Proposed Registration Decision PRD2020-13

Trinexapac-ethyl and MODDUS

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Table of Contents

Overview

Proposed registration decision for trinexapac-ethyl

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Trinexapac-ethyl Technical and MODDUS, containing the technical grade active ingredient trinexapac-ethyl, for use on spring wheat, winter wheat, barley and oat as a plant growth regulator to reduce susceptibility to lodging (falling/leaning over).

Trinexapac-ethyl is currently registered for use on turf. For details, see Proposed Regulatory Decision Document PRDD2001-05, *Trinexapac-ethyl*, and Regulatory Decision Document RDD2002-01, *Trinexapac-ethyl*.

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 trinexapac-ethyl and MODDUS.

What does Health Canada consider when making a registration decision?

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

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

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

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

Before making a final registration decision on trinexapac-ethyl and MODDUS, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on trinexapac-ethyl and MODDUS, 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 trinexapac-ethyl?

Trinexapac-ethyl is a plant growth regulator that inhibits the biosynthesis of gibberellin. Gibberellin is a plant hormone that promotes growth of various plant organs. By inhibiting gibberellin, trinexapac-ethyl treatment reduces plant height thereby reducing the tendency to lean or fall over.

Health considerations

Can approved uses of trinexapac-ethyl affect human health?

MODDUS, containing trinexapac-ethyl, is unlikely to affect your health when used according to label directions.

Potential exposure to trinexapac-ethyl may occur through the diet (food and water) or when handling and applying the end-use product, exposure may also occur when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). 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 where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient trinexapac-ethyl was of low acute toxicity by the oral, dermal, and inhalation routes. Trinexapac-ethyl was minimally irritating to the eyes, slightly irritating to the skin and caused an allergic skin reaction; consequently, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label.

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

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

In laboratory animals, the end-use product MODDUS was of low acute toxicity by the oral, dermal, and inhalation routes. MODDUS was not irritating to the skin and did not cause an allergic skin reaction. MODDUS was moderately irritating to the eyes; consequently, the signal word and hazard statement "WARNING - EYE IRRITANT" are required on the label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of trinexapac-ethyl to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on body weight, effects in the brain, and fetal death. There was an indication that the young were more sensitive than the adult animal. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in water and food

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

Aggregate acute dietary (food plus drinking water) intake estimates for females 13–49 years of age are expected to be less than 72% of the acute reference dose, and are not of health concern.

Aggregate chronic dietary (food plus drinking water) intake estimates for all population subgroups are expected to be less than 47% of the acceptable daily intake, and are 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.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

MRLs for trinexapac-ethyl determined from the acceptable residue trials conducted throughout Canada and the United States on wheat and barley can be found in the Science Evaluation section of this Consultation Document.

Occupational risks from handling MODDUS

Occupational risks are not of concern when trinexapac-ethyl is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply MODDUS as well as field workers entering recently treated fields of wheat (spring, durum and winter), barley and oats can come in direct contact with trinexapac-ethyl residues on the skin and through inhalation. Therefore, the label specifies that handlers mixing/loading and applying MODDUS must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks (gloves are not required inside a closed cab or cockpit) as well as goggles during mixing and loading.

The label also requires that workers do not enter treated fields of wheat (spring, durum and winter), barley and oats for 12 hours after application.

Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the health risk to these individuals are not of concern.

Bystander risks are not of health concern when MODDUS 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.

Environmental considerations

What happens when trinexapac-ethyl is introduced into the environment?

When used according to label directions, the risks associated with trinexapac-ethyl are acceptable from the viewpoint of environmental protection.

Trinexapac-ethyl is a plant growth regulator and can enter the environment when applied as a foliar spray to reduce height and susceptibility to lodging in cereal crops (in other words, wheat, barley and oat). It is expected to move inside the plants and inhibit the growth of leaves and stems. Trinexapac-ethyl is not expected to move through the soil and reach groundwater however, its transformation product, trinexapac acid, has a potential to persist and accumulate and can move through the soil and reach groundwater. In water bodies, trinexapac-ethyl and its breakdown products are not persistent and are not expected to move to sediments. Trinexapac-ethyl is not expected to be found in the air or to travel long distances from where it was applied. Trinexapac-ethyl and trinexapac acid are not expected to build-up in the tissues of organisms.

When trinexapac-ethyl is used in accordance with the label and the required precautions, the environmental risk is acceptable.

Value considerations

What is the value of MODDUS?

MODDUS is used to reduce height and lodging of wheat, barley and oat crops thereby maximizing harvestable yield.

Lodging can reduce photosynthesis and carbohydrate movement within plants, which contributes to uneven maturity, increased likelihood of the development of diseases on foliage and grain, reduced grain yield and quality as well as a reduction in the efficiency of the harvesting operation. MODDUS represents a new active ingredient that may be used as a crop growth management aid to reduce height and lodging in wheat and barley and is the only one available for use in oat.

Measures to minimize risk

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

The key risk-reduction measures being proposed on the label of Trinexapac-ethyl Technical and MODDUS to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

Because there is a concern with users coming into direct contact with trinexapac-ethyl on the skin or through inhalation of spray mists, anyone mixing, loading and applying MODDUS must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks (gloves are not required inside a closed cab or cockpit) as well as goggles during mixing and loading. The label also requires that workers do not enter treated fields of wheat (spring, durum and winter), barley and oats for 12 hours after application. In addition, standard label statements to protect against drift during application are present on the label.

Environment

To protect the environment, the following risk mitigation measures are being proposed:

- Precautionary statements to protect non-target terrestrial and aquatic organisms.

Next steps

Before making a final registration decision on trinexapac-ethyl and MODDUS, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). 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

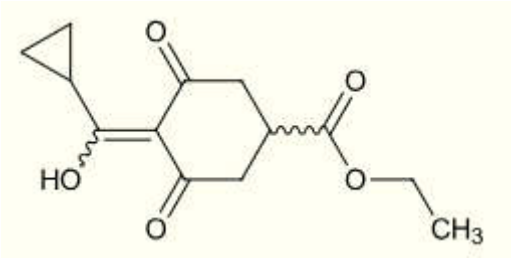
When the Health Canada makes its registration decision, it will publish a Registration Decision on trinexapac-ethyl and MODDUS (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection,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

Science evaluation

Trinexapac-ethyl and MODDUS

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Trinexapac-ethyl
Function	Plant growth regulator
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	ethyl (1*RS*,4*EZ*)-4-cyclopropyl(hydroxy)methylene-3,5-dioxocyclohexanecarboxylate
2. Chemical Abstracts Service (CAS)	ethyl 4-(cyclopropylhydroxymethylene)-3,5-dioxocyclohexanecarboxylate
CAS number	95266-40-3
Molecular formula	$C_{13}H_{16}O_5$
Molecular weight	252.3
Structural formula	
Purity of the active ingredient	97%

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

Technical product—trinexapac-ethyl technical

Property	Result
Colour and physical state	Yellow to red-brown liquid or crystals
Odour	Slightly sweet
Melting range	36.1–36.6 °C

Property	Result
Boiling point or range	Thermal decomposition starts at ~310°C
Density	1.215 g/cm^3
Vapour pressure at 25°C	2.16×10^{-3} Pa (by extrapolation)
Ultraviolet (UV)-visible spectrum	Medium / λ_{max} (nm) / ε (L/mol.cm) neutral / 240.2 / 9335 277.4 / 13976 acidic / 240.0 / 11712 280.4 / 12368 basic / 270.8 / 21320 No absorption at λ > 340 nm
Solubility in water at 25°C	pH / Solubility (g/L) 3.5 (distilled water) / 1.1 4.9 (buffer) / 2.8 5.5 (buffer) / 10.2 8.2 (buffer) / 21.2
Solubility in organic solvents at 25°C	Solvent / Solubility (g/L) acetone / >500 methanol / >500 n-octanol / 420 toluene / >500 dichloromethane / >500 ethyl acetate / >500 n-hexane / 45
n-Octanol-water partition coefficient (K_{ow})	pH / log K_{ow} 5.3 / 1.60
Dissociation constant (p*K*a)	4.57
Stability (temperature, metal)	Stable to elevated temperature and to metals (carbon steel, stainless steel, aluminum and tinplate)

End-use product—MODDUS

Property	Result
Colour	Red-orange
Odour	Sweetish with a hint of thymol
Physical state	Liquid
Formulation type	Emulsion concentrate
Guarantee	11.3%
Container material and description	Plastic totes and jugs, 1–1000 L
Density	1.07 g/mL at 20°C

Property	Result
pH of 1% dispersion in water	3.6
Oxidizing or reducing action	Not an oxidizing substance
Storage stability	Generally stable over 1 year of storage in HDPE at room temperature
Corrosion characteristics	No adverse effects to HDPE packaging after storage
Explodability	Not expected to be explosive

1.3 Directions for use

MODDUS is intended for application to spring wheat, including durum wheat, and oat at 0.83 L/ha (100 g a.i./ha), to barley at 1.03 L/ha (125 g a.i./ha) and to winter wheat at 0.83–1.03 L/ha when these crops are at the beginning of stem elongation to the flag leaf stage. Alternatively, the half rate of MODDUS may be applied twice to spring wheat, barley and oat with the first treatment at the crop tillering stage and the second at the flag leaf stage. MODDUS may be applied with a ground sprayer in a minimum spray volume of 100 L water/ha or aerially in a minimum of 50 L water/ha.

1.4 Mode of action

Trinexapac-ethyl is a plant growth regulator belonging to the cyclohexadione chemical family that inhibits the biosynthesis of gibberellin, specifically GA_1. Gibberellin is a plant hormone that promotes growth of various plant organs. The free acid of trinexapac-ethyl inhibits the hydroxylation of GA_{20} to GA_1 by competitively inhibiting the regulatory enzyme 3-ß-hydroxylase, leading to a reduction in plant height and tendency for stems to lean or fall, in other words, reduced tendency of the crop to lodge.

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

High performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS; Method GRM020.01A and QuEChERS [EN 15662:2009-2] Multi-Residue Method in plant matrices, and QuEChERS [EN 15662:2009-2] Multi-Residue Method in animal matrices) were developed and proposed for data generation and enforcement purposes. These methods

fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation.

Acceptable recoveries (70–120%) were obtained in environmental media, and acceptable recoveries (70–120%) were obtained in plant and animal matrices. Methods for residue analysis are summarized in Appendix I, Tables 1a and 1b.

The proposed livestock and plant enforcement methods were successfully validated by an independent laboratory. Adequate extraction efficiencies were demonstrated for plant enforcement Method GRM020.01A using radiolabelled grass straw, forage and seed screenings. Although adequate extraction efficiencies were not demonstrated using radiolabelled livestock or crop samples, extraction solvents used in the QuEChERS [EN 15662:2009-2] Multi-Residue Method, the proposed enforcement method for livestock matrices and a second enforcement method option for crop matrices, were similar to those used in the goat and hen and wheat metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled matrices was not required.

3.0 Impact on human and animal health

3.1 Toxicology summary

Trinexapac-ethyl (ethyl 4-[cyclopropyl(hydroxy)methylidene]-3,5-dioxocyclohexane-1-carboxylate; CGA 163935, hereafter referred to as trinexapac-ethyl) regulates the growth of plants by the inhibition of gibberellic acid (GA) biosynthesis causing a decrease of GA function in the plant thereby reducing the shoot length. Trinexapac-ethyl was originally registered in March 2002 in Canada for use on turf.

A detailed review of the toxicological database for trinexapac-ethyl was previously conducted (Proposed Regulatory Decision Document - PRDD2001-05, *Trinexapac-ethyl*). The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies were provided in the current submission, including a toxicokinetic study investigating the biliary elimination of trinexapac-ethyl, acute and short-term oral toxicity studies, neurotoxicity studies, an immunotoxicity study and a series of acute, short-term or genotoxicity studies on seven different animal- or plant-metabolites, as well as manufacturing-based impurities. The original PMRA review of the toxicological database was also revisited.

The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The human health risk assessment also considered information found in the published literature. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with trinexapac-ethyl.

The metabolism and toxicokinetics of ^{14}C-phenyl ring labelled orally administered trinexapac-ethyl were investigated in rats with single low- and high-doses by gavage administration, single-low-dose intravenous administration or single low-dose gavage following repeated low-dose

dietary administration of unlabelled test material for 14 consecutive days. Additional studies investigating biliary elimination were also conducted.

Trinexapac-ethyl was rapidly and extensively absorbed in both sexes following single or repeat oral low-dose administration or single oral high-dose administration. The highest radioactive residue levels were observed in the fat, lungs, kidneys and liver. However, the mean recovery of radioactivity in tissues and carcass at sacrifice (168 hours after dosing) was less than 0.3% of the administered dose for all dose groups indicating little potential for tissue retention. The majority of the radioactivity was rapidly excreted (within 12 hours of administration) via the urine with a small amount of radiolabel being eliminated via the feces. A minimal amount of the administered dose was recovered via expired air. There was very little biliary excretion.

The major metabolite in urine and fecal extracts was identified as CGA-179500, the free acid derivative of trinexapac-ethyl. This metabolite results from the hydrolysis of the ester bond of trinexapac-ethyl, and accounted for approximately 82–92% of the administered dose. Another minor metabolite, a more polar derivative of CGA 179500, was found in bile. There was no significant qualitative difference in absorption, distribution, metabolism or excretion of radioactivity between the sexes, between single and repeat low-dose administration, or between single low- and high-dose administrations.

Trinexapac-ethyl was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was minimally irritating to the eyes and slightly irritating to the skin of rabbits and was a dermal sensitizer in mice in the Local Lymph Node Assay (LLNA). The end-use product, MODDUS Plant Growth Regulator, was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was moderately irritating to the eyes and non-irritating to the skin of rabbits and was not a dermal sensitizer in guinea pigs in the Buehler Assay.

The short- and long-term, repeat-dose dietary toxicity of trinexapac-ethyl was investigated in the mouse, rat and dog. In the mouse, there were no treatment-related findings in either sex up to the limit dose of testing.

In short- and long-term oral toxicity studies in the rat, the kidney was the main target of toxicity. There was an increase in cytoplasmic accumulation of hyaline droplets in the kidneys observed at the LOAEL in males in both the 28-day gavage and 90-day dietary toxicity studies. This effect was also observed in males at the highest dose level tested at the 12-month interim sacrifice in the dietary combined chronic toxicity and oncogenicity study, but was reversible following a 4-week recovery period and was not observed at the 24-month terminal sacrifice. Other treatment-related histopathological findings noted in the kidneys included increased incidences of tubular basophilia and tubular casts in males at the highest dose level in the 90-day dietary study, and brown pigmentation in renal tubular epithelium in males and females at the two highest dose levels tested at the 12-month interim sacrifice in the dietary combined chronic toxicity and oncogenicity study. Urinalysis examination revealed lower urinary pH in both sexes and increased urinary specific gravity and urine volume in males at the highest dose level tested in the 90-day dietary study, and both sexes at the LOAEL in the combined chronic toxicity and oncogenicity study. Other histopathological findings noted in females at the 24-month terminal

sacrifice in the combined chronic toxicity and oncogenicity study included bile duct hyperplasia, mammary gland galactoceles, and acanthosis of the glandular stomach at the highest dose level.

In the supplemental 49-day dog dietary toxicity study, the main target organs were the kidney and the thymus. Increased tubular dilation and eosinophilia casts were seen in the kidneys as well as increased degeneration or regeneration of renal tubule epithelial cells. These kidney findings were not observed in either the 90-day or 12-month dietary dog studies at similar dose levels. Diffuse thymic atrophy was observed in both the 49-day and 90-day dog studies.

In the 12-month dietary dog toxicity study, minimal focal bilateral vacuolation of the dorsal medial hippocampus or lateral midbrain was observed in both sexes at the two highest dose levels tested. In the 90-day dog study, one male at the highest dose level also showed similar histopathology. Other treatment-related findings in the 12-month dietary study included mucoid or bloody feces and elevated serum cholesterol at the two highest dose levels tested and sporadic emesis, lower red blood cell parameters (cell counts, hematocrit and hemoglobin) in one or both sexes at the highest-dose level.

Decreased body weight, body weight gain and food consumption were observed in both sexes at the highest dose levels in the rat and dog oral toxicity studies. The decreased body weight and body weight gain were to some degree a result of palatability issues as short-term gavage toxicity studies in the rat and rabbit did not show decreased body weights with similar dose levels. In certain short-term dietary toxicity studies, such as the 49-day dog study and the 90-day rat neurotoxicity study, it was determined that within the high-dose groups, the animals were receiving much lower doses than anticipated due to diet homogeneity and food consumption issues. These findings were taken into account in the risk assessment.

In a repeat-dose (22 consecutive days) dermal toxicity study in the rabbit, there were no adverse treatment-related systemic findings up to the limit dose of testing. Increased severity of acanthosis and increased incidences of inflammation, hyperkeratosis, and crust formation were observed at the site of application in both males and females.

There was no evidence to indicate that trinexapac-ethyl was oncogenic in the 18-month dietary oncogenicity study in mice or the 24-month dietary combined chronic toxicity and oncogenicity study in rats.

Trinexapac-ethyl was negative in a battery of in vitro and in vivo genotoxicity assays.

In the dietary 2-generation rat reproductive toxicity study, decreased pup birth weight was observed at the highest dose level tested in both the F1 and F2 generations. Parental findings were limited to lower body weight, body weight gain and food consumption in P/F1 males and females at the high-dose level in the pre-mating phase. Females had decreased body weight gain during gestation but increased body weight gain in the lactation phase of the study compared to the controls. However, body weight was always lower compared to the controls in these animals. Lower pup body weights (F1/F2 pups) and a slight decrease in pup survival (F1/F2 pups) were observed at the highest dose level tested. The decrease in pup survival is considered to be a

serious effect, however concern for this finding was tempered by the fact that it occurred only in the presence of maternal toxicity at the limit dose of testing.

In the rat gavage developmental toxicity study, developmental toxicity was evident as an increased incidence of asymmetrically shaped sternebrae at the limit dose of testing in the absence of maternal toxicity, indicating sensitivity of the young. In the rabbit gavage developmental toxicity study, increased post-implantation loss was observed beginning at the mid-dose level in the absence of other signs of maternal toxicity with no effect on the number of live fetuses per litter. At the highest dose level, there was also a decreased number of live fetuses/litter in the absence of significant maternal toxicity. Based on these findings, there was evidence of a serious effect in the absence of overt maternal toxicity in rabbits.

In the rat acute oral gavage neurotoxicity study, there was a decrease in motor activity seen at the limit dose of testing. There were no treatment-related findings up to the limit dose of testing in the 90-day dietary neurotoxicity study in rats. In the 12-month dog dietary toxicity study, minimal focal bilateral vacuolation of the dorsal medial hippocampus or lateral midbrain was noted in both sexes at the two highest dose levels. The vacuolation was associated with the astrocytes and oligodendrocytes. The lesions remained confined to these supporting cells in the central nervous system and did not progress to more advanced or more extensive damage of the neural tissue. The lesions were not associated with other neuropathological findings or overt neurological signs. Similar lesions were not observed in the rat or mouse following short- or long-term dietary exposure and there was no other evidence in any species tested to indicate selective neurotoxicity.

In a 28-day dietary immunotoxicity study in mice, there was no evidence of immune system dysregulation.

Trinexapac-ethyl was evaluated in an extensive battery of in vitro assays designed to assess the potential for interaction with components of the endocrine system. Trinexapac-ethyl was negative in all of the assays, providing evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system. In addition, there were no significant findings in endocrine sensitive tissues in the animal toxicity studies.

There were several quantitative structure activity relationship (QSAR) predictions, genotoxicity assays, acute oral, dermal and inhalation toxicity studies, skin and eye irritation studies, dermal sensitization studies and 28-day oral gavage or dietary studies carried out on the metabolites listed in Appendix I, Table 2. All the metabolites tested in the genotoxic assays were negative up to cytotoxic, precipitating or limit concentrations. Metabolites CGA 158377, CGA 275537, CGA 313458 and CGA 329773 were of low acute oral toxicity. Metabolite CGA 158377 was severely irritating to the rabbit eye. The 28-day oral toxicity studies conducted for the metabolites CGA 158377 (gavage) and CGA 329773 (dietary) demonstrated that these metabolites were no more toxic than trinexapac-ethyl.

The identification of select metabolites is presented in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with trinexapac-ethyl and its associated end-

use product are summarized in Appendix I, Tables 3 and 4. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 5.

Health incident reports

As of 11 May 2020, three human incident reports and one domestic animal incident report involving trinexapac-ethyl had been reported to the PMRA.

There were two human incidents that were serious in nature and involved individuals who were reported to have been exposed to various pesticides at a golf course over a period of many years. One individual was diagnosed with leukemia and died, and the other individual was diagnosed with Parkinson's disease. The incident reports were found to contain insufficient information on the respective exposure scenarios to assess whether the reported effects were related to the active ingredients. In the third human incident, which was minor in severity, an individual ran by a treated field and his symptoms of headache, sore throat and malaise were found to have some association to the potential pesticide exposure.

