 in Cucumber, DACO: 6.3
3328827	2019, Metabolism of [^{14}C]Acynonapyr in Lettuce, DACO: 6.3
3328829	2021, Plant Metabolism of [^{14}C] NA-89 in Apples, DACO: 6.3
3328833	2013, Acute Oral Toxicity Study of NA-89 in Rats, DACO: 4.2.1
3328835	2013, Acute Dermal Toxicity Study of NA-89 in Rats, DACO: 4.2.2
3328839	2014, An Acute Toxicity Study of NA-89 by Inhalation Administration in Rats, DACO: 4.2.3
3328841	2013, Eye Irritation Study of NA-89 in Rabbits, DACO: 4.2.4
3328843	2013, Skin Irritation Study of NA-89 in Rabbits, DACO: 4.2.5
3328845	2014, Skin Sensitization Study of NA-89 in Guinea Pigs (Maximization Test), DACO: 4.2.6

3328847	2014, An Acute Neurotoxicity Study of NA-89 by Oral Gavage in Rats, DACO: 4.5.12
3328849	2011, 74-2793 - 28-Day Repeated Dose Oral Toxicity Study in Mice, DACO: 4.3.3
3328851	2016, 74-2793 - 28-Day Repeated Dose Toxicity Study in Rats, DACO: 4.3.3
3328853	2013, A 13 Week Dietary Study of 74-2793 in Mice, DACO: 4.3.1
3328855	2013, A 13 Week Dietary Study of 74-2793 in Rats, DACO: 4.3.1
3328857	2012, 74-2793 - 90-Day Repeated Dose Oral Toxicity Study in Rats, DACO: 4.3.1
3328860	2014, A 4 Week Oral (Capsule) Dose Range Finding Study of NA-89 in Dogs, DACO: 4.3.3
3328862	2016, A 13 Week Oral (Capsule) Study of NA-89 in Dogs, DACO: 4.3.2
3328864	2016, A 52 Week Oral (Capsule) Toxicity Study of NA-89 in Dogs, DACO: 4.3.2
3328866	2014, An Embryo-Fetal Development Study of NA-89 by Oral Gavage in Rats, DACO: 4.5.2
3328868	2013, A Dosage Range-Finding Embryo-Fetal Development Study of NA-89 by Oral (Stomach Tube) in Rabbits, DACO: 4.5.3
3328870	2014, An Embryo-Fetal Development Study of NA-89 by Oral (Stomach Tube) in Rabbits, DACO: 4.5.3
3328872	2014, A Dosage Range-Finding Developmental and Perinatal/Postnatal Reproduction Study of NA-89 Diet in Rats, Including a Postnatal Behavioral/Functional Evaluation, DACO: 4.5.1
3328878	2016, Two-Generation (One Litter per Generation) Reproduction Study of NA-89 Diet in Rats, DACO: 4.5.1
3328880	2016, NA-89: The Metabolism of [Pyridine-2,6-^{14}C] NA-89 in the Rat, DACO: 4.5.9
3328882	2016, NA-89: The Metabolism of [Phenyl-U-^{14}C] NA-89 in the Rat, DACO: 4.5.9
3328884	2016, Investigation of the Biotransformation of [Pyridine-2,6-^{14}C]-NA-89 in Rats Following Oral Administration, DACO: 4.5.9
3328886	2016, Investigation of the Biotransformation of [Phenyl-U-^{14}C]-NA-89 in Rats Following Oral Administration, DACO: 4.5.9
3328888	2018, Validation of Methodologies for the Formulation and Analysis of 74-2793 in Dietary Formulations, DACO: 4.2.9,4.3.8,4.4.5
3328890	2018, Analytical Method Validation for the Analysis of NA-89 in 0.5% Carboxymethylcellulose / 0.1% Tween 80 Dosing Formulations, DACO: 4.2.9,4.3.8,4.4.5
3328892	2018, Analytical Method Validation for the Analysis of NA-89 in Meal Form of Certified Rodent Diet Dosing Formulations, DACO: 4.2.9,4.3.8,4.4.5
3328894	2010, Stability Study (2) of 74-2793 (28-2031(II)) with Diet, DACO: 4.2.9, 4.3.8,4.4.5
3328925	2015, Acute Oral Toxicity Study of NA-89 20%SC in Rats, DACO: 4.6.1
3328927	2015, Acute Dermal Toxicity Study of NA-89 20%SC in Rats, DACO: 4.6.2
3328929	2015, Eye Irritation Study of NA-89 20%SC in Rabbits, DACO: 4.6.4
3328931	2015, Skin Irritation Study of NA-89 20%SC in Rabbits, DACO: 4.6.5

3328933	2015, Skin Sensitization Study of NA-89 20%SC in Guinea Pigs, DACO: 4.6.6
3352905	2017, A 2 Year Combined Toxicity and Carcinogenicity Dietary Study of NA-89 in Rats - Report Amendment 2, DACO: 4.4.1,4.4.2,4.4.4
3386717	2021, Validation of the Analytical Method for the Determination of NA-89 and its Metabolites (AP, AP-2, AY, AY-1-Glc, and AY-3) in Hops Raw Agricultural Commodities and Processed Fractions, DACO: 171 - 4a,171 - 4c,171 - 4m,171-4a-4b,171-4c-4d,7.2.3A,IIA 4.2.6,IIIA 5.3.1,b,d
3386718	2021, Validation of the Analytical Method for the Determination of NA-89 and its Metabolites (AP, AP-2, AY, AY-1-Glc, and AY-3) in Citrus Raw Agricultural Commodities and Processed Fractions, DACO: 171 - 4a,171 - 4c,171 - 4m,171-4a-4b,171-4c-4d,7.2.3A,860.1300,860.1340,860.1360,IIA 4.2.6,IIIA 5.3.1,b,d
3386719	2021, Part 2: Independent Laboratory Validation of Analytical Methods for the Determination of NA-89 and its Metabolites AP, AP-2, AY, AY-1-Glc and AY-3 in Almond, Hops, and Citrus Commodities, DACO: 171 - 4a,171 - 4c,171 - 4m,171-4a-4b,171-4c-4d,7.2.3A,860.1300,860.1340,860.1360,IIA 4.2.6,IIIA 5.3.1,b,d
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3.0 Environment

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4.0 Value

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B. Additional information considered

None.