In the domestic animal incident, which was minor in severity, it was reported that birds and a dog were exposed to a field that had been sprayed with a trinexapac-ethyl product. They developed malaise and other unspecified effects an unknown amount of time later. There was insufficient information to assess an association with the pesticide.

Overall, based on the low number of incident reports and the lack of information within the serious incident reports, no additional mitigation measures are proposed based on the incident report review.

3.1.1 *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.

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

With respect to potential prenatal and postnatal toxicity, evidence of sensitivity of the young was observed in both the rat and rabbit gavage developmental toxicity studies. In the rat, an increased number of skeletal variations, asymmetrically-shaped sternebrae, was observed at the limit dose in the absence of maternal toxicity. In the rabbit developmental toxicity study, an increase in post-implantation loss was observed in the absence of overt maternal toxicity. At the mid-dose level, this increase in post-implantation loss was not reflected in a decrease in the number of live fetuses per litter or other indications of reduced fetal viability. In the dietary 2-generation rat

reproductive toxicity study, a serious effect, decreased pup survival, was observed at the limit dose of testing in the presence of maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young. Although the serious effect of increased post-implantation loss was observed in the absence of overt maternal toxicity, this particular concern was tempered by the absence of a decrease in the number of live fetuses per litter at the LOAEL in the rabbit developmental toxicity study. Therefore, the *Pest Control Products Act* factor (PCPA factor) was reduced to 3-fold when using the rabbit development study to establish the point of departure for assessing risk to women of child-bearing age. For other exposure scenarios, the risk was considered well characterized, there were sufficient margins to the serious effects observed in the young, and therefore, the PCPA factor reduced to onefold.

3.2 Acute reference dose (ARfD)

As the toxicological studies were conducted with trinexapac-ethyl, reference values should be multiplied by a factor of 0.9 when calculating the trinexapac-ethyl acid equivalent.

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

Establishment of an acute reference dose is not required for the general population, as an endpoint of concern attributable to a single exposure at a relevant dose level was not identified in the oral toxicity studies for this population.

Females 13–49 years of age

To estimate acute dietary risk for females 13–49 years of age, a NOAEL of 10 mg/kg bw/day from the gavage developmental toxicity study in the rabbit was selected for risk assessment based on increased post-implantation loss observed at the LOAEL of 60 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to threefold. **The composite assessment factor (CAF) is thus 300.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{10 mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw of trinexapac-ethyl}$$

3.3 Acceptable daily intake (ADI)

As the toxicological studies were conducted with trinexapac-ethyl, reference values should be multiplied by a factor of 0.9 when calculating the trinexapac-ethyl acid equivalent.

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

To estimate risk following repeated dietary exposure for the general population, the NOAEL of 32 mg/kg bw/day from the 12-month dietary toxicity study in the dog was selected. At the LOAEL of 366 mg/kg bw/day, increased vacuolation in the brain was observed. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to onefold. **The CAF is thus 100.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{32 \text{ mg/kg bw/day}}{100} = 0.3 \text{ mg/kg bw/day of trinexapac-ethyl}$$

The ADI provides a margin of > 2400 to the NOAEL for decreased pup survival in the 2-generation dietary rat reproductive toxicity study.

Females 13–49 years of age

To estimate risk following repeated dietary exposure for females 13–49 years of age, a NOAEL of 10 mg/kg bw/day from the developmental study in the rabbit with was selected for risk assessment based on increased post-implantation loss observed at the LOAEL of 60 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to threefold. **The CAF is thus 300.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw/day of trinexapac-ethyl}$$

The ADI provides a margin > 24 000 to the NOAEL for decreased pup survival in the 2-generation dietary rat reproductive study and ≥ 6000 to the NOAEL for skeletal variations observed in the gavage rat developmental toxicity study.

Cancer assessment

There was no evidence of oncogenicity and therefore, a cancer risk assessment was not necessary.

3.4 Occupational and residential risk assessment

3.4.1 Toxicology reference values

Exposure to trinexapac-ethyl is expected to be mainly via the dermal and inhalation routes for mixer/loader/applicators and through the dermal route for postapplication workers. Exposure is

expected to be short- to intermediate-term in duration since the product can be applied twice during the growing season by farmers and over 30 days per season by custom applicators.

3.4.1.1 Dermal absorption

A previously established dermal absorption value of 77.5% was used to estimate worker exposure to trinexapac-ethyl. This value is based on the results obtained from the low dose group at an exposure period of 10 h in a rat in vivo dermal absorption study. This estimate is considered conservative since 21.9% of the applied dose is retained in the skin and is not considered likely to become systemically available. For more information, see PRDD2001-05.

Short-, intermediate-term dermal

For short- and intermediate-term dermal risk assessment, a NOAEL of 10 mg/kg bw/day from the gavage developmental toxicity study in rabbits was selected. At a dose level of 60 mg/kg bw/day, increased post-implantation loss was observed in the absence of overt maternal toxicity. The existing short-term dermal toxicity study did not address the endpoint of concern, thus necessitating the use of an oral study for risk assessment.

For occupational scenarios, the target margin of exposure (MOE) for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity, as outlined in the PCPA Hazard Characterization section, an additional 3-fold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13–49 years of age.

For residential scenarios, the MOE selected for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to 3-fold. The selection of this study and target MOE is considered to be protective of all populations, including the unborn children of exposed women.

Short-, intermediate-term inhalation

For short- and intermediate-term occupational inhalation risk assessment, a NOAEL of 10 mg/kg bw/day from the gavage developmental toxicity study in rabbits was selected. At a dose level of 60 mg/kg bw/day, increased post-implantation loss was observed in the absence of overt maternal toxicity. A repeat-dose inhalation toxicity study was not available, thus necessitating the use of an oral study for risk assessment.

The target MOE for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity, as outlined in the *Pest Control Pest Act* Hazard Characterization section, an additional threefold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13–49 years of age.

Aggregate risk assessment

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- and intermediate-term aggregate exposure to trinexapac-ethyl may be comprised of food, drinking water and residential exposure via the dermal route.

The toxicology endpoint selected for aggregation for all populations was post-implantation loss. The existing short-term dermal toxicity study did not address the endpoint of concern, thus necessitating the use of an oral study for the dermal endpoint. For the oral and dermal routes, the NOAEL of 10 mg/kg bw/day from the rabbit developmental toxicity study was selected with a target MOE of 300. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to threefold.

Cumulative assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for trinexapac-ethyl. Other pesticides of the same class that are known to target the inhibition of GA are registered in Canada, however, there is insufficient evidence to link the apical endpoints observed in the toxicology databases to a specific mode of action. Furthermore, the toxicological effects following exposure to this class of plant growth regulators are considered indicative of more generalized toxicity, and a common mechanism of toxicity has not been identified. Therefore, a cumulative health risk assessment is not required at this time.

3.4.2 Occupational exposure and risk

3.4.2.1 Mixer/loader/applicator exposure and risk assessment

Individuals have potential for exposure to MODDUS during mixing, loading and application. Exposure to workers mixing, loading and applying MODDUS is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders and applicators applying MODDUS to wheat (winter, spring and durum), barley and oat fields using groundboom and aerial application equipment.

The exposure estimates are based on mixers/loaders/applicators wearing coveralls over a single layer and chemical-resistant gloves (unless inside a closed cab or cockpit).

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers were estimated using data from the Agricultural Handlers Exposure Task Force (AHETF), to which the applicant is a member. AHETF are compilations of generic mixer/loader and applicator passive dosimetry data, which facilitate the generation of scenario-specific exposure estimates.

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and 77.5% dermal absorption. 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 µg/kg bw/day by using 80 kg adult body weight.

Dermal and inhalation exposure estimates were compared to the relevant trinexapac-ethyl toxicology reference value (no observable adverse effect level [NOAEL] = 10 mg/kg bw/day) to obtain the margins of exposure (MOEs); the target MOE is 300. Tables 3.4.2.1.1 and 3.4.2.1.2 present the AHETF unit exposure values and estimates of exposure and risk, respectively. Acceptable MOEs were calculated for workers who wear the proposed personal protective equipment (PPE), use the engineering controls, and follow the restrictions on the product label. The target MOE is 300. The risk assessment was completed for wheat (winter) and barley as those crops have the highest application rate and so should not underestimate exposure for workers mixing/loading and applying to oats and spring wheat which can be treated at lower rates.

Table 3.4.2.1.1 AHETF unit exposure estimates for mixer/loaders and applicators handling MODDUS (µg/kg a.i. handled)

Scenario		Dermal	Inhalation[1]
Mixer/loader AHETF estimates			
A	Open Mix/Load Liquids (Coveralls over a single layer, CR gloves)	31.32	0.63
Applicator AHETF estimates			
B	Open Cab Groundboom Liquid Application (Coveralls over a single layer, CR gloves)	14.19	1.68
C	Aerial Closed Cockpit liquid application (Coveralls over a single layer)	2.18	0.00969
Mixer/loader + applicator AHETF estimates			
A+B	Open Mix/Load Liquids and Open Cab Groundboom Liquid Application (Coveralls over a single layer, CR gloves)	45.51	2.31

[1] Light inhalation rate

Table 3.4.2.1.2 Mixer/loader/applicator risk assessment

Exposure scenario	ATPD (ha/day)[1]	Rate (kg a.i./ha)	Dermal exposure (µg/kg bw/day)[2]	Inhalation exposure (µg/kg bw/day)[2]	Combined dermal and inhalation exposure[3]	Combined MOE (target 300)[4]
PPE: (Coveralls over a single layer, CR gloves except in closed cab or cockpit)						
Farmer (M/L/A)	107	0.125	5.90	0.299	6.20	1614
Custom (M/L/A)	360		19.84	1.00	20.85	480
Aerial (M/L)	400		15.17	0.39	15.56	642
Aerial (A)	400		1.06	0.006	1.06	9416

[1] Default Area Treated Per Day tables (2015)
[2] Exposure = (Unit exposure [µg/kg a.i.] × ATPD [ha] × Rate [kg/ha] × [77.5% DA, dermal route only]) / (80 kg bw × 1000 µg/mg)
[3] Dermal and inhalation exposure can be combined since they both rely on the same reference value
[4] Based on NOAEL = 10 mg/kg bw/day, target MOE = 300

3.4.2.2 Exposure and risk assessment for workers entering treated areas

Trinexapac-ethyl has a vapour pressure of 2.16×10^{-6} kPa (by extrapolation) at 25°C. This is lower than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product at 1×10^{-4} kPa for outdoor uses at 20–30°C. Inhalation risk is not of health concern for postapplication workers as trinexapac-ethyl is considered to be non-volatile and the restricted-entry interval (REI) of 12 hours will allow residues to dry, suspended particles to settle and vapours to dissipate.

Postapplication dermal exposure may occur when workers enter treated fields of wheat (winter, spring and durum), barley and oats to perform various activities. The duration of exposure is considered to be short- to intermediate-term as these activities may occur throughout the growing season.

Dermal exposure to workers entering treated areas is estimated by combining default dislodgeable foliar residue (DFR) values and a 77.5% dermal absorption with activity-specific transfer coefficients.

The exposure estimates were compared to the trinexapac-ethyl dermal toxicology reference value (NOAEL = 10 mg/kg bw/day) to obtain the MOE; the target MOE is 300. Since these values exceed the target MOE of 300 (Table 3.4.2.2.1) for wheat (winter, spring and durum), barley and oats, the level of postapplication exposure is not of health concern.

Table 3.4.2.2.1 Postapplication exposure and risk estimate for trinexapac-ethyl on day 0 after the last application

Postapplication activity	Peak DFR (µg/cm^2)[1]	Transfer coefficient (cm^2/hr)[2]	Dermal exposure (mg/kg bw/day)[3]	MOE (target 100)[4]	REI[5]
Hand weeding	0.3125	70	0.0017	5899	12 hours
Scouting	0.3125	1100	0.0266	375	12 hours

[1] Calculated using the default peak residue value of 25% and a default daily dissipation rate of 10%
[2] Transfer coefficients obtained from PRO2014-02: Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides
[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours × 77.5% DA) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 10 mg/kg bw/day, target MOE = 300
[5] Minimum REI is 12 hours to allow residues to dry, suspended particles to settle and vapours to dissipate.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk

MODDUS is not a domestic class product; therefore, a residential handler assessment is not required.

3.4.3.2 Postapplication exposure and risk

MODDUS is not a domestic class product and is not proposed for use in residential areas; therefore, a residential postapplication exposure assessment is not required.

3.4.3.3 Bystander exposure and risk

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 Exposure from drinking water

3.5.1 Concentrations in drinking water

Estimated Environmental Concentrations in Drinking Water Sources

The Estimated Environmental Concentrations (EECs) in potential sources of drinking water was modelled for the combined residue of trinexapac-ethyl and four of its transformation products: trinexapac acid (CGA179500), M5 (CGA300405; 3-ethoxycarbonyl-pentanedioic acid), M2 (3-carboxylic acid ethyl ester-7-hydroxypropyl-5-oxo,7-hydroxyheptanoic acid), and WaterM3photolysis (identified by EFSA as an isomer of trinexapac-ethyl).

Trinexapac-ethyl is proposed for use on several grain crops, and is already registered for use on turf using a higher rate. The modelling was conducted to cover all uses on the label and thus considered both the proposed use on grains and the existing use on turf. All results are presented in Table 3.5.1.2.

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 timing, and geographic scenario. Level 1 EECs cover all regions of Canada.

Level 1 modelling for surface water used a standard scenario, a small reservoir adjacent to agricultural fields. EECs in groundwater were calculated by selecting the highest EEC from a set

of standard scenarios representing different regions of Canada. For trinexapac-ethyl, Level 1 EECs were calculated using the highest application rate on turf.

Given their conservative nature, resulting Level 1 EECs may be used to assess risks from the proposed use on grains or the existing use on turf. These may also be used to support future expansions into other crops or turf, using spray applications not exceeding a seasonal application rate of 2708 g a.i./ha.

It is however recognized that Level 1 EECs may be overly conservative to assess risks from the proposed use on grains given the difference in rate. Therefore, refined Level 1 EECs were generated using the same Level 1 scenarios as above, but limiting the application rate to the proposed uses on grain crops. Refined Level 1 EECs are appropriate to assess risks from the proposed use on grains but not existing uses on turf. These may also be used to support expansions into other crops, using one spray applications up to a rate of 125 g a.i./ha.

Furthermore, Level 2 EECs for turf were calculated using scenarios specific to turf and region specific application timing. Level 2 modelling used a wide set of scenarios covering several regions of Canada. Resulting Level 2 EECs may only be used to assess uses on turf and cannot be used for expansions to other crops or regions.

The EECs in potential drinking water sources are calculated for both groundwater and surface water (Table 3.5.1.1). All EECs were calculated using the Pesticide Water Calculator model (PWC, version 1.52). All scenarios were run for 50 years, except the Okanagan scenario for groundwater, which was run for 100 years. For surface water, the 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. The EECs are calculated by modelling a total land area of 173 ha draining into a 5.3 ha reservoir with a depth of 2.7 m. For groundwater, the EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1m of a water table.

Table 3.5.1.1 lists the application information and main environmental fate characteristics used in the simulations.

Table 3.5.1.1 Major fate inputs for the drinking water modelling

Fate parameter	Value (drinking water)
Residues modelled	Trinexapac-ethyl + trinexapac acid (CGA179500) + M5 (CGA300405; 3-ethoxycarbonyl-pentanedioic acid) + M2 (3-carboxylic acid ethyl ester-7-hydroxypropyl-5- oxo,7-hydroxyheptanoic acid) + WaterM3Photolysis (an isomer of trinexapac-ethyl)
K_{oc}	94 L/kg
Water half-life	441 days at 20°C
Sediment half-life	223 days at 20°C
Photolysis half-life	23.5 days at 40° latitude
Hydrolysis	Stable
Soil half-life	327 days at 20°C

Table 3.5.1.2 Estimated environmental concentrations of a combined residue of trinexapac-ethyl, trinexapac acid, M5, M2, and waterM3Photolysis in potential sources of drinking water as the parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Level 1 for all uses: 7 applications of 386.9 g a.i./ha with a 6 day interval	1440	1440	119	27
Level 1 for grain uses only: 1 application of 125 g a.i./ha	66	66	4.4	1.3
Level 2 for turf uses only: 7 applications of 386.9 g a.i./ha with a 28 day interval	369	368	38	24

[1] 90th percentile of daily concentrations
[2] 90th percentile of 365-day moving average concentrations
[3] 90th percentile of the peak concentrations from each year
[4] 90th percentile of yearly average concentrations

Water monitoring data

As this chemical is currently registered for use in Canada, a search for water monitoring data on trinexapac-ethyl in Canada was undertaken. United States databases were also searched for data on trinexapac-ethyl in water.

Based on available monitoring data, trinexapac-ethyl was not detected in any of the samples from either Canadian or American sources. Available water monitoring data were limited, with a relatively small number of samples (less than 500 samples). Thus, conclusions regarding the potential exposure in drinking water sources could not be made based on the available data. The modelling EECs will be used to assess the potential risk to humans through drinking water.

3.6 Food residues exposure assessment

3.6.1 Residues in plant and animal foodstuffs

The residue definitions in plant products and animal commodities is trinexapac acid (free and conjugated) for risk assessment and trinexapac acid for enforcement purposes. The data gathering/enforcement analytical methods are valid for the quantitation of trinexapac-ethyl as trinexapac acid residues in crop and livestock matrices. The residues of trinexapac acid are stable in wheat grain and hay for up to 24 months, and in wheat straw for up to 20 months when stored in a freezer at -20°C. The raw agricultural commodities, wheat grain and barley grain, were processed, and trinexapac-ethyl residues concentrated in the following processed commodities: pearled barley (1.25×), barley bran (1.8×) and wheat bran (1.9×). Adequate feeding studies were carried out to assess the anticipated residues in livestock matrices resulting from the current uses.

Crop field trials conducted throughout Canada and the United States using end-use products containing trinexapac-ethyl at supported rates in or on wheat and barley are sufficient to support

the proposed maximum residue limits. Field rotational crop studies were not conducted since no residues of concern were observed at the 30-day plant-back interval in the confined accumulation rotational crop studies.

3.6.2 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 year 2005–2010.

3.6.2.1 Acute dietary exposure results and characterization

The following assumptions were applied in the refined acute analysis for trinexapac-ethyl: 100% crop treated, default and experimental processing factors where applicable, highest average field trial (HAFT) residues in/on cereal crops, MRLs on imported crop commodities, and anticipated residues in edible animal commodities. The refined acute dietary exposure (food alone) for all supported trinexapac-ethyl uses and imported commodities is estimated to be 13.0% (0.005262 mg/kg bw/day) of the ARfD expressed in acid equivalents ($ARfD_{acideq}$) for females 13–49 years old (95^{th} percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: 71.2% of the $ARfD_{acideq}$ for females 13–49 years old.

3.6.2.2 Chronic dietary exposure results and characterization

The following criteria were applied to the basic chronic analysis for trinexapac-ethyl: 100% crop treated, default and experimental processing factors (where available), recommended MRLs on cereal crops and imported commodities, and recommended MRLs for all edible animal commodities. Two separate ADIs were established: one for females 13–49 years of age and one for the remaining population subgroups. The basic chronic dietary exposure from all supported trinexapac-ethyl food uses (alone) for females 13– 49 years of age is less than 22% of the acceptable daily intake (ADI_{acideq}). The basic chronic dietary exposure from all supported trinexapac-ethyl food uses for the total population, including infants and children, is less than 8% of the acceptable daily intake (ADI_{acideq}).

Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to trinexapac-ethyl from food and drinking water is less than 12% (0.031459 mg/kg bw/day) of the ADI_{acideq} for the total population (except females 13–49 years of age) and is 46.1% (0.012443 mg/kg bw/day) of the ADI_{acideq} for females 13–49 years of age.

3.6.3 Maximum residue limits

Table 3.6.3.1 Recommended maximum residue limits

MRL (ppm)	Food commodity
4	Wheat bran
3	Barley, oats, wheat
0.02	Meat byproducts of cattle, goats, hogs, horses, poultry and sheep
0.01	Eggs; fat and meat of cattle, goats, hogs, horses, poultry and sheep; milk

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

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

4.0 Impact on the environment

The foliar use of trinexapac-ethyl for managing growth of turfgrass on golf courses and commercial sod farms (Use-site Category #30) has been previously reviewed and the regulatory decision on these uses has been published (Proposed Regulatory Decision PRDD2001-05, Trinexapac-ethyl; Regulatory Decision Document RDD2002-01, Trinexapac-ethyl).

An environmental risk assessment for trinexapac-ethyl uses in terrestrial feed (Use-site Category #13) and food (Use-site Category #14) crops was conducted. The proposed application rate range for these uses is 100−125 g a.i./ha per crop season which is lower than the currently registered application rate range (338.8–2708.4 g a.i./ha).

4.1 Fate and behaviour in the environment

The fate and behaviour of trinexapac-ethyl and its major transformation products in the environment are summarized in Appendix I, Tables 8 to 11.

Terrestrial environment: In the terrestrial environment, trinexapac-ethyl can undergo hydrolysis in the presence of water. Trinexapac-ethyl can transform rapidly via hydrolysis under alkaline conditions at environmentally relevant temperatures and is an important route of transformation under these conditions. Under acidic and neutral pHs, the route of transformation via hydrolysis is much slower. Photolysis is not a major route of transformation in soils.

In soil, trinexapac-ethyl is non-persistent in aerobic and anaerobic soils and transforms more rapidly under aerobic conditions as compared to anaerobic conditions. The major transformation product, trinexapac acid (CGA179500), is a common transformation product produced under

various processes including hydrolysis, phototransformation and biotransformation. Another major transformation product, 3-ethoxycarbonyl-pentanedioic acid (CGA300405), was formed during biotransformation but was not observed under field conditions. Trinexapac-ethyl has a low potential for residue carry over under field conditions. Trinexapac-ethyl and trinexapac acid have a low potential to reach groundwater based on terrestrial field dissipation and laboratory mobility studies. Moreover, the groundwater ubiquity score (GUS) leaching potential index indicated that trinexapac-ethyl is a non-leacher (Appendix I, Table 11).

Aquatic environment: In the aquatic environment, trinexapac-ethyl transforms rapidly via hydrolysis under alkaline conditions and environmentally relevant temperatures and is an important route of transformation under these conditions. At neutral and acidic pHs, hydrolysis is considerably slower. Photolysis is a major route of transformation in water. Several major transformation products including 3-ethoxycarbonyl-pentanedioic acid (CGA300405), 3-carboxylic acid ethyl ester-7-hydroxypropyl-5- oxo,7-hydroxyheptanoic acid (M2) and WaterM3Photolysis (an isomer of trinexapac-ethyl), were formed when exposed to light in water. The major transformation product, trinexapac acid (CGA179500) is a common transformation product produced under various processes including hydrolysis, phototransformation and biotransformation. Trinexapac-ethyl is non-persistent in aerobic aquatic systems. Based on log K_{ow} values and fish bioaccumulation studies, trinexapac-ethyl is not expected to bioaccumulate.

Air: Trinexapac-ethyl has a low vapour pressure and a low Henry's law Constant which indicate that it has a low potential for volatilization from moist soil and water surfaces under field conditions.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications.

The concentration of trinexapac-ethyl in various environmental compartments were estimated based on calculation using maximum exposure scenarios. It was assumed that, in accordance with the proposed Canadian label for MODDUS, the maximum seasonal environmental rate for trinexapac-ethyl is 125 g a.i./ha based on the proposed single maximum seasonal application rate on winter wheat.

Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted with uncertainty factors to account for potential differences in species sensitivity as well as varying

protection goals (in other words, protection at the community, population, or individual level) (Appendix I, Tables 12 and 13).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate (EEC) by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1 for most species, 0.4 for acute risk to pollinators and 2 for beneficial arthropods). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to terrestrial organisms

In determining the risk to terrestrial organisms, uncertainty factors are applied to acute toxicity endpoints (for example, LC_{50} or LD_{50}) to generate endpoint values that are used in calculating risk quotients (RQ = exposure/endpoint value). No uncertainty factors are applied to chronic endpoints (for example, NOEC). For earthworms, the acute endpoint is divided by the uncertainty factor of 2.0 and the resulting RQ is compared to the level of concern (LOC) of 1. For birds and mammals, the acute endpoint is divided by the uncertainty factor of 10 and the resulting RQ is also compared to the LOC of 1. For bees, the acute endpoint is typically used directly without the uncertainty factor to calculate the RQ which is compared to the LOC of 0.4. With terrestrial plants, the acute endpoint (for example, ER_{25}) is used directly without an uncertainty factor to calculate the RQ which is then compared to the LOC of 1. A summary of terrestrial toxicity data is presented in Appendix I, Table 12.

In summary, when used according to the proposed label directions, environmental risks associated with ground and aerial foliar applications of trinexapac-ethyl on cereals at a rate of 125 g a.i./ha are acceptable for the following terrestrial organisms:

- Terrestrial invertebrates (earthworms, pollinators)
- Terrestrial vertebrates (birds and mammals)
- Non-target terrestrial plants

4.2.1.1 Screening level risk assessment for terrestrial organisms

The screening level risk assessment for trinexapac-ethyl was based on the single maximum seasonal application rate for trinexapac-ethyl of 125 g a.i./ha on winter wheat and the most

sensitive endpoints within each group of terrestrial organisms and is summarized in Appendix I, Tables 14 and 15.

Terrestrial invertebrates

Earthworms (Appendix I, Table 14): The major route of exposure for earthworms (*Eisenia fetida*) is through ingested soil in treated fields. The level of concern for both acute and chronic exposures of earthworms to trinexapac-ethyl was not exceeded in the screening level risk assessment. Thus, the environmental risk to earthworms from application of trinexapac-ethyl is acceptable when used according to label directions.

Honeybees (Appendix I, Table 14): During foliar application, pollinators may be exposed by contacting trinexapac-ethyl spray droplets during flight or through contacting dried spray residues on plants. Pollinators can also be exposed orally by feeding on pollen and nectar after spray droplets were deposited on open flowers or from systemic movement of trinexapac-ethyl residues to pollen and nectar following application before and during bloom.

Toxicity studies were available for acute oral and contact exposure for adults, chronic oral exposure for both adult and larval bees. Trinexapac-ethyl is practically non-toxic to honeybees.

An acute and chronic foliar application screening level risk assessment for bees was conducted using the single maximum seasonal application rate of trinexapac-ethyl of 125 g a.i./ha. The level of concern was not exceeded at the screening level f or bee larvae and adult bees from contact and oral exposures to trinexapac-ethyl therefore, the risks associated with the application of trinexapac-ethyl to cereal crops are acceptable when used according to label directions.

Non-target arthropods (Appendix I, Table 14): No adverse effects of trinexapac-ethyl were observed in all studies conducted. The level of concern was not exceeded in the screening level risk assessment; therefore, the environmental risks associated with the application of trinexapac-ethyl to non-target arthropods are acceptable when used according to label directions.

Terrestrial vertebrates

Birds and Mammals (Appendix I, Table 15): The major route of exposure for birds and mammals is through ingestion of trinexapac-ethyl residues on food sources following application. Based on acute oral toxicity, trinexapac-ethyl is slightly toxic to zebra finch (*Taeniopygia guttata*) with an LD_{50} of 1684 mg a.i./kg bw; however, the level of concern for acute oral, acute dietary and chronic exposures of several bird species was not exceeded at the screening level risk. Therefore, the risks to wild birds from application of trinexapac-ethyl are acceptable when used according to label directions.

Acute oral, 90-day dietary and chronic exposures of trinexapac-ethyl to mammals were investigated. Trinexapac-ethyl is slightly toxic to mammals [in other words, rat (*Rattus norvegicus*)] based on acute oral toxicity; however, the screening level risk assessment did not exceed the level of concern for mammals. Therefore, the risks to wild mammals from application of trinexapac-ethyl are acceptable when used according to label directions.

Terrestrial plants

Non-target terrestrial plants (Appendix I, Table 14): Non-target terrestrial plants can be exposed from spray drift during the application of trinexapac-ethyl to target terrestrial crops. The toxicity of trinexapac-ethyl on seedling emergence and vegetative vigour of several monocotyledonous and dicotyledonous plants was evaluated. Among the non-target terrestrial plants evaluated, carrot was the most sensitive plant species with an EC_{25} value of 299 g a.i./ha based on plant dry weight. The level of concern to trinexapac-ethyl was not exceeded in the screening level risk assessment. Therefore, the risks to non-target terrestrial plants from application of trinexapac-ethyl are acceptable when used according to label directions.

4.2.2 Risks to aquatic organisms

In determining the risk to aquatic organisms, uncertainty factors are applied to acute toxicity endpoints (for example, LC_{50}) to generate endpoint values that are used in calculating risk quotients (RQ = exposure/endpoint value). No uncertainty factors are applied to chronic endpoints (for example, NOEC). For aquatic invertebrates, algae and aquatic vascular plants, the acute endpoint is divided by the uncertainty factor of 2.0 and the resulting RQ is compared to the LOC of 1. For fish and amphibians, the acute endpoint is divided by the uncertainty factor of 10 and the resulting RQ is also compared to the LOC of 1. A summary of aquatic toxicity data is presented in Appendix I, Table 13.

In summary, when used according to the proposed label directions, environmental risks associated with ground and aerial foliar applications of trinexapac-ethyl on cereals at a rate of 125 g a.i./ha are acceptable for the following aquatic organisms:

- Freshwater invertebrates, algae and plants
- Fish and amphibians
- Marine organisms

4.2.2.1 Screening level risk assessment for aquatic organisms

The screening level risk assessment was based on the single maximum seasonal application rate for trinexapac-ethyl of 125 g a.i./ha on winter wheat assuming water density of 1 g/mL, and the most sensitive endpoints within each group of terrestrial organisms. The screening level EECs considered were 0.0834 mg a.i./L (amphibian habitat) and 0.0156 mg a.i./L (shallow pond).

At the screening level risk assessment for freshwater invertebrates, algae, and plants, fish and amphibians, and marine organisms, the level of concern was not exceeded (Appendix I, Table 16). Thus, the environmental risk to aquatic organisms from the application of trinexapac-ethyl is acceptable when used according to label directions.

4.2.3 Incident reports

Based on the review completed on 27 January 2020, no environmental incident reports involving trinexapac-ethyl were found in a search conducted using available databases (PMRA incident reporting and the United States Ecological Incident Information System).

5.0 Value

Lodging can reduce grain yield and quality by interfering with photosynthesis and carbohydrate movement within the plant which can contribute to uneven maturity, reduced grain number and grain weight, fostering a microclimate that favours development of foliar diseases, grain loss through stem breakage, and reducing the efficiency of the harvesting operation thereby increasing time and cost.

There are few alternative products available for reducing plant height and lodging in cereal crops. These products contain either chlormequat chloride, which inhibits gibberellic acid synthesis, or ethephon, which increases the production of the plant hormone ethylene. Products containing either of these active ingredients are registered for use on winter and spring wheat while only ethephon is registered for use on barley. MODDUS is the first plant growth regulator that may be used to reduce height and lodging in oat.

The application of MODDUS as either a single or split application would not alter current management practices used in small grain cereal crops, such as in the application of other pest control products to control weeds, diseases and insect pests.

As a plant growth regulator inhibitor, resistance development of crop plants to the effects of trinexapac-ethyl is not expected. There have been no reports of resistance development in any countries in which this active ingredient was already registered.

The use of MODDUS is expected to result in a substantial economic benefit to growers by protecting harvestable grain yield and grain quality, and reducing the amount of straw that is processed through the combine thereby reducing engine load and fuel consumption. Crops that lodge may result in smaller grains as well as a longer period of time to dry down to a harvestable moisture level since heads and straw are all compiled together near the ground. This increase in the delay of harvest increases the risk of potential frost damage to the crop and increases the time the heads are at elevated moisture, which can lead to sprouting and grain moulds. These effects often result in a reduced quality grade and a lower return for the producer. A lodged crop is more difficult and slower to harvest since the grain heads are closer to the ground, which may increase the risk of damaging the combine's cutter bar due to stones or uneven ground. A standing crop offers the grower the option to harvest at a quicker ground speed thereby completing the harvest in a shorter timeframe.

Value information in support of the registration of MODDUS was submitted in the form of data generated in small-scale efficacy studies conducted in spring and winter wheat, barley and oat in Canadian and the American Trials were designed to assess the effect of MODDUS on crop height, crop lodging and grain yield as affected by one or more of application rate, application timing for a single application, split application (the half-rate applied twice), application method (ground vs aerial) and tank mixing with a fungicide on all or a subset of labelled crops.

The data demonstrated that when MODDUS is applied at the labelled rates and timings that height and lodging are reduced. While no significant differences in yield were reported between untreated crops and MODDUS-treated crops, a reduction in lodging can be expected to increase

harvestable yield and grain quality, particularly where lodging is moderate to severe, such as often observed under intensive management practices and during periods of high winds and rainfall. Tank mixing with a fungicide or application in a smaller spray volume that is typical of aerial application did not affect performance of MODDUS in reducing height and lodging.

There were no reports of crop injury in any of the efficacy studies. The tolerance of spring and winter wheat to MODDUS was also assessed in dedicated crop tolerance studies in which MODDUS was applied at 125 g a.i./ha and 250 g a.i./ha, which is twice the maximum winter wheat rate. Crop injury, assessed as percent phytotoxicity, was not usually evident except in winter wheat where minor early season injury was occasionally observed in the MODDUS double rate treatment. However, this did not impact grain yield.

MODDUS is supported for use as a growth management aid to reduce the potential for lodging when foliarly applied to spring wheat and oat at 0.83 L/ha (100 g a.i./ha), to barley at 1.03 L/ha (125 g a.i./ha) and to winter wheat at 0.83–1.03 L/ha when these crops are at the beginning of stem elongation to the flag leaf stage. Alternatively, MODDUS is supported for two applications each at the half rate to spring wheat, barley and oat with the first treatment at the crop tillering stage and the second at the flag leaf stage. MODDUS is supported for application in tank mixtures as well as with either ground or aerial spray equipment.

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*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

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

Please refer to Appendix I, Table 17 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.*[5] The list is

[5] SI/2005-114, last amended on June 25, 2008. See Justice Laws website, Consolidated Regulations, *List of*

used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations, including the *Toxic Substance Management Policy*[7] and *Formulants Policy,*[8] and taking into consideration the *Ozone-Depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act*, 1999, (substances designated under the *Montreal Protocol*).

7.0 Summary

7.1 Human health and safety

The toxicology database is adequate to characterize the potential health hazards associated with trinexapac-ethyl. There was no evidence of oncogenicity in rats or mice after long-term dosing. There was evidence of increased sensitivity of the young in a rat developmental toxicity study and a serious effect was observed in the presence of maternal toxicity in the rat reproductive toxicity study. There was evidence of a serious effect in the absence of overt maternal toxicity in the rabbit developmental study. Trinexapac-ethyl was not neurotoxic in the rat but there was evidence of increased vacuolation in the brain of the dog. In short- and long-term dietary studies on laboratory animals, the primary target organ was the kidney in the rat and the brain in the dog. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders and applicators handling MODDUS and workers entering treated fields of wheat (winter, spring and durum), barley and oats are not expected to be exposed to levels of trinexapac-ethyl that will result in health risks of concern when MODDUS is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is trinexapac acid (free and conjugated) in plant products and in animal matrices. The proposed use of trinexapac-ethyl on wheat, barley and oats does not constitute a health risk of concern for acute or chronic dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of trinexapac-ethyl.

Pest Control Product Formulants and Contaminants of Health or Environmental Concern.

6 PMRA's Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New *Pest Control Products Act*.

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

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

MRL (ppm)	Food commodity
4	Wheat bran
3	Barley, oats, wheat
0.02	Meat byproducts of cattle, goats, hogs, horses, poultry and sheep
0.01	Eggs; fat and meat of cattle, goats, hogs, horses, poultry and sheep; milk

7.2 Environmental risk

The risks associated with the use of MODDUS containing the active ingredient trinexapac-ethyl at the proposed label rates for non-target terrestrial and aquatic organisms are acceptable from an environmental perspective when label directions are followed.

7.3 Value

The information submitted to register MODDUS is adequate to demonstrate the value of its use as a growth management aid to reduce susceptibility of spring wheat, winter wheat, barley and oat to lodging.

8.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Trinexapac-ethyl Technical and MODDUS, containing the technical grade active ingredient trinexapac-ethyl, for use on spring wheat, winter wheat, barley and oat as a plant growth regulator to reduce susceptibility to lodging (falling/leaning over).

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.

List of abbreviations

↑	increased
↓	decreased
♀	female
♂	male
%	percent
λ	wavelength
°C	degrees Celsius
^{14}C	Carbon-14 radioactive isotope
µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
AB	Alberta
abs	absolute
AD	administered dose
ADI	acceptable daily intake
ADI_{acideq}	acceptable daily intake expressed as acid equivalents
ADME	absorption, distribution, metabolism and elimination
AFC	antibody-forming cell
AGF	aspirated grain fractions
AHETF	Agricultural Handlers Exposure Task Force
ALS	acetolactate synthase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
A.R.	percent applied radioactivity
AR	Arkansas
ARfD	acute reference dose
$ARfD_{acideq}$	acute reference dose expressed as acid equivalents
ARTF	Agricultural Reentry Task Force
atm	atmosphere
AST	aspartate aminotransferase
ATPD	area treated per day
BAF	bioaccumulation factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
Bq	becquerel
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
CA	California
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CHO	Chinese hamster ovary
chol	cholesterol
cm	centimetres

CMC	carboxymethylcellulose
CNS	central nervous system
CO	Colorado
creat	creatinine
CR	chemical-resistant
d	days
DA	dermal absorption
DACO	data code
DAT	days after treatment
DF	dry flowable
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EC	emulsifiable concentrate formulation
EC_{10}	effective concentration on 10% of the population
EC_{20}	effective concentration on 20% of the population
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated dietary exposure
EEC	estimated environmental concentration
EFSA	European Food Safety Authority
EPA	United States Environmental Protection Agency
ER_{25}	effective rate for 25% of the population
ER_{50}	effective rate for 50% of the population
F1	first generation
F2	second generation
fc	food consumption
FDA	*Food and Drugs Act*
FGS	Feekes growing stage
FIR	food ingestion rate
g	gram(s)
GA	gibberellic acid
GA_1	gibberellin #1
GA_{20}	gibberellin #20
GD	gestation day
GGT	gamma-glutamyl transpeptidase
glu	glucose
GUS	groundwater ubiquity score
h	hour
ha	hectare(s)
HAFT	highest average field trial
Hb	hemoglobin

HC	historical control
Hct	hematocrit
HDPE	high-density polyethylene
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
hr(s)	hour(s)
HRPT	hypoxanthine-guanine phosphoribosyl transferase
IA	Iowa
ID	Idaho
IN	Indiana
ILV	independent laboratory validation
IUPAC	International Union of Pure and Applied Chemistry
K^+	potassium ion
KBq	kilobecquerel
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
KS	Kansas
L	litre(s)
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LLNA	local lymph node assay
LOC	level of concern
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	low observed effect concentration
LOQ	limit of quantitation
LSC	liquid scintillation counting
LR_{50}	lethal rate 50%
mg	milligram
min	minutes
mL	millilitre
M/L/A	mixer/loader/applicator
MAS	maximum average score for 24, 48 and 72 hours
MB	Manitoba
MBq	megabecquerel
ME	micro-emulsion concentrate
MIS	maximum irritation score
MN	Minnesota
MO	Missouri

MOA	mode of action
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
MRM	multiresidue method
MS	mass spectrometry
MTD	maximum tolerated dose
N	North
N.A.	not applicable
NAFTA	North American Free Trade Agreement
ND	North Dakota
N.D.	not detected or below detection limit; not determined
ND	not determined
NE	Nebraska
NKC	natural killer cell
nm	nanometre(s)
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
N/R	not required
NR	not reported
NZW	New Zealand white
OC	organic carbon content
OK	Oklahoma
OM	organic matter content
OR	Oregon
P	parental generation
Pa	Pascal
PA	Pennsylvania
PAS	periodic acid Schiff
PBI	plantback interval
PCPA	*Pest Control Products Act*
pF	soil moisture tension
pH	measure of the acidity or basicity of an aqueous solution
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppb	parts per billion
PPE	Personal protective equipment
ppm	parts per million
ppt	parts per trillion
PO_4^-	phosphate ion
PRDD	Proposed Regulatory Decision Document
PWC	Pesticide Water Calculator

QC	Quebec
QSAR	quantitative structure-activity relationship
RAC	raw agricultural commodity
RBC	red blood cells
RD	residue definition
REI	restricted entry interval
rel	relative
RQ	risk quotient
RSD	relative standard deviation
SC	soluble concentrate
SD	South Dakota
SD	Sprague-Dawley
SDEV	standard deviation
SFO	single first-order
SI	stimulation index
SK	Saskatchewan
SL	solution formulation
S9	mammalian metabolic activation system
STMdR	supervised trial median residue
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TC	transfer coefficient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TX	Texas
UAN	urea ammonium nitrate
UDS	scheduled DNA synthesis
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
VA	Virginia
v/v	volume per volume dilution
vol	volume
WBC	white blood cells
wc	water consumption
WI	Wisconsin
wt	weight

Appendix I Tables and figures

Table 1a Residue analysis

Matrix	Method ID	Analyte	Method type	LOQ	Reference
Soil	GRM020.03A	parent	HPLC-MS/MS	10 ppb	2723388, 2723389, 2723390, 2723391, 2723392
	GRM020.04A	CGA 179500			
	GRM020.10A	CGA 300405			
Water	GRM020.02A	parent		50 ppt	2723395, 2723399, 2723401, 2723402, 2723404, 2723405
	GRM020.02A	CGA 179500			
	GRM020.11A	CGA 300405			
	GRM020.08B	CGA 313458		10 ppb	

Table 1b Residue analysis

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ	Reference
Livestock Commodities					
Enforcement Method	Whole milk and egg, bovine muscle and liver and animal fat	Trinexapac acid	QuEChERS (EN 15662:2009-2) Multi-Residue Method HPLC-MS/MS	0.1 ppm all matrices	PMRA# 2723366
Data-Gathering Method	Egg; milk; muscle; liver; kidney; fat	Trinexapac acid	Method REM 137.14 HPLC-MS/MS	0.1 ppm egg, kidney, liver muscle and fat 0.005 ppm milk	PMRA# 2723347
ILV of Enforcement Method	Bovine muscle, liver, fat, and whole milk, and eggs	Trinexapac acid	QuEChERS (EN 15662:2009-2) Multi-Residue Method HPLC-MS/MS	0.1 ppm all matrices	PMRA# 2723365
Radiovalidation	Goat liver and egg white	Total trinexapac-ethyl derived residues	N/A	N/A	PMRA# 2723356

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ	Reference
Plant Commodities					
Enforcement Methods:	Field grown grass commodities (forage, straw seed screenings and seeds	Trinexapac acid (free and conjugated forms)	GRM020.01A HPLC-MS/MS	0.01 ppm all matrices	PMRA# 2723353
	Lettuce, whole orange, wheat grain, dried broad bean, oilseed rape seed	Trinexapac acid	QuEChERS [EN 15662: 2009-2] Multi-Residue Method HPLC-MS/MS	0.01 ppm all matrices	PMRA# 2723367
Data-Gathering Methods:	Cereal grain and straw	Trinexapac acid	GRM020.09A HPLC-MS/MS	0.01 ppm for cereal grain 0.05 ppm for cereal straw	PMRA# 2723348
	Barley (grain, hay, straw), tomato, apple and sunflower seed.	Trinexapac acid	GRM020.05A HPLC-MS/MS	0.01 ppm	PMRA# 2723349, 2723357
	Cereal grain, flour, bran, bread and beer	CGA224439 (Cyclopropanecarboxylic acid as the 2-hydrazinoquinoline (HQ)	GRM020.15A HPLC-MS/MS	0.01 ppm	PMRA# 2723350, 2723362
	Dry broad beans, oilseed rape seeds, cereal grain and cereal straw.	Trinexapac acid	GRM020.09B HPLC-MS/MS	0.01 ppm for dry broad beans, oilseed rape seeds and cereal grain 0.05 ppm for cereal straw	PMRA# 2723351, 2723358
	Wheat grain and straw; barley grain and straw; and rapeseed	Trinexapac acid	REM 137.02 HPLC with UV detection	0.02 ppm all matrices	PMRA# 2723352, 2723363

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ	Reference
	Dry broad beans and oilseed rape seeds	Trinexapac acid	GRM020.16A HPLC-MS/MS	0.01ppm all matrices	PMRA# 2723358
	Wheat grain and straw	Trinexapac acid	GRM020.009A HPLC-MS/MS	0.01 ppm for cereal grain 0.05 ppm for cereal straw	PMRA# 2723360
	Beer, bread, bran, wheat grain and flour	CGA313458 (2-(4-cyclopropyl-2,4-dioxo-butyl)-succinic acid)	GRM020.013A HPLC-MS/MS	0.01 ppm all matrices	PMRA# 2723361
	Beer and bread	CGA113745 (3-hydroxy-5-oxocyclohex-3-enecarboxylic acid)	GRM020.14A HPLC-MS/MS	0.01 ppm all matrices	PMRA# 2723361
ILV of Enforcement Methods	Wheat grain, wheat forage, and wheat straw	Trinexapac acid (free and conjugated forms)	GRM020.01A [HPLC-MS/MS]	0.01 ppm all matrices	PMRA# 2723354
	Lettuce, whole orange, wheat grain, dried broad bean and oilseed rape seed	Trinexapac acid	QuEChERS [EN 15662: 2009-2] Multi-Residue Method [HPLC-MS/MS]	0.01 ppm all matrices	PMRA# 2723364
Radiovalidation	Extraction solvents used in the method are similar to those used in the spring wheat metabolism studies.	All trinexapac-ethyl derived residues reported as parent equivalents.	QuEChERS [EN 15662: 2009-2] Multi-Residue Method [HPLC-MS/MS]	N/A	PMRA# 2723367
	Forage, straw and seed screenings from a grass metabolism study.	All trinexapac-ethyl derived residues reported as parent equivalents.	GRM020.01A [HPLC-MS/MS]	N/A	PMRA# 2723359

Table 2 Identification of select metabolites of trinexapac-ethyl

Code	Chemical Name
CGA 179500	4-[cyclopropyl(hydroxyl)methylene]-3,5-dioxocyclohexanecarboxylic acid
CGA 113745	3-hydroxy-5-oxo-cyclohex-3-enecarboxylic acid
CGA 158377 or CA875	CGA 113745 analogue
CGA 224439	cyclopropanecarboxylic acid
CGA 275537	1,2,3-propanetricarboxylic acid
CGA 300405	3-ethoxycarbonyl-pentanedioic acid
CGA 313458	2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid
CGA 329773	4-cyclopropanecarbonyl-3,5-dihydroxy-benzoic acid

Table 3 Toxicity profile of end-use product MODDUS plant growth regulator containing trinexapac-ethyl

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

Acute toxicity studies – end use product – MODDUS plant growth regulator	
Acute Oral Toxicity Rat (Sprague Dawley) PMRA# 1050696	$LD_{50} \geq 5050$ mg/kg bw (♂/♀) One female found dead (Day 1); Clinical signs include ↓ activity, piloerection, ↑ sensitivity to touch (resolved by Day 3) **Low Acute Toxicity**
Acute Dermal Toxicity Rabbit (NZW) PMRA# 1050697	$LD_{50} > 2020$ mg/kg bw (♂/♀) Clinical signs included ↑soft feces **Low Acute Toxicity**
Acute Inhalation Toxicity Rat (Sprague Dawley) PMRA# 1050698	$LC_{50} > 2.57$ mg/L (♂/♀) Clinical signs included ↑ fur coated with urine and feces, piloerection **Low Acute Toxicity**
Eye irritation Rabbit (NZW) PMRA# 1050699	Unwashed eyes: MAS = 15.5/110 MIS=18.3/110 at 48 hrs Washed eyes: MAS = 19.9/110 MIS = 21.7/110 at 24 hrs Due to persistence of ocular irritation up to and including day 7 in both washed and unwashed eyes, classification was upgraded to: **Moderately irritating**
Dermal irritation Rabbit (NZW) PMRA# 1050700	MAS = 0/8 MIS = 0.17/8 at 1 hr **Non-irritating**

Dermal Sensitization (Buehler method) Guinea Pig (Hartley albino) PMRA# 1050701	**Negative**

Table 4 Toxicity profile of trinexapac-ethyl technical

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

Study type/animal/PMRA#	Study results
ADME Studies -trinexapac-ethyl technical (CGA 163935 technical)	
ADME Rats (Tif: RAI f) 2 studies : PMRA# 1048177 and 2723327	Metabolism of trinexapac-ethyl was studied in male and female Crl:CD BR rats after single low- and high- dose administration of [^{14}C] trinexapac-ethyl, a single low intravenous dose, as well as repeat low doses of trinexapac-ethyl for 14 days followed by a single low dose of [^{14}C] trinexapac-ethyl on day 15. Biliary elimination of trinexapac-ethyl was also studied in male and female Tif: RAI f rats after a single low- and high- dose oral administration of [^{14}C] trinexapac-ethyl. Absorption: Trinexapac-ethyl was rapidly and extensively absorbed in both sexes following single or repeat low-dose administration and single high-dose administration. Greater than 95% of the AD was absorbed following single or repeat low-dose administration and single high-dose administration. Maximum blood levels were achieved 15 minutes after dosing, and the radioactivity was rapidly eliminated from the blood with half-lives of less than one hour. Distribution: The highest residues were observed in fat, lungs, kidneys and liver, however, mean recovery of radioactivity in tissues/carcasses at sacrifice (at 168 hrs post-dosing) was < 0.3% of the AD for all dose groups indicating little potential for tissue retention. Elimination: Excretion was rapid, with the majority of radioactivity being eliminated within 12 hrs post-dosing via urine (≥ 70% of the AD), and within 24 hrs via feces (≤ 2% of the AD). Biliary excretion plays a minor role in excretion. Metabolism: The major component in urine, fecal and bile extracts was identified as CGA-179500, the free acid derivative of trinexapac-ethyl resulting from hydrolysis of the ester bond of the parent compound accounting for ~82.0-92% of the AD. In bile, a more polar derivative of CGA 179500, was identified as the major metabolite. The only other component found (fecal extract only) was identified as the parent compound trinexapac-ethyl, accounting for <0.1% of the AD. There were no significant qualitative differences in absorption, distribution, metabolism or excretion of trinexapac-ethyl between the sexes, between single and repeat low-dose administration or between single low-dose (oral and intravenous) and high-dose administration.
Acute Toxicity Studies – Technical Grade Active Ingredient - trinexapac-ethyl technical (CGA 163935 technical)	
Acute Oral Toxicity (gavage) Rat (Sprague Dawley) PMRA# 1048309	LD_{50} = 4610/4210 mg/kg bw (♂/♀) Clinical signs included ↑ diarrhea, salivation, polyuria (♂/♀) **Low Acute Toxicity**

Acute Dermal Toxicity Rat (SPF) PMRA# 2891809	LD_{50} > 4000 mg/kg bw (♂/♀) Clinical signs included ↑ dyspnea, ↑ ruffled fur, ↓ activity (♂/♀) **Low Acute Toxicity**
Inhalation Toxicity (nose-only) Rat (Sprague Dawley) PMRA# 1048311	LC_{50} > 5.3 mg/L (♂/♀) Clinical signs included slight dyspnea, ↑ ruffled fur (♂/♀) **Low Acute Toxicity**
Eye Irritation Rabbit (NZW) PMRA# 1048312	MAS = 0.89/110 (washed eyes) MIS = 5.33/110 at 1 hr (washed and unwashed eyes) **Minimally irritating**
Dermal Irritation Rabbit (NZW) PMRA# 1048313	MAS = 1.0/8 MIS = 1.83/8 at 1 hr **Slightly irritating**
Dermal Sensitization (Optimization Method) Guinea Pig (Pirbright White) PMRA# 1048314	**Negative**
Dermal Sensitization (Maximization Method) Guinea Pig (Dunkin-Hartley) PMRA# 2723269	**Negative**
Dermal Sensitization (LLNA) Mouse (CBA/J) PMRA# 2896446	Positive Fortified with higher level of impurities **Dermal Sensitizer**
Short-Term Toxicity Studies -trinexapac-ethyl technical (CGA 163935 technical)	
90-Day Oral Toxicity (dietary) Mouse (CD-1) PMRA# 1051403	NOAEL = 1552/1970 mg/kg bw/day (♂/♀) LOAEL = not established (♂/♀)
28-Day Oral Toxicity (gavage) Rat (Sprague Dawley) PMRA# 1051389	NOAEL = 100 mg/kg bw/day (♂/♀) LOAEL = 1000 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ wc, ↑ K^+, ↑ prothrombin time, ↑ liver wt, ↑ kidney wt, ↑ severity of inflammatory cell infiltration in myocardium (♂/♀); ↑ PO^{4-}, ↑ hepatocellular hypertrophy, ↑ PAS droplets (♂); ↑ urea, ↑ ALT, ↑ heart wt, ↑ enlarged livers, ↑ in severity of glycogen deposit in liver (♀)

90-Day Oral Toxicity (dietary) Rat (Sprague Dawley) PMRA# 1048315, 1048316	NOAEL = 34/395 mg/kg bw/day (♂/♀) LOAEL = 346/1551 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ urine vol, ↑ urine specific gravity, ↑ liver wt (rel), ↑ tubular casts and ↑ tubular basophilia in the kidney, ↑ cytoplasmic accumulation of hyaline droplets in the kidneys (♂); ↓ bw, ↓ bwg, ↓ fc, ↓ urinary pH, ↓ ALP, ↑ kidney wt, ↑ prothrombin time, ↓ PO_4^- (♀)
49-Day Oral Toxicity (dietary) -non-guideline Dog (Beagle) PMRA# 1048319, 1048320	Supplemental range-finding study ≥15 000 ppm: ↑ thymic atrophy (♀) Day 1–3 = 15000 ppm; Day 4-28=30000 ppm; Day 29–49 = 50000 ppm: ↓ bw, ↓ bwg, ↓ fc, ↑ chol, ↑ diffuse thymic atrophy (all ♂/♀), ↑ tubular dilation in kidneys, ↑ degeneration/regeneration of renal tubule epithelial cells, congestion of spleen (♂/♀);↑ creat, ↑ rel kidney wt, ↑ eosinophilic casts in kidneys (♂); ↓ thymus wt, ↑ adrenal wt (♀)
90-Day Oral Toxicity (dietary) Dog (Beagle) PMRA# 1048321, 1048322 PMRA 2723277 (re-examination of brain tissue)	NOAEL = 516/582 mg/kg bw/day (♂/♀) LOAEL = 927/891 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw, ↓ bwg, ↓ fc, ↑ diffuse thymic atrophy, (♂/♀); emaciation, ↓ glu, ↓ thymus wt, ↑ vacuolation in the lateral midbrain (♂)
12-Month Oral Toxicity (dietary) Dog (Beagle) PMRA# 1048317, 1048318 Supplemental studies: PMRA 2723275 to 2723277 (re-examination of brain tissue) PMRA# 2723274 and 2891810 (uterus and estrous cycle)	NOAEL = 32/40 mg/kg bw/day (♂/♀) LOAEL = 366/357 mg/kg bw/day (♂/♀) Effects at LOAEL: mucoid or bloody feces, ↑ chol, ↑ vacuolation in the dorsal medial hippocampus or lateral midbrain (associated with astrocytes and oligodendrocytes) (♂/♀); ↓ RBC (♀)
22-Day Dermal Toxicity Rabbit (NZW) PMRA# 2891809	NOAEL (systemic toxicity) = 1000 mg/kg bw/day (♂/♀) LOAEL = Not determined ≥100 mg/kg bw/day: ↑ severity of acanthosis, ↑ incidence of inflammation, ↑ hyperkeratosis, ↑ crust formation (♂/♀)

Chronic Toxicity and Oncogenicity Studies -trinexapac-ethyl technical (CGA 163935 technical)	
18-Month Oncogenicity (dietary) Mouse (CD-1) PMRA# 1048105 to 1048114	NOAEL = 912/1073 mg/kg bw/day (♂/♀) LOAEL = Not determined **No evidence of oncogenicity.**
24-Month Chronic Toxicity/Oncogenicity (dietary) Rat (Sprague Dawley) PMRA# 1048115 to 1048121; 1048150 to 1048151; 1048154 to 1048158; 1048331	NOAEL = 116/147 mg/kg bw/day (♂/♀) LOAEL = 393/494 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ urinary pH (♂/♀); ↑ brown pigmentation in renal tubular epithelium (♀) **No evidence of oncogenicity.**
Developmental/Reproductive Toxicity Studies -trinexapac-ethyl technical (CGA 163935 technical)	
2-generational reproductive toxicity study (dietary) Rat (Sprague Dawley) PMRA# 1048152, 1048153, 1048159, 1048160, 1048346	Parental Toxicity NOAEL = 592/737 mg/kg bw/day (♂/♀) LOAEL = 1169/1410 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw (P/ F1), ↓ bwg (P/F1 premating and gestation phases), ↑ bwg (P/F1 lactation phase), ↓ fc Offspring Toxicity NOAEL = 737 mg/kg bw/day (♀) LOAEL = 1410 mg/kg bw/day (♀) Effects at LOAEL: ↓ pup wt PND 4-21 (F1/F2 pups), ↓ survival PND 0-4 (F1/F2) and PND 4-21 (F1) Reproductive Toxicity NOAEL = 1169/737 mg/kg bw/day (♂/♀) LOAEL = ND/1410 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ birth wt (F1/F2 ♀) **No evidence of sensitivity of the young.**
Developmental toxicity (gavage) Rat (Tif:RAI f) PMRA# 1048161, 1048162 HC: PMRA# 2891811	Maternal Toxicity NOAEL = 1000 mg/kg bw/day LOAEL = Not determined Developmental Toxicity NOAEL = 200 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Effects at LOAEL: ↑ incidence of asymmetrically shaped sternebrae **No evidence of treatment-related malformations.** **Evidence of sensitivity of the young.**

Developmental toxicity (gavage) Rabbit (NZW) PMRA# 1048163	Maternal Toxicity NOAEL = 10 mg/kg bw/day LOAEL = 60 mg/kg bw/day Effects at LOAEL: ↑ post-implantation loss, Developmental Toxicity NOAEL = 10 mg/kg bw/day LOAEL = 60 mg/kg bw/day Effects at LOAEL: ↑ post-implantation loss **No evidence of treatment-related malformations.** **Evidence of serious effect in the absence of overt maternal toxicity.**
Genotoxicity Studies -trinexapac-ethyl technical (CGA 163935 technical)	
Bacterial Reverse Mutation Assay *S*. Typhimurium (TA98, TA100, TA1535, TA1537) PMRA# 1048164, 1048165	Negative ± metabolic activation Tested up to limit concentration
Bacterial Reverse Mutation Assay *S*. Typhimurium (TA98, TA100, TA102, TA1535, TA1537) *E. coli* (WP2 uvrA) PMRA# 2723293	Negative ± metabolic activation Tested up to limit concentration
Bacterial Reverse Mutation Assay *S*. Typhimurium (TA98, TA100, TA1535, TA1537) *E. coli* (WP2 uvrA pKM 101, WP2 pKM 101) PMRA# 2723296	Negative ± metabolic activation Tested up to limit concentration
Gene Mutation Assay Mouse lymphoma L5178Y/TK PMRA# 1048168	Negative ± metabolic activation Tested up to limit of solubility
In vitro Mammalian Clastogenicity (chromosomal aberration assay) Human lymphocytes PMRA# 1048176	Negative ± metabolic activation Tested up to limit of solubility

In Vitro M##ammalian Clastogenicity (chromosomal aberration assay) Chinese hamster ovary cells PMRA# 2723311	Negative ± metabolic activation Tested up to limit of solubility
In Vitro Mammalian Clastogenicity (chromosomal aberration assay) Human lymphocytes PMRA# 2723312	Negative ± metabolic activation Tested up to limit of solubility
Unscheduled DNA synthesis assay Rat primary hepatocytes PMRA# 1048173,1048174	Negative Tested up to limit of solubility
Unscheduled DNA synthesis assay Human fibroblasts PMRA# 1048175	Negative Tested up to limit of solubility
Micronucleus Assay Tif:MAGf mouse bone marrow PMRA# 118170, 118171	Negative 3000 mg/kg bw: ↑ mortality
Micronucleus Assay Tif:MAGf mouse bone marrow PMRA# 118172	Negative 4000 mg/kg bw: ↑ mortality
Neurotoxicity Studies -trinexapac-ethyl technical (CGA 163935 technical)	
Acute Neurotoxicity (gavage) Rat (Sprague-Dawley) PMRA# 2723289	NOAEL = 1000/2000 mg/kg bw (♂/♀) LOAEL = 2000/ND mg/kg bw (♂/♀) Effects at LOAEL: ↓ motor activity, ↓ bwg (♂) **No evidence of selective neurotoxicity.**
90-Day Subchronic Neurotoxicity (dietary) Rat (Sprague-Dawley) PMRA# 2723290	NOAEL = 948/1171 mg/kg bw/day (♂/♀) LOAEL = not determined (♂/♀) **No evidence of selective neurotoxicity.**

Immunotoxicity Studies -trinexapac-ethyl technical (CGA 163935 technical)	
28-Day Oral Immunotoxicity (dietary) B6C3F1 mice AFC and NKC Assays PMRA# 2891812	NOAEL = 1530 mg/kg bw/day (♀) LOAEL = not determined **No evidence of immune dysregulation.**
Special Studies – QSAR and Endocrine studies – trinexapac-ethyl technical (CGA 163935 technical)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity
ToxCast In Vitro assays PMRA# 2891813	Trinexapac-ethyl was evaluated in an extensive battery of assays designed to assess the potential for interaction with components of the endocrine system. Trinexapac-ethyl was negative in all of these assays, providing evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system.
Special Studies – metabolite CGA 179500 (main metabolite in rats)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity
Special Studies – metabolite CGA 113745 (animal metabolite)	
QSAR Predictions Derek Nexus Prediction Report PMRA 2723322	No new alerts were triggered for the following endpoints: Genotoxicity
In vitro gene mutation assay Chinese hamster (V79) cells (HPRT) PMRA# 2723305	Negative ± metabolic activation Tested up to the limit concentration
Special Studies – CGA 158377 (read-across analogue for metabolite CGA 113745)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity
Acute Oral Toxicity (gavage) Rat (Tif: RAI f) PMRA# 2723255	LD_{50} > 2000 mg/kg bw (♂/♀) **Low acute toxicity.**
Acute Dermal Toxicity Rat (Tif: RAI f) PMRA# 2723261	LD_{50} > 2000 mg/kg bw (♂/♀) **Low acute toxicity.**
Acute Inhalation Toxicity (nose only) Rat (Tif: RAI f) PMRA# 2723263	LC_{50} > 5.0 mg/L (♂/♀) **Low acute toxicity.**

Eye Irritation Rabbit (NZW) PMRA# 2723265	MAS = 42/110 (unwashed eyes), with persistence to day 21 MIS = 42/110 at 24 hrs **Severely irritating**
Dermal Irritation Rabbit (NZW) PMRA# 2723267	MAS = 2.2/8 MIS = 2.3/8 at 24 hrs and 48 hrs **Mildly irritating.**
Dermal Sensitization (Optimization Method) Guinea Pig (Pirbright White) PMRA# 2723270	**Negative**
Dermal Sensitization (Maximization Method) Guinea Pig (Pirbright White) PMRA# 2723271	**Negative**
28-Day Oral Toxicity (gavage) Rat (Tif: RAI f) PMRA# 2723279	NOAEL = 100 mg/kg bw/day (♂/♀) LOAEL = 1000 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ kidney wt, ↓ chol (♂/♀); ↓ bw, ↓ bwg, ↓ fc, ↑ platelets (thrombocytosis) (♂); ↑ prothrombin time (♀)
Bacterial Reverse Mutation Assay *S*. Typhimurium (TA98, TA100, TA1535, TA1537) *E. coli* (WP2 uvrA) PMRA# 2723297	Negative ± metabolic activation Tested up to limit concentration
In Vitro Mammalian Clastogenicity (chromosomal aberration assay) Chinese hamster ovary cells (CHO) PMRA# 2723317	Negative ± metabolic activation Tested up to the limit concentration
Special Studies – metabolite CGA 224439 (cyclopropane carboxylic acid)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity

Bacterial Reverse Mutation Assay *S.* Typhimurium (TA98, TA100, TA1535, TA1537) *E. coli* (WP2 uvrA pKM 101, WP2 pKM 101) PMRA# 2723301	Negative ± metabolic activation Tested up to limit concentration
Gene Mutation Assay CHO V79 cells (HPRT locus) PMRA# 2723308	Negative ± metabolic activation Tested up to limit concentration
In Vitro Mammalian Clastogenicity (chromosomal aberration assay) Human lymphocytes PMRA# 27233316	Negative ± metabolic activation Tested up to limit concentration
Special Studies – metabolite CGA 275537 (plant metabolite)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity
Acute Oral Toxicity (gavage) Rats (HanBrl:WIST) PMRA# 2723257	LD_{50} > 2000 mg/kg (♂) LD_{50} > 1000 mg/kg (♀) Clinical signs included ↓ activity (♂); ↑ mortality (♀) **Slight Acute Toxicity**
Bacterial Reverse Mutation Assay *S.* Typhimurium (TA97, TA98, TA100, TA102, TA104, TA1535, TA1537) *E. coli* (WP2 uvrA) PMRA# 2723302	Negative ± metabolic activation Tested up to limit concentration
Special Studies – metabolite CGA 300405 (plant metabolite)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity

Bacterial Reverse Mutation Assay *S*. Typhimurium (TA98, TA100, TA1535, TA1537) *E. coli* (WP2 uvrA pKM 101, WP2 pKM 101) PMRA# 2723299	Negative ± metabolic activation Tested up to limit concentration
Gene Mutation Assay Mouse lymphoma L5178Y cells PMRA# 27233306	Negative ± metabolic activation Tested up to limit concentration
In Vitro Mammalian Clastogenicity (chromosomal aberration assay) Human lymphocytes PMRA# 27233316	Negative ± metabolic activation Tested up to limit concentration
Special Studies – metabolite CGA 313458 (plant metabolite)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity
Acute Oral Toxicity (gavage) HanBrl:WIST rats PMRA# 2723258	LD_{50} > 2000 mg/kg bw (♂/♀) **Low acute toxicity**
Bacterial Reverse Mutation Assay *S*. Typhimurium (TA97, TA98, TA100, TA102, TA1535, TA1537) *E. coli* (WP2 uvrA) PMRA# 2723300	Negative ± metabolic activation Tested up to limit concentration
Gene Mutation Assay CHO V79 cells (HPRT locus) PMRA# 2723307	Negative ± metabolic activation Tested up to limit concentration
In Vitro Mammalian Clastogenicity (chromosomal aberration assay) Human lymphocytes PMRA# 27233315	Negative ± metabolic activation Tested up to limit concentration
Special Studies – metabolite CGA 329773 (plant metabolite)	
QSAR Predictions Derek Nexus Prediction Report PMRA# 2723322	No new alerts were triggered for the following endpoints: Genotoxicity

Acute Oral Toxicity (gavage) Rat (Tif:RAI f) PMRA# 2723256	LD_{50} > 2000 mg/kg bw (♂/♀) **Low acute toxicity.**
28-Day Oral Toxicity (diet) Rat (Tif:RAI f) PMRA# 2723282	NOAEL = 363/345 mg/kg bw/day (♂/♀) LOAEL = 1050/1021 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ fc (♂/♀); ↓ urea, ↓ thyroid wt (♂); ↓ bwg, ↑ AST (♀) Note: at 28-days plus 4-week recovery these findings were reversible: ↓ fc (♂/♀); ↓ thyroid wt (♂); ↓ bwg, ↑ AST (♀); Partially reversible: ↓urea (♂)
Bacterial Reverse Mutation Assay *S.* Typhimurium (TA97, TA98, TA100, TA102, TA1535, TA1537) *E. coli* (WP2 uvrA) PMRA# 2723298	Negative ± metabolic activation Tested up to limit concentration
Gene Mutation Assay CHO V79 cells (HPRT locus) PMRA# 2723304	Negative ± metabolic activation Tested up to limit of solubility
In Vitro Mammalian Clastogenicity (chromosomal aberration assay) Human lymphocytes PMRA# 27233313	Clastogenic ± metabolic activation at cytotoxic doses
Micronucleus Assay Alpk APf SD rat bone marrow PMRA# 27233318	Negative Tested up to cytotoxic doses

Table 5 Toxicology reference values for use in health risk assessment for trinexapac-ethyl

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
Acute dietary general population excluding females 13–49 years of age	Not selected	No appropriate endpoint identified for this population	
	ARfD was not established		
Acute dietary females 13–49 years of age	Oral developmental toxicity in the rabbit	NOAEL = 10 mg/kg bw/day Increased post-implantation loss	300
	ARfD = 0.03 mg/kg bw		

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
Repeated dietary general population excluding females 13–49 years of age	12-month dietary toxicity in the dog	NOAEL = 32 mg/kg bw/day Vacuolation in the brain	100
	ADI = 0.3 mg/kg bw/day		
Repeated dietary females 13–49 years of age	Oral developmental toxicity in the rabbit	NOAEL = 10 mg/kg bw/day Increased post-implantation loss	300
	ADI = 0.03 mg/kg bw/day		
Short-term, intermediate-term dermal[2]	Oral developmental toxicity in the rabbit	NOAEL = 10 mg/kg bw/day Increased post-implantation loss	300
Short-term, intermediate-term inhalation[3]	Oral developmental toxicity in the rabbit	NOAEL = 10 mg/kg bw/day Increased post-implantation loss	300
Short-term, intermediate-term aggregate (Oral and dermal)	Oral developmental toxicity in the rabbit	Common endpoint: Increased post-implantation loss Oral and dermal: NOAEL = 10 mg/kg bw/day	300
Cancer	A cancer risk assessment was not required		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor (77.5%) was used in a route-to-route extrapolation.
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.
NOTE: Adjust by × 0.9 to use trinexapac-ethyl acid equivalent.

Table 6 Integrated food residue chemistry summary

NATURE OF THE RESIDUE IN LAYING HEN – Study 1 (2006 Study)		**PMRA# 2723336**
Species and Numbers	Five laying hens (White Leghorn Hyline W-36)	
Radiolabel position	[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl (specific activity: 1513.3 Bq/µg; 40.9 µCi/mg)	
Average dose	8.14 to 10.1 ppm, for both labels (corresponding to 0.122 to 0.156 kg/day).	
Treatment Regimen	Once per day, orally via gelatin capsule.	
Study period	10 consecutive days.	
Collection time	Eggs were collected daily and the whites and yolks were separated. On average, the hens produced one egg per day. Excreta were collected once daily and cage wash was collected after sacrifice.	
Tissues collected	Whole blood samples were collected just prior to sacrifice. After sacrifice, the peritoneal fat, subcutaneous fat with skin attached, liver, kidney, muscle (breast and thigh), and the GI tract with contents were collected.	
Interval from last dose to sacrifice	22 hours	
Plateau of residues in eggs	The TRR were <0.01 ppm (<0.003 to 0.009 ppm) in egg yolks, therefore, they were not further investigated. The TRR expressed as ppm trinexapac-ethyl equivalents in egg whites from all five hens ranged from 0.005 to 0.031 ppm. Residues in the egg samples appeared to reach a plateau by Day 6 and peak on Day 8	
Extraction solvent	Egg Whites: ACN/water (80:20, v/v)	
Matrices	**[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl**	
	% of Administered Dose	**TRR (ppm)**

Excreta (Average; days 1-10)	8.85	Not reported
GI Tract and Contents	0.09	0.070
Pooled Egg Yolk (Day 6–10)	0	0.008
Pooled Egg White (Day 6–10)	0.01	0.017
Liver	0.00	0.005
Kidney	0.00	<0.003
Fat	0.00	<0.003
Muscle (breast and thigh)	0.00	<0.003

Summary of Major Identified Metabolites in Hen Matrices – Study 1 (2006 Study)	
Radiolabel Position	[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl
Metabolites Identified	Major Metabolites
Egg Whites	Trinexapac-ethyl and trinexapac acid

NATURE OF THE RESIDUE IN LAYING HEN – Study 2 (1992 Study)	**PMRA# 2723335, 2723334**
Species and Numbers	Six laying hens (White Leghorn)
Radiolabel position	[1,2-^{14}C-cyclohexyl]-trinexapac-ethyl
Average dose	Two hens received 3.82 ppm in the feed, and the remaining 4 hens received 179.7 ppm in the feed, with one hen in the latter high dose group inadvertently given an extra capsule for a total on day 4 of 347 ppm in the feed.
Treatment Regimen	Once per day, orally via gelatin capsule.
Study period	4 consecutive days.
Collection time	Eggs were collected over a 24-hour period during the acclimation period prior to administration of the first dose, and following administration of the first dose, eggs were collected throughout the day and in the morning prior to the dose administration over 24-hour intervals up to 76 hours post first dose administration. No egg samples were collected postmortem. During the acclimation period, excreta were collected at ambient temperature over a 24-hour period for 2 days prior to administration of the first dose and subsequently, on the morning of the first dosing day, prior to the first dose, and daily at 24 hour intervals thereafter up to 76 hours after the initial dose.
Tissues collected	Kidneys, liver, muscle (leg, thigh and breast), skin with attached fat, peritoneal fat, gizzard and crop contents, and blood (plasma).
Interval from last dose to sacrifice	4 hours
Plateau of residues in eggs	TRRs reached a plateau at the end of dosing.
Extraction solvent	Excreta: Once with acetonitrile and 3 times with acetonitrile:water (4:1, v/v). Separately pooled egg white and yolk: Acetonitrile Gizzard; composite muscle, liver and kidney: Acetonitrile:water (1:1, v/v) Fat, and skin with attached fat: Methylene chloride:methanol (4:1, v/v)

The majority of the administered dose (AD) was eliminated via excreta (mean of 89% of the AD at the low dose level and 85.4% of the AD at the high dose). Throughout the study period, only 0.01% and 0.02% of the AD for the low and high dose rates, respectively, was transferred to eggs (mean concentrations in egg yolk and whites of 0.002–0.055 ppm and 0.007–0.327 ppm trinexapac-ethyl equivalents, respectively), and ≤0.2% of the AD was transferred to edible tissues in hens treated at both dose levels. The highest residue concentrations in the tissues were detected in the kidneys, followed by the liver, lean meat, skin including fat and peritoneal fat.

Matrices	**[1,2-^{14}C-cyclohexyl]-trinexapac-ethyl**			
	Low Dose Group		**High Dose Group**	
	% of Administered Dose	**TRRs (ppm)**	**% of Administered Dose**	**TRRs (ppm)**
Excreta: 0–24 hr	96.1	3.65	88.0	158.0
24–48 hr	95.3	3.62	90.3	162.5
48–72 hr	97.4	3.7	87.3	157.1
72–76 hr	65.6	2.5	79.9	143.9
Skin including attached fat	Not reported	0.011	Not reported	0.36
Eggs[1]	0.02	0.008	0.03	0.375
Whites[1]	0.02	0.007	0.03	0.327
Yolks[2]	<0.01	0.002	<0.01	0.055
Liver	0.02	0.013	0.03	0.60
Kidney	0.02	0.043	0.02	1.770
Muscle (composite of leg, breast and thigh)	0.04	0.002	0.06	0.118

[1] Maximum value (24–48 hour samples)
[2] Maximum value (72–76 hour samples – low dose; 48–72 - high dose)

Summary of Major Identified Metabolites in Hen Matrices – Study 2 (1992 Study)	
Radiolabel Position	[1,2-^{14}C-cyclohexyl]-trinexapac-ethyl
Metabolites Identified	Major Metabolites
Muscle	Trinexapac acid (both dose groups)
Fat	
Kidney	
Liver	
Skin plus fat	
Egg Whites	Trinexapac-ethyl (both dose groups); trinexapac acid (high dose group only)
Egg Yolks	Trinexapac acid (both dose groups); trinexapac-ethyl (low dose group only)

NATURE OF THE RESIDUE IN LACTATING GOAT – Study 1 (2002 Study)	**PMRA# 2723337**
Species and Numbers	Two dairy goats (*Capra hircus*)
Radiolabel position	[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl (specific activity: 42.3 μCi/mg)
Average dose	150 mg a.i./goat/day, equivalent to nominal feeding levels of 100 ppm per goat based on feed consumption of 1500 g feed/goat/day.
Treatment Regimen	Once per day, orally via gelatin capsule.
Study period	4 consecutive days.

Collection time	Feces and urine were collected daily, milk was collected twice daily, and blood was collected immediately before sacrifice, ~6 hours after the final dose.
Tissues collected	Muscle (leg and tenderloin), fat (perirenal and omental), kidneys, liver, bile and gastro-intestinal (GI).
Interval from last dose to sacrifice	~6 hours
Plateau of residues in milk	Residues in the milk samples reached a plateau within one day of dosing at 0.078 ppm.
Extraction solvents	Kidney, liver, fat: Acetonitrile:water (4:1, v/v)

Matrices	**[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl**	
	% of Administered Dose	**TRRs (ppm)**
Feces: 0–24 hours	0.35	0.35
24–48 hours	1.05	1.05
48–72 hours	0.56	0.56
72–78 hours	0.58	0.58
Composited 0–78 hours	**2.54**	**2.54**
Urine: 0–24 hours	21.05	21.05
24–48 hours	22.87	22.87
48–72 hours	22.55	22.55
72–78 hours	14.05	14.05
Composited 0–78 hours	**80.52**	**80.52**
GI Tract	3.37	1.655
Milk: 0–7 hours	0.01	0.078
7–24 hours	0.01	0.018
24–31 hours	0.01	0.076
31–48 hours	0.00	0.021
48–55 hours	0.01	0.072
55–72 hours	0.00	0.020
72–78 hours	0.01	0.065
Composited 0–78 hours	**0.05**	**0.350**
Liver	0.8	0.802
Kidney	5.9	5.903
Fat (Perirenal and omental)	0.11	0.106
Muscle (leg and tenderloin)	0.275	0.275

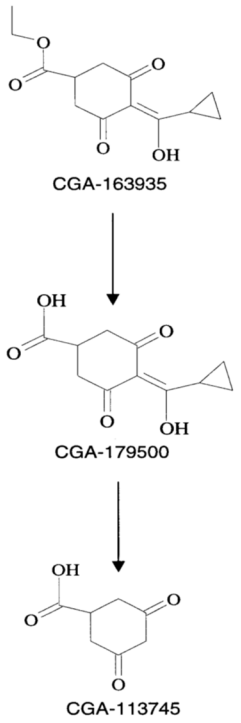
Summary of Major Identified Metabolites in Goat Matrices - Study 1 (2002 Study)	
Radiolabel Position	**[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl**
Metabolites Identified	Major Metabolites
Milk, fat, kidney, liver, milk	Trinexapac acid

NATURE OF THE RESIDUE IN LACTATING GOAT – Study 2 (1992 AND 1993 Studies)	**PMRA# 2723333, 2723332**
Species and Numbers	Two dairy goats (*Capra hircus*) (for high and low dose samples) – British Saanen
Radiolabel position	[1,2-^{14}C-cyclohexyl]-trinexapac-ethyl
Average dose	A low dose of 7.2 mg/kg (ppm) feed (corresponding to 0.2 mg/kg bw/day) and a high dose of 694 mg/kg (ppm) feed (corresponding to 19.9 mg/kg bw/day).
Treatment Regimen	Once per day, orally via gelatin capsule
Study period	4 consecutive days
Collection time	Milk was collected twice a day in the morning and afternoon and the samples were pooled, and the excreta (urine, feces and cage wash) were collected once a day over 24 hour intervals throughout the study period.
Tissues collected	Liver, kidney, fat (omental, renal and subcutaneous), muscle (loin, hindquarter and forequarter) and the gastrointestinal (GI) tract (rumen) and contents.
Interval from last dose to sacrifice	4 hours (~76 hours post first dose); total radioactive residues (TRRs) in all samples were determined with Liquid Scintillation Counting (LSC) and/or combustion analysis/LSC.
Plateau of residues in milk	Radioactivity in milk from both morning and evening samplings did not exceed 0.002 ppm and 0.008 ppm (low dose; maxima achieved on day-4) and 0.314 ppm and 0.829 ppm (high dose; maxima achieved days 2 and 3, respectively) trinexapac-ethyl equivalents, respectively.
Extraction solvents:	Milk, muscle, kidney, liver: successive solutions of methanol:water (1:1, v/v), acetonitrile (ACN):water (1:1, v/v) and ACN. Fat: chloroform:methanol (4:1, v/v), followed by sodium phosphate buffer (0.1M, pH 8) partitioning.

Matrices	**[1,2-^{14}C-cyclohexyl]-trinexapac-ethyl**			
	Low dose (AD = 7.2 ppm)		**High dose (AD = 694 ppm)**	
	% of Administered Dose	**TRRs (ppm)**	**% of Administered Dose**	**TRRs (ppm)**
Urine – Composited: 0-76 hrs	50.0	NR	62.2	NR
Feces – Composited: 0–76 hrs	16.3	NR	19.0	NR
Milk – Composited: 0–76 hrs	0.02	0.0014	0.02	0.139
Total excreted:	**75.0**	--	**87.1**	--
Muscle: Hindquarter	0.49	0.035	0.274	1.899
Forequarter	0.597	0.043	0.358	2.485
Loin	0.486	0.035	0.309	2.147
Composite Muscle:	2.17	0.156	1.20	8.33
Fat: Omental	0.33	0.024	0.223	1.549
Subcutaneous	1.31	0.094	0.173	1.202
Renal	1.00	0.017	0.203	1.406
Composite Fat:	0.34	0.0244	0.10[4]	4.157
Kidney	0.18	0.5	0.14	41.92
Liver	0.55	0.25	0.27	12.12
GI tract (rumen contents)	3.88	0.267	3.12	31.42

Summary of Major Identified Metabolites in Goat Matrices - Study 2 (1992 and 1993 Studies)	
Radiolabel Position	**[1,2-^{14}C-cyclohexyl]-trinexapac-ethyl**
Metabolites Identified	Major Metabolites
Muscle, fat, kidney, liver, milk	Trinexapac acid

Proposed Metabolic Scheme in Livestock



CGA-163935 = trinexapac-ethyl; CGA-179500 = trinexapac acid

FREEZER STORAGE STABILITY IN ANIMAL MATRICES		
Tested Matrices	**Analyte**	**Tested Intervals (months)**
Muscle (cattle and poultry)	Trinexapac acid	32 days (poultry) 91 days (cattle)
Liver (cattle and poultry)		59 days (poultry) 94 days (cattle)
Kidney (cattle and poultry)		53 days (poultry) 95 days (cattle)
Fat (cattle and poultry)		59 days (poultry) 101 days (cattle)
Skin + Fat attached		59 days
Milk		121 days
Eggs		82 days

LIVESTOCK FEEDING – Dairy cattle	PMRA# 2723383

Lactating dairy cows were administered trinexapac acid at dose levels of 1.92 ppm, 5.20 ppm and 19.40 ppm in the feed once a day for 29–30 consecutive days. The dose levels of 1.92 ppm, 5.20 ppm and 19.40 ppm represent 1.8×, 4.9× and 18.3×, respectively, the estimated more balanced diet (MBD) to beef cattle and 1.4×, 3.7× and ~14×, respectively, for dairy cattle. Animals were sacrificed approximately 20–22 hours after the last dose.

The results from the dairy cattle feeding study showed that quantifiable residues of trinexapac acid were observed only at the highest feeding level in liver, fat and milk; quantifiable residues were not observed at any feeding level in muscle. Quantifiable residues of trinexapac acid were detected in kidneys on average at 0.03 ppm, 0.04 ppm, and 0.17 ppm at the 1.92 ppm, 5.2 ppm, and 19.4 ppm doses, respectively.

Commodity/Collection Day	Actual Feeding Level (ppm)	Highest Residues (ppm)	Mean Residues (ppm)
Whole milk	19.4	0.011 (day 5)	0.0073
Fat	19.4	<0.02	<0.02
Liver	19.4	0.03	0.03
Kidney	1.92	0.03	0.03
	5.2	0.05	0.04
	19.4	0.29	0.17
Muscle	19.4	<0.02	<0.02

Anticipated Residues in Animal Matrices			
Matrices	**Residue Definition**	**Dietary Burden (ppm)**	**Anticipated Residues of Trinexapac Acid (ppm)**
Beef/Dairy Cattle			
Whole milk	Trinexapac acid	1.34 (dairy cattle) 0.99 (beef cattle)	0.001
Fat			0.001
Liver			0.002
Kidney			0.02
Muscle			0.001
Swine			
Fat	Trinexapac acid	0.79	0.001
Liver			0.001
Kidney			0.012
Muscle			0.001

LIVESTOCK FEEDING – Laying hens	PMRA# 2723382

Laying hens were administered trinexapac acid at dose levels of 3.7 ppm, 10 ppm and 37 ppm in the feeds for 28 consecutive days. The dose levels of 3.7 ppm, 10 ppm and 37 ppm represent 4×, 11×, and 40×, respectively, the estimated MBD to poultry. Animals were sacrifices approximately 20-22 hours after the last dose.

Residues were below the LOQ for the 3.7 ppm and 10 ppm feeding doses for all samples except in kidneys. Average residue levels in kidney samples were 0.064 ppm, 0.045 ppm, and 0.455 ppm at 3.7 ppm, 10 ppm, and 37 ppm feed doses, respectively. Average residues for eggs, fat, liver, and muscle tissues at the 37 ppm feed dose were 0.013 ppm, 0.026 ppm, 0.015 ppm, and <0.01 ppm, respectively.

Commodity/Collection Day	Actual Feeding Level (ppm)	Highest Residues (ppm)	Mean Residues (ppm)
Whole Eggs	37	0.01	0.01
Fat	37	0.03	0.03
Liver	37	0.03	0.02
Kidney	3.7	0.08	0.06

	10	0.05	0.04
	37	0.54	0.45
Muscle	37	<0.01	<0.01

Anticipated Residues in Poultry Matrices			
Matrices	**Residue Definition**	**Dietary Burden (ppm)**	**Anticipated Residues of Trinexapac Acid (ppm)**
Eggs	Trinexapac acid	0.84	0
Fat			0.001
Liver			0.001
Kidney			0.012
Muscle			0

NATURE OF THE RESIDUE IN WHEAT – Study 1 (1993 study)		**PMRA# 2723342**
Radiolabel Position	[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl	
Treatment		
Test Site	Outdoor field plot seeded with spring wheat (foliar applications) and greenhouse grown wheat plants (stem injections).	
Treatment	Field experiments: A single postemergent foliar treatment was made to six-week old (one-node stage) spring wheat plants during internode elongation. Stem injection and cellular incubation experiments were also performed in order to generate additional amounts of selected grain metabolites for detailed analyses. Plants were grown under greenhouse conditions, and 6-week old plants were injected with 40-50 µg [^{14}C]trinexapac-ethyl dissolved in acetone. For the cellular incubation experiment, green leaf blades were cut, homogenized and suspended in water. [^{14}C]Trinexapac-ethyl was dissolved in methanol and added to the suspension, which was then incubated for 45 days by shaking at room temperature.	
Total Rate	Field experiment: 150 g a.i./ha	
Formulation	Emulsifiable concentrate (EC); 250 g/L trinexapac-ethyl	
Harvest	Wheat plants were harvested at maturity from both the field test (71 DAT) and the stem-injection (69 DAT) experiments, and the plants were separated into grain, straw and husks.	
Extraction solvents	Methanol (MeOH)/water (8:2) and subsequent partitioning with methylene chloride (CH_2Cl_2) and ethyl acetate (EtOAc).	
Matrices	**PHI (days)**	**[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl**
		TRR (ppm)
Grain	69-71	The TRRs were not reported.
Husks		
Straw		

Summary of Major Identified Metabolites in Plant Matrices – Study 1 (1993 study)	
Radiolabel Position	**[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl**
Metabolites Identified	**Major Metabolites (>10% of the TRR)**
Grain	Trinexapac acid; CGA-329773
Husks	Trinexapac acid
Straw	Trinexapac acid

NATURE OF THE RESIDUE IN WHEAT – Study 2 (2015 study)		PMRA# 2723344
Radiolabel Position	[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl	
Treatment		
Test Site	Plants growing under natural outdoor climatic conditions in containers. The studies were conducted in Europe (Switzerland).	
Treatment	Foliar spray application at growth stage BBCH 37.	
Total Rate	211 g a.i./ha	
Formulation	Microemulsion	
Harvest	Samples were harvested at three growth stages: at the forage stage (BBCH 43), 7 days after application; at the hay stage (BBCH 77), 34 days after application; and at maturity (BBCH 89), 62 days after application.	
Extraction solvents	Acetonitrile (ACN)/water (4:1, v/v; three times) and once with ACN/water (1:1, v/v).	
Matrices	**PHI (days)**	**[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl TRR (ppm)**
Forage	7	1.846
Hay	34	1.967
Grain	62	1.515
Straw		1.378

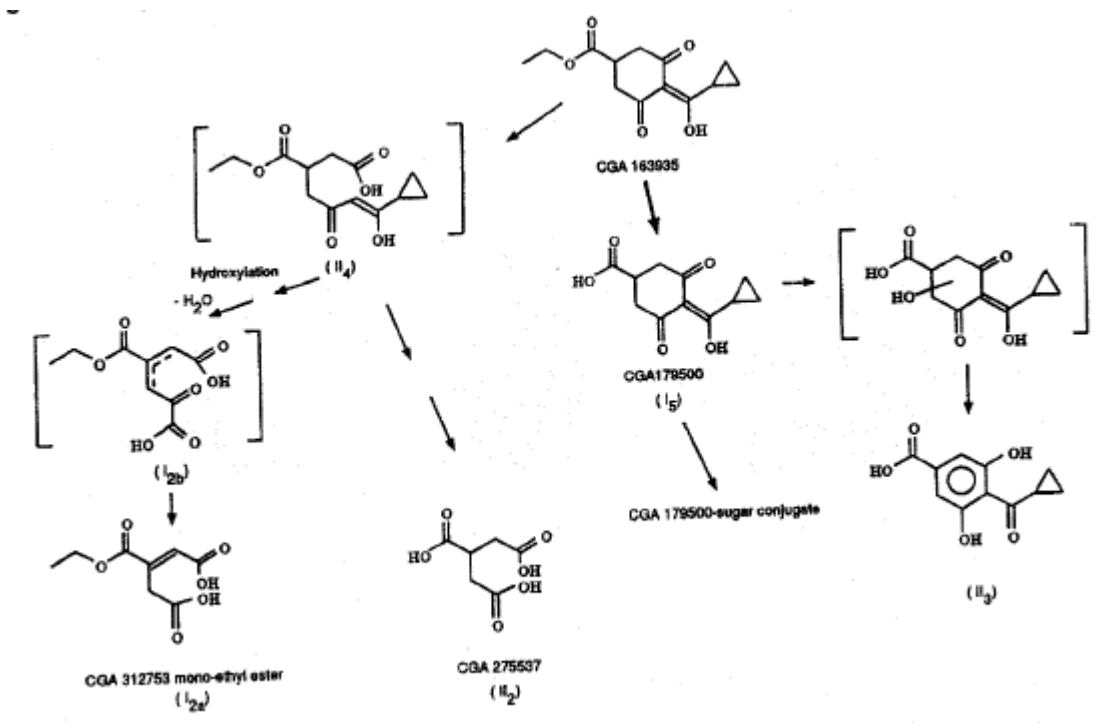
Summary of Major Identified Metabolites in Plant Matrices – Study 2 (2015 study)	
Radiolabel Position	**[1,2,6-^{14}C-cyclohexyl]-trinexapac-ethyl**
Metabolites Identified	**Major Metabolites (>10% of the TRR)**
Forage	Trinexapac acid, tricarboxylic acid ethyl ester (CGA300405)
Hay	Trinexapac acid, tricarboxylic acid metabolite (CGA275537)
Grain	Trinexapac acid
Straw	--

NATURE OF THE RESIDUE IN WHEAT – Study 3 (1990 study)		PMRA# 2723343
Radiolabel Position	[1,2 -^{14}C-cyclohexyl]-trinexapac-ethyl	
Treatment		
Test Site	Outdoor field plot seeded with spring wheat and greenhouse grown wheat plants.	
Treatment	Over-the-top spray application to two week old plants grown in a climate-controlled greenhouse and 6 week old plants (one node stage) growing in an outdoor plot (field experiment).	
Total Rate	150 g a.i./ha	
Formulation	Emulsifiable concentrate (EC); 250 g/L trinexapac-ethyl	
Harvest	Greenhouse-grown wheat aerial plant portions and roots, as well as whole-pot soil samples from control pots were collected for analysis at intervals of 0.5 hours, 4 hours, 24 hours (1 day), 48 hours (2 days), 168 hours (7 days), 336 hours (14 days) and 504 hours (21 days) postapplication. In field-grown wheat, immature whole plant samples were harvested 3 hours postapplication, and ears and green part samples were harvested from plants at ear emergence (25 days postapplication) and milky stage (48 days postapplication). In mature crops, samples of grain, husks and straw were harvested 71 days postapplication.	
Extraction solvents	Field-cultivated spring wheat samples: methanol:water (8:2, v/v) Greenhouse-cultivated wheat plant samples: acetonitrile:water solutions	

Matrices	PHI (days)	[1,2 -^{14}C-cyclohexyl]-trinexapac-ethyl
		TRR (ppm)
Whole tops	~0.5 hours	0.801
Ears	25	0.256
Leaves	25	0.255
Ears	48	0.473
Leaves	48	0.428
Grain	71	0.462
Husks	71	0.440
Straw	71	0.542

Summary of Major Identified Metabolites in Plant Matrices – Study 3 (1990 study)	
Radiolabel Position	**[1,2-^{14}C-cyclohexyl]-trinexapac-ethyl**
Metabolites Identified	**Major Metabolites (>10% of the TRR)**
Whole tops (~0.5 hours)	Trinexapac-ethyl; trinexapac acid
Ears (25 days)	Trinexapac acid
Leaves (25 days)	Trinexapac acid
Ears (48 days)	Trinexapac acid
Leaves (48 days)	--
Grain (71 days)	Trinexapac acid
Husks (71 days)	Trinexapac acid
Straw (71 days)	--

Proposed Metabolic Scheme in Plants



FREEZER STORAGE STABILITY IN PLANT MATRICES	PMRA# 2723368, 2723369

Samples of wheat grain, wheat straw and rapeseed seed were fortified with trinexapac acid at a level of 0.5 ppm and put into frozen storage at -20ºC. At intervals of 0, 3, 6, 12, and 24 months, stored samples and freshly fortified samples were analyzed for residues of trinexapac acid.

Samples of wheat germ, wheat bran and wheat flour were fortified with trinexapac acid at a level of 0.1 ppm and put into frozen storage at -20ºC. At intervals of 0, 3, 9 and 12 months, stored samples and freshly fortified samples were analyzed for residues of trinexapac acid.

Category[1]	Tested Matrices	Tested Intervals (months)	Temperature (°C)	Demonstrated stability (months)
High-starch	Wheat grain	0, 3, 6, 12 and 24	-20°C	24
	Wheat bran	0, 3, 9 and 12		12
	Wheat flour	0, 3, 9 and 12		12
High-oil	Rapeseed	0, 3, 6, 12 and 24		24
Other	Wheat straw	0, 3, 6, 12 and 24		12
	Wheat germ	0, 3, 9 and 12		12

[1] According to OECD Guideline for Testing of Chemicals, Stability of Pesticide Residues in Stored Commodities, 506, Annex 1.

CROP FIELD TRIALS AND RESIDUE DECLINE ON WHEAT - 2010 American Study	PMRA# 2723381

Twenty wheat field trials were conducted in 2007–2008 in the United States in growing regions 2 (VA; 1 trial), 4 (AR; 1 trial), 5 (KS, ND, MN, MO, IN; 5 trials), 6 (OK; 1 trial), 7 (ND, SD, NE; 5 trials), 8 (TX, OK; 6 trials) and 11 (ID; 1 trial). An emulsifiable concentrate (EC) formulation, was applied to wheat as a single foliar spray application at a target rate of 129 g a.i./ha at approximately Feekes Growing Stage (FGS) 7 (BBCH 32; Treatment 2) or at 45 days prior to harvest of mature grain (Treatments 3 and 4). Wheat forage and hay were harvested from each plot at a 30-day preharvest interval (PHI) and wheat straw and grain were harvested at a 45-day PHI. An adjuvant was not added to the spray mixture for any applications.

Residue decline data show that residues of trinexapac acid generally declined from the shortest to the longest preharvest intervals in/on wheat forage, hay, straw and grain. Adequate storage stability data are available. Samples were analyzed using a validated analytical method.

Crop Matrix	Total Application Rate [g a.i./ha]/ Formulation	PHI (days)	Residue Levels (ppm)[1]					
			n	LAFT	HAFT	Median	Mean	SDEV
Forage	129/EC	30	20	0.0102	0.938	0.0884	0.162	0.21
Hay		30	20	0.025	1.18	0.1755	0.273	0.29
Straw		45	20	0.0125	0.599	0.147	0.196	0.17
Grain		45	20	0.071	3.32	0.498	0.733	0.73

n = number of independent trials; LAFT = lowest average field trial; HAFT = highest average field trial.
[1] Expressed as trinexapac acid.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON WHEAT - 2014 CDN Study	PMRA# 2723370

Twenty wheat field trials were conducted in Canada encompassing growing regions 5 (MB, 2 trials), 7 (SK, 7 trials), 7A (AB, 1 trial), and 14 (MB, SK, AB; 10 trials) during the 2014 growing season. Each trial location included one treated plot in which trinexapac-ethyl, formulated as a micro-emulsion concentrate (ME), was applied to wheat as a single foliar spray application at a target rate of 125 g a.i./ha at approximately BBCH 39. At three sites, solution (SL) and emulsifiable concentrate (EC) formulations of trinexapac-ethyl were similarly applied in side-by-side plots for the purpose of comparing residue levels obtained using the three formulations. Single control and duplicate treated samples of wheat forage and hay were harvested from each plot at 29–31-day PHIs, and wheat straw and grain were harvested at normal commercial harvest (maturity), at PHIs of 56–77 days. An adjuvant was added to the spray mixture for all applications. In one trial, samples were collected at different time intervals (PHIs of 7, 13, 20, 29 and 38 days for forage and hay, and PHIs of 54, 60, 64, 69 and 74 days for grain and straw) to monitor residue decline. Independence of trials was assessed. Residue decline data show that residues of trinexapac acid in wheat forage and wheat hay decreases with longer PHIs, and tends to remain constant over increasing PHIs in grain and straw. Adequate storage stability data are available. Samples were analyzed using two different validated analytical methods: Method GRM020.05A, which determines residues of free trinexapac acid and is acceptable for data gathering purposes; and, Method GRM020.01A, which determines residues of free and conjugated trinexapac acid and has been deemed acceptable for enforcement purposes.

Crop Matrix	Total Application Rate (g a.i./ha)/ Formulation	PHI (days)	Residue Levels (ppm)[1]					
			n	LAFT	HAFT	Median	Mean	SDEV
Method GRM020.05A (Data gathering method)								
Forage	125/ME	29–31	20	0.0545	0.31	0.120	0.135	0.07
Hay		29–31	20	0.052	0.49	0.13	0.147	0.09
Straw		56–77	20	<0.01	0.044	0.017	0.022	0.01
Grain		56–77	20	0.074	0.86	0.308	0.317	0.20
Forage	125/EC	29–31	3	0.059	0.205	0.089	0.118	0.08
Hay		29–31	3	0.084	0.22	0.11	0.138	0.07
Straw		56–77	3	<0.01	0.84	0.024	0.29	0.47
Grain		56–77	3	0.076	0.34	0.32	0.245	0.15
Forage	125/SL	29–31	3	0.087	0.2	0.099	0.129	0.06
Hay		29–31	3	0.12	0.26	0.13	0.17	0.08
Straw		56–77	3	0.01	0.027	0.016	0.018	0.01
Grain		56–77	3	0.0885	0.42	0.4	0.303	0.19
Method GRM020.01A (Proposed enforcement method)								
Forage	125/ME	29–31	20	0.103	0.51	0.217	0.254	0.12
Hay		29–31	20	0.205	1.15	0.532	0.596	0.28
Straw		56–77	20	0.0525	0.55	0.123	0.173	0.12
Grain		56–77	20	0.19	1.65	0.62	0.661	0.39
Forage	125/EC	29–31	3	0.098	0.25	0.21	0.19	0.08
Hay		29–31	3	0.36	0.525	0.46	0.448	0.08
Straw		56–77	3	0.0615	0.595	0.12	0.26	0.3
Grain		56–77	3	0.205	0.61	0.595	0.47	0.23
Forage	125/SL	29–31	3	0.145	0.285	0.215	0.215	0.07
Hay		29–31	3	0.445	0.535	0.51	0.497	0.05
Straw		56–77	3	0.072	0.135	0.125	0.111	0.03
Grain		56–77	3	0.26	0.77	0.73	0.59	0.28

n = number of independent trials; LAFT = lowest average field trial; HAFT = highest average field trial.
[1] Expressed as trinexapac acid.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON BARLEY - 2008 American Study	**PMRA# 2723380**

Twelve field trials for trinexapac-ethyl on barley were conducted in 2008 in the United States encompassing growing regions 1 (PA; 1 trial), 5 (IA, WI, ND; 3 trials), 7 (ND; 4 trials), 9 (CO; 1 trial), 10 (CA; 1 trial), and 11 (OR, ID, 2 trials). At each trial location, trinexapac-ethyl, formulated as an EC, was applied to barley as a foliar spray at a target rate of 129 g a.i./ha at BBCH32, or at 45 days prior to harvest of mature grain. Samples of barley hay were harvested at a 30-day PHI, and barley straw and grain were harvested at a 45-day PHI. An adjuvant was not added to the spray mixture for any applications. Residue decline behaviour was evaluated at a single trial with additional samples collected (PHIs = 0, 10, 20, 30 and 37 days for hay; and, 24, 31, 38, 45 and 52 days for straw and grain).
Independence of trials was assessed. Residue decline data show that residues of trinexapac acid in barley hay and straw decrease with time, and remain the same in barley grain, with increasing PHIs. Adequate storage stability data are available. Samples were analyzed using a validated analytical method.

Crop Matrix	**Total Application Rate [g a.i./ha]/ Formulation**	**PHI (days)**	**Residue Levels (ppm)[1]**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Hay	129/EC	30	12	<0.01	0.475	0.155	0.19	0.15
Straw		45	12	<0.01	0.24	0.095	0.11	0.07
Grain		45	12	0.03	1.2	0.56	0.59	0.33

n = number of independent trials; LAFT = lowest average field trial; HAFT = highest average field trial.
[1] Expressed as trinexapac acid.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON BARLEY - 2014 CDN Study	**PMRA# 2723371**

Twelve barley field trials were conducted in Canada encompassing growing regions 5 (QC; 1 trial), 7 (SK; 2 trials), 7A (AB; 1 trial), and 14 (MB, SK, AB; 8 trials) during the 2014 growing season. Each trial location included one treated plot in which trinexapac-ethyl (ME formulation) was applied to barley as a single foliar spray application at a rate of 125 g a.i./ha at approximately BBCH 39. At three sites, two additional treated plots were established to generate bridging data with an EC formulation and a solution (SL) formulation containing trinexapac-ethyl. Samples of barley hay were harvested from each plot at 29–31 day PHIs and barley straw and grain were harvested at normal commercial harvest (maturity; PHIs of 51–76 days). An adjuvant was added to the spray mixture for all applications.
At two trial sites, additional samples of barley hay from crops treated with the ME formulation were collected to monitor residue decline behaviour at 7, 14, 21/22, 30 (normal commercial harvest) and 37/38 days after application. Samples of grain and straw from the same treated crops were collected at maturity (normal commercial harvest; PHI of 51/59 days), as well as 5 and 10 days before harvest (PHIs of 41/49 and 47/53 days, respectively), and 5 and 10 days after harvest (PHIs of 57/65 and 62/70 days, respectively). Independence of trials was assessed. Residue decline data show that trinexapac-ethyl residues decreased in barley hay, and remained approximately the same in barley grain and straw. Adequate storage stability data are available. Samples were analyzed using two different validated analytical methods: Method GRM020.05A, which determines residues of free trinexapac acid and is acceptable for data gathering purposes; and, Method GRM020.01A, which determines residues of free and conjugated trinexapac acid and has been deemed acceptable for enforcement purposes.

Crop Matrix	**Total Application Rate (g a.i./ha)/ Formulation**	**PHI (days)**	**Residue Levels (ppm)[1]**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Method GRM020.05A (Data gathering method)								
Hay	125/ME	29–31	12	0.024	0.255	0.067	0.093	0.07
Straw		51–76	12	<0.01	0.084	0.033	0.04	0.02

Grain		51–76	12	0.051	0.57	0.22	0.25	0.16
Hay	125/EC	29–31	3	0.05	0.19	0.065	0.102	0.08
Straw		51–76	3	0.02	0.05	0.025	0.034	0.016
Grain		51–76	3	0.11	0.26	0.21	0.20	0.08
Hay	125/SL	29–31	3	0.057	0.26	0.115	0.14	0.104
Straw		51–76	3	0.015	0.052	0.049	0.039	0.02
Grain		51–76	3	0.11	0.26	0.23	0.20	0.08
Method GRM020.01A (Proposed enforcement method)								
Hay	125/ME	29–31	12	0.18	1.02	0.44	0.50	0.25
Straw		51–76	12	0.02	0.35	0.14	0.16	0.11
Grain		51–76	12	0.13	1.25	0.54	0.59	0.35
Hay	125/EC	29–31	3	0.33	0.63	0.38	0.45	0.16
Straw		51–76	3	0.054	0.195	0.19	0.146	0.08
Grain		51–76	3	0.36	0.60	0.6	0.52	0.14
Hay	125/SL	29–31	3	0.225	0.5	0.37	0.36	0.14
Straw		51–76	3	0.048	0.31	0.19	0.18	0.13
Grain		51–76	3	0.31	0.7	0.63	0.53	0.20

n = number of independent trials; LAFT = lowest average field trial; HAFT = highest average field trial.
[1] Expressed as trinexapac acid.
For computation, values <LOQ are assumed to be at the LOQ.

PROCESSED FOOD AND FEED – WHEAT AND BARLEY **PMRA# 2723381 & 2723380**

Processing studies in wheat and barley were conducted for trinexapac-ethyl. Two trials for each crop were conducted in the United States in growing regions 5 (one wheat trial; two barley trials) and 8 (one wheat trial) in which Trinexapac-ethyl 250EC was applied as a foliar broadcast spray to crops at an exaggerated rate of 644 g a.i./ha Wheat and barley grain was harvested 45 days after treatment. Wheat grain was processed into aspirated grain fractions (AGF), bran, flour, germ, middlings and shorts, and barley grain was processed into pearled barley, flour and bran using simulated commercial practices. Adequate storage stability data are available. All barley and wheat samples were analyzed using a validated analytical method.

RAC	Processed Fractions	HAFT[RAC] (ppm)	Median Processing Factor of Trinexapac-ethyl	Anticipated Residues of Trinexapac-ethyl (ppm)
Wheat grain	Wheat aspirated grain fractions	1.65	0.57	0.9
	Wheat bran		1.9	3.1
	Wheat flour		0.44	0.7
	Wheat middlings		0.5	0.8
	Wheat shorts		0.59	1
	Wheat germ		1.0	1.6
Barley grain	Pearled barley	1.25	1.7	2.1
	Barley flour		0.45	0.6
	Barley bran		1.5	1.9

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, radish and wheat	**PMRA# 2723373**
Radiolabel Position	[^{14}C-Cyclohexanedione-1, 2, 6] (specific activity: 2,449 KBq/mg)
Treatment	
Test Site	Outdoor test plots located in Madera, California
Soil Type	Sandy loam

Treatment	Bare soil was treated at 0.333-0.334 kg a.i./ha and aged for 30, 120, 270, and 309 (radish only) days prior to planting/after treatment (DAT).
Formulation	Emulsifiable concentrate formulation of trinexapac-ethyl (guarantee: not reported)
Extraction solvent	ACN:water; due to low TRR values, extraction was carried out for lettuce (30-day PBI samples only) and wheat (30-day PBI forage and hay samples and 120-day PBI forage, hay, and grain samples) only.

PBI (days)	Matrices	[^{14}C-Cyclohexanedione-1, 2, 6] TRR (ppm)
30	Lettuce, immature	0.010
	Lettuce, mature	0.018
	Radish, foliage	0.005
	Radish, roots	0.002
	Wheat, forage	0.010
	Wheat, hay	0.009
	Wheat, straw	0.003
	Wheat, grain	0.005
120	Lettuce, immature	0.004
	Lettuce, mature	0.004
	Radish, foliage	0.007
	Radish, roots	0.002
	Wheat, forage	0.004
	Wheat, hay	0.009
	Wheat, straw	0.004
	Wheat, grain	0.008
270	Lettuce, immature	0.007
	Lettuce, mature	0.001
	Radish, foliage	0.001
	Radish, roots	0.001
	Wheat, forage	0.002
	Wheat, hay	0.008
	Wheat, straw	0.004
	Wheat, grain	0.003

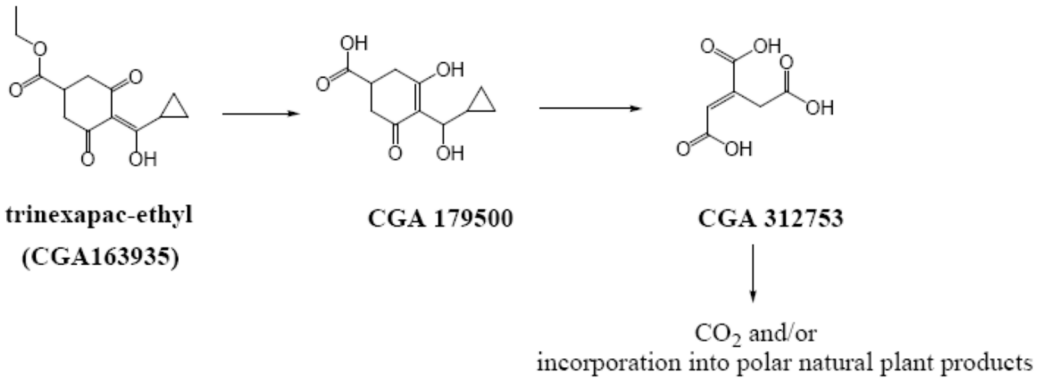
CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, wheat, sugar beets and corn	**PMRA# 2723372***
**this study is limited in scope and considered to be supplemental only.*	
Radiolabel Position	Not specified other than *"[^{14}C-Cyclohexyl]Trinexapac-ethyl*" (specific activity: 1.71 MBq/mg)
Treatment	
Test Site	Outdoor test plots (1m^2) within a confined field plot of 2 × 2 m at Ciba-Geigy Farm, Klus, Switzerland.
Soil Type	Sandy loam

Treatment	Bare soil was treated at 150 g a.i./ha. The following crops were planted at the indicated intervals to aged soil after treatment: Lettuce - 69 days Winter wheat - 119 days Sugar beets - 299 days Corn - 338 days
Formulation	Emulsifiable concentrate (EC 250) formulation of trinexapac-ethyl (guarantee: not reported)
Extraction solvent	None used. Fresh plant part samples were homogenized under liquid nitrogen and dry plant parts (stalk, grain, hulls) were homogenized in a disc mill. After homogenization, each sample was radioassayed by combustion/LSC analysis.

PBI (days)	Matrices	[^{14}C-Cyclohexanedione-1, 2, 6] TRR (ppm)
TRR values in all RACs, with one exception, were at or below the limit of detection of 0.001 ppm. Winter wheat stalks had the highest residues at 0.002 ppm. Given the low residues in the crop matrices, no further extraction/analyses were conducted.		

Summary of Major Identified Metabolites in Rotated Crops (Study PMRA# 2723373 only)			
Plant-back Intervals (PBI)	1st Rotation (30-day PBI)	2nd Rotation (120-day PBI)	3rd Rotation (270-day PBI)
Radiolabel Position	[^{14}C-Cyclohexanedione-1, 2, 6]		
Metabolites Identified	Major Metabolites		
Lettuce - immature and mature	None detected	Not analysed	
Wheat forage	Trinexapac acid (20% of the TRRs; 0.002 ppm)	None detected	Not analysed
Wheat hay	Tricarboxylic acid (CGA312753; 18.2% of the TRRs; 0.002 ppm)	Tricarboxylic acid (11.1% of the TRR; 0.001 ppm)	Not analysed
Wheat grain	Not analysed	None detected	Not analysed

Proposed Metabolic Scheme in Rotational Crops



(CGA 179500 = trinexapac acid; CGA 312753 = tricarboxylic acid)

RESIDUE DATA IN ROTATIONAL CROPS	**PMRA# N/A**
Given that TRRs in the majority of sampled crop matrices from both studies were not >0.01 ppm in crop parts used for food at the proposed 30-day PBI, field accumulation studies are not required.	

Table 7 Food residue chemistry overview of metabolism studies and risk assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (Wheat)** **Rotational crops (Lettuce, radish, wheat, sugar beets and corn)**	Trinexapac acid
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (Wheat)** **Rotational crops (Lettuce, radish, wheat, sugar beets and corn)**	Trinexapac acid (free and conjugated)
METABOLIC PROFILE IN DIVERSE CROPS	The profile in diverse crops cannot be determined because only a small cereal grain (wheat) was investigated.
ANIMAL STUDIES	
ANIMALS	**Ruminant and Poultry**
RESIDUE DEFINITION FOR ENFORCEMENT	Trinexapac acid
RESIDUE DEFINITION FOR RISK ASSESSMENT	Trinexapac acid (free and conjugated)
METABOLIC PROFILE IN ANIMALS **(goat, hen, rat)**	The metabolic profile is similar in all animals investigated.
FAT SOLUBLE RESIDUE	No

DIETARY RISK FROM FOOD AND DRINKING WATER			
Intermediate acute dietary exposure analysis, 95th percentile **$ARfD_{acideq}$ = 0.027 mg/kg bw** **Estimated acute drinking water concentration (EEC_{acideq}) = 332 ppm**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Drinking Water**
	Females 13-49 years	13.0	71.2

	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Drinking Water**
Basic chronic dietary exposure analysis **ADI_{acideq}:** **Total Population: 0.27 mg/kg bw/day** **Estimated chronic drinking water concentration (EEC) $_{acideq}$ = 331 ppm**	All infants <1 year	2.4	11.7
	Children 1–2 years	7.5	10.9
	Children 3–5 years	7.0	9.8
	Children 6–12 years	4.9	7.0
	Male Youth 13–19 years	2.9	4.6
	Male Adults 20–49 years	2.4	4.8
	Adults 50+ years	2.0	4.4
Basic chronic dietary exposure analysis	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	

		Food Alone	Food Alone
ADI_{acideq}: **Females 13-49 years: 0.027 mg/kg bw/day** **Estimated chronic drinking water concentration (EEC) $_{acideq}$ = 331 ppm**	Females 13-49 years	21.9	46.1

Fate and behaviour in the environment

Table 8 Physical and chemical properties of trinexapac-ethyl relevant to the environment*

Property	Value	Comments
Water solubility (g/L) at 25°C	pH — Solubility 3.5 (distilled water) — 1.1 4.9 (buffer) — 2.8 5.5 (buffer) — 10.2 8.2 (buffer) — 21.2	Very soluble under all pH conditions.
Vapour pressure	Vapour pressure = 1.03×10^{-3} Pa at 20°C 2.16×10^{-3} Pa at 25°C (by extrapolation of curve from 38.0−170.2°C)	Low volatility under field condition.
Henry's Law Constant	K = 5.27×10^{-10} atm m^3/mole (pH 5.5) K = 2.54×10^{-10} atm m^3/mole (pH 8.2)	Non-volatile from a water or moist soil surface. Laboratory study on volatilization not required.
Dissociation constant (pK_a)	pK_a = 4.57	Likely mobile in soil at environmentally relevant pH.
Octanol/water partition coefficient (K_{ow})	Log K_{ow} = 2.10 at pH 3 Log K_{ow} = 1.6 at pH 5.3 Log K_{ow} = -0.38 at pH 7	Bioconcentration/bioaccumulation is unlikely.
UV/visible absorption spectrum	Medium — λ (nm) — λ (nm) neutral — 240.2 — 277.4 acidic — 240.0 — 280.4 basic — 270.8 No absorption at λ maxima of 340 to 750 nm.	Low potential for phototransformation.

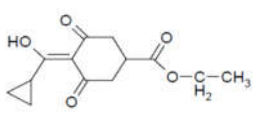
***** Based from the previously published regulatory document, Proposed Regulatory Decision PRDD2001-05; *Trinexapac-ethyl*

Table 9 Physical and chemical properties of trinexapac acid (CGA-179500) relevant to the environment*

Property	Value	Comments
Water solubility (g/L) at 25°C	pH / Solubility 5 / 13 6.8 / 200 8.4 / 260	Very soluble.
Vapour pressure	Vapour pressure = 1.0×10^{-6} Pa at 20°C; 2.3×10^{-6} Pa at 25°C	Relatively non-volatile under field conditions.
Henry's la Constant	K = 3.916×10^{-13} atm m^3/mole (pH 5); K = 2.546×10^{-14} atm m^3/mole (pH 6.8); K = 1.958×10^{-14} atm m^3/mole (pH 8.4)	Non-volatile from-water or moist soil surfaces. Laboratory study on volatilization not required.
Dissociation constant in water (20°C)	pK_a 1 = 5.32 pK_a 2 = 3.93	Potentially mobile in environmentally relevant pH's.
Octanol/water partition coefficient (K_{ow})	25°C Log K_{ow} = 1.8 at pH 2	Bioconcentration/bioaccumulation is unlikely.
UV/visible absorption spectrum	λ (nm) 239.3 and 280.0 No absorption at λ maxima of 340 to 750 nm.	Low potential for phototransformation.

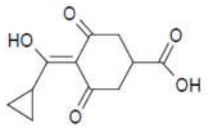
* Based from the previously published regulatory document, Proposed Regulatory Decision PRDD2001-05; *Trinexapac-ethyl*.

Table 10 Transformation products of trinexapac-ethyl and their occurrence

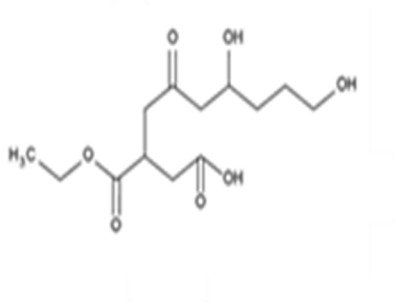
Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
PARENT			
Trinexapac-ethyl (CGA163935) **IUPAC Name:** 4-(cyclopropyl--Hydroxyl--methylene)-3,5-dioxocyclohexanecarboxylic acid ethyl ester] **CAS Number:** 95266-40-3 **SMILES:** C(O)(C2CC2)=C1C(=O)CC(C(=O)OCC)CC1=O  $C_{13}H_{16}O_5$	Hydrolysis (study 1) / 2723416	pH 4, 24.7°C **100.0** (0 d)	**79.4** (64 d)
		pH 4, 40°C **100.0** (0 d)	**27.6** (64 d)
		pH 4, 50°C **97.6** (0 d)	**14.0** (40 d)
		pH 7, 50°C **98.5** (0 d)	**91.6** (5 d)
		pH 9, 24.7°C **100.0** (0 d)	**17.3** (30 d)
		pH 9, 35.3°C **100.0** (0 d)	N.D. (30 d)
		pH 9, 50°C **97.6** (0 d)	N.D. (40 d)
	Hydrolysis (study 2) / 1048192	pH 5, 25 ± 1°C, Dark **100** (3 h)	**90** (30 d)
		pH 7, 25 ± 1°C, Dark **103** (6 h)	**96** (30 d)
		pH 9, 25 ± 1°C, Dark **97** (6 h)	**7** (30 d)
	Hydrolysis / (study 3)	pH 5 **99.5** (0 h)	**77.5** (179 d)

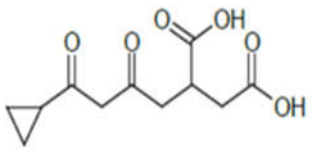
Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
	1048193	pH 7 **99.4** (0 h)	**84.3** (179 d)
	Soil Phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N **95.2** (0 d)	0.4 (17 d)
		Dry Soil; Dark **95.2** (0 d)	0.5 (17 d)
		Moist Soil; Irradiated 30 to 50°N **100.3** (0 d)	0.2 (17 d)
		Moist Soil; Dark **100.3** (0 d)	<0.1 (17 d)
	Water Phototransformation / 2723423	Irradiated **102.9** (0 d)	N.D. (25 d)
		Dark **101.6** (7 d)	**101.3** (25 d)
	Aerobic soil / 2723437	Gartenacker (Loam, Switzerland, pH = 7.7) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **54.3** (65 min)	0.1 (32 d)
		18 Acres (Sandy clay loam, United Kingdom pH = 7.0) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **34.9** (65 min)	0.2 (32 d)
		Capay (Clay loam, United States, pH = 6.6) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **90.8** (65 min)	0.8 (60 d)
		Sarpy (Silt loam, United States, pH = 6.7) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **38.1**(65 min)	0.5 (32 d)
		East Anglia (Sandy loam, United Kingdom, pH = 6.9) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **20.6** (65 min)	0.1 (32 d)

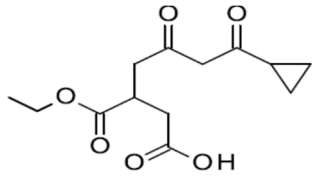
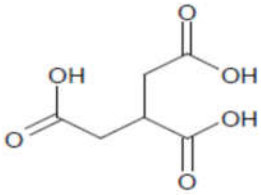
Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland, pH = 7.3) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) **30.6** (0 d of anaerobic conditions)	N.D. (121 d)
		18 Acres (Sandy clay loam, United Kingdom, pH = 6.0) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) **9.7** (0 d)	N.D. (121 d)
		Capay (Clay loam, United States, pH = 6.6) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) **56.9** (0 d)	N.D. (121 d)
		Sarpy (Silt loam, United States, pH = 6.7) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 9.6 (0 d)	N.D. (121 d)
	Aerobic aquatic / 2723445	Low Dose (20 µg/L) Dark; 20.9 ± 0.2°C **99.7** (0 d)	**13.2** (62 d)
		High Dose; Natural Water (100 µg/L) Dark; 20.9 ± 0.2°C **100.2** (0 d)	**14.4** (62 d)
		High Dose; Sterile Water (100 µg/L) Dark; 20.9 ± 0.2°C **106.1** (3 d)	**61.3** (62 d)
	Anaerobic aquatic 2723448 /	North Dakota water and sediment, pH 7.08, 20°C ± 2°C, total system **104.9**(0.1 d)	N.D. (360 d) (LOQ/LOD not reported)
	Koc	60–628 mL/g	
TRANSFORMATION PRODUCTS			
Trinexapac-acid (CGA179500) **IUPAC Name:** 4-[cyclopropyl(hydroxyl)methylene]-3,5-dioxocyclohexanecarboxylic	Hydrolysis (study 1) / 2723416	pH 7, 50°C **6.9** (5 d)	6.9 (5 d)
		pH 9, 24.7°C **85.6** (30 d)	**85.6** (30 d)
		pH 9, 35.3°C **103.4** (30 d)	**103.4** (30 d)

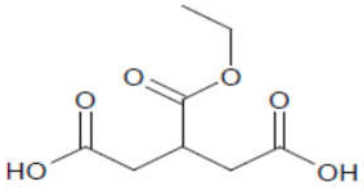
Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
Acid **CAS Name:** 4-(cyclopropyl-α-hydroxy-methylene)-3,5-dioxocyclohexanecarboxylic acid **CAS Number:** 104273-73-6 **SMILES:** C(O)(C2CC2)=C1C(=O)CC(C(=O)O)CC1=O  $C_{11}H_{12}O_5$		pH 9, 50°C **98.1** (5 d)	**93.6** (40 d)
	Hydrolysis (study 2) / 2723418	pH 4, 20°C **45.2** (91 d)	**45.2** (91 d)
		pH 4, 44°C **100** (0 d)	N.D. (62 d)
		pH 5, 20°C **100** (0 d)	**43.5** (91 d)
		pH 5, 44°C **100** (0 d)	N.D. (62 d)
	Hydrolysis (study 3) / 1048192	pH 5, 25 ± 1°C, Dark 5.17 (30 d)	5.17 (30 d)
		pH 7, 25 ± 1°C, Dark 4.12 (30 d)	4.12 (30 d)
		pH 5, 25 ± 1°C, Dark **88.20** (30 d)	**88.20** (30 d)
	Hydrolysis (study 4) / 1048193	pH 5 **18.0** (179 d)	**16.0** (179 d)
		pH 7 **16.0** (179 d)	**16.0** (179 d)
	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N **22.8** (2 d)	0.4 (17 d)
		Dry Soil; Dark **96.9** (10 d)	**90.8** (17 d)
		Moist Soil; Irradiated 30 to 50°N **61.5** (2 d)	0.1 (17 d)
		Moist Soil; Dark **94.3** (5 d)	**89.2** (17 d)
	Aerobic soil / 2723437	Gartenacker (Loam, Switzerland, pH = 7.7) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **74.2** (1 d)	0.1 (32 d)
		18 Acres (Sandy clay loam, United Kingdom, pH = 7.0) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **43.6** (1 d)	1.4 (32 d)
		Capay (Clay loam, United States, pH = 6.6) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **41.2** (1 d)	3.1 (60 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
		Sarpy (Silt loam, United States, pH = 6.7) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **31.6** (65 min)	6.2 (32 d)
		East Anglia (Sandy loam, United Kingdom, pH = 6.9) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) **66.6** (3 h 5 min)	1.0 (32 d)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) **86.7** (121 d)	**86.7** (121 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) **84.1** (121 d)	**84.1** (121 d)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) **85.2** (121 d)	**85.2** (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) **72.4** (59 d)	**70.2** (121 d)
	Aerobic aquatic / 2723445	Low Dose (20 µg/L) Dark; 20.9 ± 0.2°C **82.9** (62 d)	**82.9** (62 d)
		High Dose; Natural Water (100 µg/L) Dark; 20.9 ± 0.2°C **82.8** (62 d)	**82.8** (62 d)
		High Dose; Sterile Water (100 µg/L) Dark; 20.9 ± 0.2°C **37.1** (62 d)	**37.1** (62 d)

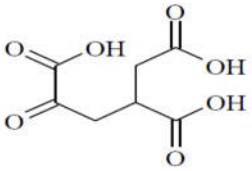
Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
	Anaerobic aquatic / 2723448	North Dakota water and sediment, pH 7.08, 20 ± 2 **87.9** (18 d; total system)	N.D. (360 d) (LOD/LOQ not reported)
	K_{oc}	145−609 mL/g	
M2 **IUPAC name: 3-carboxylic acid ethyl ester-7-hydroxypropyl-5- oxo,7-hydroxyheptanoic acid** 	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 2.3 (17 d)	2.3 (17 d)
		Dry Soil; Dark 0.5 (17 d)	0.5 (17 d)
		Moist Soil; Irradiated 30 to 50°N 1.8 (17 d)	1.8 (17 d)
		Moist Soil; Dark 0.3 (10 d)	0.0 (17 d)
	Aqueous phototransformation*	pH 7 buffered solution **17.9** (5 d)	9.5 (15 d)
	Aerobic soil / 2723437	Gartenacker (Loam, Switzerland) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 4.8 (3 d)	1.1 (32 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 3.1 (14 d)	1.4 (32 d)
		Capay (Clay loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 2.4 (32 d)	1.8 (60 d)
		Sarpy (Silt loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2) 2.8 (14 d)	1.9 (32 d)
		East Anglia (Sandy loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 4.9 (14 d)	3.2 (32 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.8 (0.25 d)	0.1 (121 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.7 (14 d)	N.D. (121 d)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.1 (0 d, 0.25 d, 14 d)	N.D. (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.4 (14 d)	N.D. (121 d)
CGA313458 [also referred to as M2 (CGA313458) by study authors of PMRA# 2723416, but it is NOT the same as M2 identified by EFSA above] **IUPAC name:** 2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid **Chemical name:** 3-carboxyl-7-cyclopropyl-5,7-dioxoheptanoic acid or 2-(4-cyclopropyl-2,4-dioxobutyl)-succinic acid **SMILES:** O=C(CC(CC(=O)O)C(=O)O)CC(=O)C1CC1  $C_{11}H_{14}O_6$	Hydrolysis (study 1) / 2723416	pH 4, 24.7°C 2.5 (51 d)	0.9 (64 d)
		pH 4, 40°C **15.1** (64 d)	**15.1** (64 d)
		pH 4, 50°C **22.0** (64 d)	**22.0** (64 d)
		pH 7, 50°C 0.3 (1 d)	N.D. (5 d)
	Hydrolysis (study 2) / 2723418	pH 4, 20°C **31.4** (91 d)	**31.4** (91 d)
		pH 4, 44°C **43.4** (62 d)	**43.4** (62 d)
		pH 5, 20°C **21.5** (91 d)	**21.5** (91 d)
		pH 5, 44°C **34.3** (23 d)	**31.4** (62 d)
WaterM3Hydrolysis **IUPAC name: 7-cyclopropyl-3-ethoxycarbonyl-5,7-dioxo-heptanoic acid**	Hydrolysis / 2723416	pH 4, 24.7°C **22.8** (64d)	**22.8** (64 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
 $C_{13}H_{18}O_6$		pH 4, 40°C **55.8** (64 d)	**55.8** (64 d)
		pH 4, 50°C **60.7** (64 d)	**60.7** (64 d)
WaterM3Photolysis **IUPAC name: (isomer of parent)**	Aqueous phototransformation*	pH 7 buffered solution **16.9** (5 d)	5.2 (15 d)
M4 (CGA275537) Tricarballylic acid **IUPAC name:** 1,2,3-Propanetricarboxylic acid **SMILES:** OC(=O)CC(CC(=O)O)C(=O)O  $C_6H_8O_6$	Soil phototransformation / 2723425	Dry Soil; Irradiated 30–50°N **10.8** (2 d)	5.5 (17 d)
		Dry Soil; Dark 2.6 (2 d)	0.9 (17 d)
		Moist Soil; Irradiated 30–50°N 6.5 (1 d)	4.2 (17 d)
		Moist Soil; Dark 0.8 (10 d)	0.2 (17 d)
	Aerobic soil / 2723437	Gartenacker (Loam, Switzerland) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.4 (3 h 5 min)	<0.1 (32 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.1 (1 d)	N.D. (32 d)
		East Anglia (Sandy loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.7 (1 d)	N.D. (32 d)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 3.8 (1 d)	N.D. (121 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.4 (3 d)	N.D. (121 d)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.0 (59 d)	N.D. (121 d)
	K_{oc}	4.3–1,2421 mL/g	
M5 **(CGA300405)** **IUPAC Name**: 3-ethoxycarbonyl-pentanedioic acid **SMILES:** OC(=O)CC(CC(=O)O)C(=O)OCC  $C_8H_{12}O_6$	Hydrolysis / 2723416	pH 4, 50°C 0.4 (0d)	ND (64 d)
		pH 9, 50°C 0.4 (0 d)	ND (40 d)
	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N **12.5** (2 d)	0.2 (17 d)
		Dry Soil; Dark 1.2 (2 d)	N.D. (17 d)
		Moist Soil; Irradiated 30 to 50°N 1.5 (5 d)	1.1 (17 d)
		Moist Soil; Dark 1.5 (17 d)	1.5 (17 d)
	Water phototransformation / 2723423	Irradiated **79.2** (7 d)	**60.1** (25 d)
		Dark 6.7 (25 d)	6.7 (25 d)
	Aqueous phototransformation*	pH 7 buffered solution **41.0** (15 d)	Continuously formed during the study
	Aerobic soil / 2723437	Gartenacker (Loam, Switzerland, pH = 7.0) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.9 (1 d)	0.1 (32 d)
		18 Acres (Sandy clay loam, United Kingdom, pH = 6.1) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.4 (3h 5min)	N.D. (32 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
		Capay (Clay loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.4 (14 d, 60 d)	N.D. (60 d)
		Sarpy (Silt loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.1 (3 h 5 min, 1 d)	N.D. (32 d)
		East Anglia (Sandy loam, United Kingdom, pH = 7.0) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.6 (65 min, 1 d)	N.D. (32 d)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 4.5 (0.25 d)	N.D. (121 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 3.7 (14 d)	N.D. (121 d)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 3.3 (0 d, 30 d)	N.D. (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 3.4 (14 d)	0.1 (121 d)
	K_{oc}	1.0 mL/g	
Soil M3 **SYN549229**	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 2.1 (5 d)	0.3 (17 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
IUPAC name: 4-oxobutane- 1,2,4-tricarboxylic acid  $C_7H_8O_7$		Dry Soil; Dark 0.2 (2 d)	N.D. (17 d)
		Moist Soil; Irradiated 30 to 50°N 3.3 (1 d)	0.1 (17 d)
	Aerobic soil / 2723437	Gartenacker (Loam, Switzerland) (20.6/20.8°C ± 0.2°C, dark and pF 2) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 2.0 (65 min)	0.8 (32 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 1.8 (65 min)	0.3 (32 d)
		Capay (Clay loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.2 (14 d, 60 d)	0.2 (60 d)
		Sarpy (Silt loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.3 (3 d, 14 d, 32 d)	0.3 (32 d)
		East Anglia (Sandy loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) (1 d, 14 d)	0.5 (32 d)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 3.7 (1 d)	0.2 (121 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.4 (121 d)	0.4 (121 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 2.0 (14 d)	0.1 (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 2.2 (14 d)	0.1 (121 d)
M6	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 2.1 (5 d)	0.3 (17 d)
		Dry Soil; Dark 0.2 (2 d)	N.D. (17 d)
		Moist Soil; Irradiated 30 to 50°N 3.3 (1d)	0.1 (17 d)
	Anaerobic soil / 2723443	Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.1 (0 d)	N.D. (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) < 0.1 (1 d)	N.D. (121 d)
M7	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 0.7 (10 d)	0.5 (17 d)
	Aerobic soil / 2723437	Gartenacker (Loam, Switzerland) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.1 (14 d)	N.D. (32 d)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.1 (0.25 d, 1 d)	N.D. (121 d)

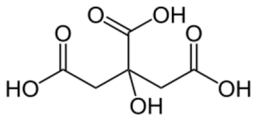
Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.1 (0 d)	N.D. (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) < 0.1 (1 d)	N.D. (121 d)
M8	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 0.6 (10 d)	0.1 (17 d)
		Dry Soil; Dark 0.3 (2 d)	N.D. (17 d)
		Moist Soil; Irradiated 30 to 50°N 0.1 (5 d)	N.D. (17 d)
	Aerobic soil / 2723437	18 Acres (Sandy clay loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.1 (14 d)	N.D. (32 d)
		Capay (Clay loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.2 (14 d)	N.D. (60 d)
		Sarpy (Silt loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.1 (3 d)	N.D. (32 d)
		East Anglia (Sandy loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.2 (1 d)	N.D. (32 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
	Anaerobic soil / 2723443	18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.5 (3 d)	N.D. (121 d)
M10	Hydrolysis / 2723416	pH 4, 40°C 1.2 (64 d)	1.2 (64 d)
		pH 4, 50°C 1.9 (32 d)	1.7 (64 d)
		pH 7, 50°C 0.2 (0 d)	N.D. (5 d)
		pH 9, 50°C 0.1 (0 d)	N.D. (40 d)
	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 0.1 (17 d)	0.1 (17 d)
		Moist Soil; Irradiated 30 to 50°N <0.1 (17 d)	<0.1 (17 d)
		Moist Soil; Dark 1.3 (10 d)	N.D. (17 d)
	Aerobic soil / 2723437	East Anglia (Sandy loam, United Kingdom) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.1 (1 d)	N.D. (32 d)
M11	Hydrolysis / 2723416	pH 4, 50°C 0.9 (0 d)	N.D. (64 d)
		pH 7, 50°C 0.5 (0 d)	N.D. (5 d)
		pH 9, 50°C 0.9 (0 d)	N.D. (40 d)
	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N <0.1 (17 d)	<0.1 (17 d)
		Moist Soil; Irradiated 30 to 50°N <0.3 (10 d)	<0.1 (17 d)
M12	Hydrolysis / 2723416	pH 4, 50°C 0.6 (0 d)	N.D. (64 d)
		pH 7, 50°C 0.5 (0 d)	N.D. (5 d)
		pH 9, 50°C 0.6 (0 d)	N.D. (40 d)
	Aerobic soil / 2723437	Capay (Clay loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.2 (14 d)	N.D. (60 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.4 (0 d)	N.D. (121 d)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.5 (3 d)	N.D. (121 d)
M13	Hydrolysis / 2723416	pH 4, 50°C 0.3 (0 d)	N.D. (64 d)
		pH 7, 50°C 0.3 (0 d)	N.D. (5 d)
		pH 9, 50°C 0.3 (0 d)	N.D. (40 d)
	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 1.4 (5 d)	0.2 (17 d)
		Dry Soil; Dark 3.7 (2 d, 17 d)	3.7 (17 d)
	Aerobic soil / 2723437	Capay (Clay loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 1.2 (14 d)	1.2 (60 d)
	Anaerobic soil / 2723443	Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 4.6 (3 d)	N.D. (121 d)
M14	Soil phototransformation / 2723425	Moist Soil; Irradiated 30 to 50°N 0.1 (10 d)	0.0 (17 d)
	Aerobic soil / 2723437	Capay (Clay loam, United States) (20.6/20.8°C ± 0.2°C, dark and pF 2 moisture tension) 0.1 (3 h 5 min)	N.D. (60 d)
	Anaerobic soil / 2723443	Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 0.2 (0 d)	N.D. (121 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
M16	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 0.3 (5 d)	<0.1 (17 d)
		Dry Soil; Dark 1.2 (2 d)	N.D. (17 d)
		Moist Soil; Irradiated 30 to 50°N 1.7 (1 d)	0.2 (17 d)
		Moist Soil; Dark 2.8 (1 d)	0.9 (17 d)
M17	Soil phototransformation / 2723425	Dry Soil; Irradiated 30 to 50°N 0.2 (10 d)	N.D. (17 d)
M20	Soil phototransformation / 2723425	Moist Soil; Irradiated 30 to 50°N 0.5 (10 d)	N.D. (17 d)
M21	Soil phototransformation / 2723425	Moist Soil; Irradiated 30 to 50°N 0.2 (10d)	N.D. (17 d)
		Moist Soil; Dark 0.1 (17 d)	0.1 (17 d)
CO_2 **Carbon dioxide** **CAS Number**: 124-38-9 	Aerobic aquatic / 2723445	Low Dose (20 µg/L) Dark; 20.9 ± 0.2°C <5 (62 d)	<5 (62 d)
		High Dose; Natural Water (100 µg/L) Dark; 20.9 ± 0.2°C <5 (62 d)	<5 (62 d)
		High Dose; Sterile Water (100 µg/L) Dark; 20.9 ± 0.2°C <5 (62 d)	<5 (62 d)
	Anaerobic aquatic / 2723448	North Dakota water and sediment, pH 7.08, 20 ± 2°C **82.9** (360 d)	**82.9** (360 d)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 7.1 (90 d)	5.0 (121 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 8.4 (121 d)	8.4 (121 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 6.5 (121 d)	6.5 (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 8.4 (121 d)	8.4 (121 d)
Other volatile organics	Water phototransformation / 2723423	Irradiated 3.6 (25 d)	3.6 (25 d)
		Dark 0 (25 d)	0 (25 d)
	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) < 0.1 (in all sampling times)	< 0.1 (121 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) < 0.1 (in all sampling times)	< 0.1 (121 d)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) < 0.1 (in all sampling times)	< 0.1 (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) < 0.1 (in all sampling times)	< 0.1 (121 d)

Code and chemical name	Study PMRA#	Max % A.R.	% A.R. at study end (study length)
Not analysed[3]	Anaerobic soil / 2723443	Gartenacker (Loam, Switzerland) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.5 (90 d)	N.D. (121 d)
		18 Acres (Sandy clay loam, United Kingdom) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.7 (90 d)	N.D. (121 d)
		Capay (Clay loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 1.1 (90 d)	N.D. (121 d)
		Sarpy (Silt loam, United States) (20.9 ± 0.2°C, continuous darkness, pF 2 moisture tension) 2.7 (59 d)	1.5 (121 d)
Polars[4]  3-carboxy-2-hydroxy-pentanedioc acid (iso-citric acid) or 3-carboxy-3-hydroxy-pentanedioc acid (citric acid)	Water phototransformation / 2723423	Irradiated **19.8** (25 d)	**19.8** (25 d)
		Dark 0.6 (25 d)	0.6 (25 d)

[1] min = minutes; h = hour; d = days
[2] after treatment; d = days
[3] Not analysed due to low radioactive content
[4] Radioactivity not retained by the reverse-phase HPLC column

* Confirmatory fate data were not submitted by the registrant but were included in the EFSA review (PMRA# 2931283 and 2931285).

A.R. – applied radioactivity
N.D. – Not detected or below detection limit
TP – transformation product

Bolded when appearing at >10% A.R. (considered as major transformation product)

Table 11 Fate and behaviour in the environment

Characteristic	Test substance	Value	Comment	Transformation products	PMRA#
Abiotic transformation: • Hydrolysis is an important route of dissipation in alkaline media. • Phototransformation in soil is not expected to be an important route of dissipation for trinexapac-ethyl in the environment. • Phototransformation in water is an important route of dissipation for trinexapac-ethyl in the environment.					
Hydrolysis	Trinexapac-ethyl	**At 25°C (SFO):** pH 5–228 d (stable) pH 7–455 d (stable) pH 9–8.1 d	Sterile aqueous buffered solutions incubated for 30 days under dark conditions at 25°C.	At pH 9, 25°C and 30 days of incubation: CGA179500 (90% A.R.)	1048192*
		At 25°C: pH 5: 485–562 d pH 7: 828–908 d	Sterile buffer solutions incubated for up to 179 days in the dark at 25°C.	At pH 5, 25°C during the 13-month study: CGA179500 and ethyl ester of tricarballylic acid [3-(ethoxycarbonyl) pentane dioicacid] (> 10% A.R.)	1048192*
		DT_{50} (SFO) **At 24.7°C:** pH 4: 188.3 d pH 9: 11.3 d **At 40°C:** pH 4: 39.0 d pH 9: 3.4 d **At 50.0°C:** pH 4: 14.2 d pH 9: 0.7 d At pH 7 and 50.0°C, trinexapac-ethyl is hydrolytically stable. Under acidic and alkaline conditions, trinexapac-ethyl was considered hydrolytically unstable at environmentally relevant temperatures.		Trinexapac-ethyl was considered hydrolytically unstable under acidic and alkaline conditions at environmentally relevant temperatures. At pH 4, and elevated temperatures (40 and 50°C), degradation was to M3, which consisted of hydrolytically ring-opened CGA163935 in two tautomeric forms, and CGA313458 (M2), which were observed over 10% A.R. At 24.7°C, only M3 was detected over 10% A.R., after 64 days. At pH 9, CGA179500 (M1) was the only metabolite formed	2723416** 2723417** 2931284***

Characteristic	Test substance	Value	Comment	Transformation products	PMRA#
				over 10% A.R. At pH 4 and 24.7°C, M3 was detected over 10% A.R., after 64 days. At pH 9, trinexapac acid was the only metabolite formed over 10% A.R.	
	Trinexapac acid (CGA179500)	**20°C** pH 4 = 81.9 d pH 5 = 80.4 **44°C** pH 4 = 3.4 pH 5 = 3.2 **50°C** pH 4 = 4.3 pH 5 = 6.4 pH 7 = Stable; no hydrolysis pH 9 = Stable; no hydrolysis	Sterile aqueous buffer solutions in the dark for a maximum of 91 days. The 20°C samples were incubated for 91 days and the 44°C samples were incubated for 62 days.	**At 20°C** pH 4: CGA313458 = 31.4% (at 91 days) M3 = 24.7% (at 91 days) pH 5: CGA313458 = 21.5% (at 91 days) M2 = 34.6% (at 91 days) **At 44°C** pH 4: - M2 (CGA313458) = 43.4% (at day 62) - M3 (unknown) = 56.1% (at day 45) - M4 (unknown) = 4.5% (at day 35) pH 5: - M2 (CGA313458) = 34.3 % (at day 23) - M3 (unknown) = 64.9% (at day 35) - M4 (unknown) = 5.2% (at day 45)	2723418** 2931284***
Phototrans-formation: Soil	Trinexapac-ethyl	Moist viable soil Irradiated: half-life (SFO) = 0.037 hours Dark conditions: half-life (SFO) = 8.31 hours Dry sterile soil Irradiated: half-life (SFO) = 79.1 days Dark conditions: half-life (SFO) = 122.8 days Half-life: 43.7 d	sandy loam soil for 30 days at 25°C Dry sterile soil: Irradiated and dark conditions Moist soil: Irradiated and dark conditions	CGA179500 = 52.2% (at day 7) open-chain CGA-163935 (at day 7)	1048195*

Characteristic	Test substance	Value	Comment	Transformation products	PMRA#
		Trinexapac-ethyl Dry soil: Stable Moist soil: Stable **CGA179500** Dry soil: 5.5 days Moist soil: 2.4 days	Dry soil: Irradiated and dark conditions Moist soil: Irradiated and dark conditions CGA163935 degraded at a similar rate under irradiated conditions and in the corresponding dark controls, indicating phototransformation is not a route of dissipation. However, the degradation rate was faster in moist soil than in the dry soils. Degradation proceeded with the formation of several transformation products, carbon dioxide and non-extractable residues. The most predominant transformation product was the hydrolysis product CGA179500, which was photosensitive and stable in the dark controls.	Dry soil, irradiated: CGA179500, CGA275537 (M4) and CGA300405 (M5) Dry soil, dark: CGA179500 = 94.3% (at day 10) Moist soil, irradiated: CGA179500, CGA275537 (M4) Moist soil, dark: CGA179500 = 94.3% (at day 5)	2723425** 2723426** 2723427** 2723428**
Phototrans-formation: Water	Trinexapac-ethyl	Half-life: 63.5 hours	Phototransformation played an important role in the transformation of trinexapac-ethyl in aqueous solutions. The opening of the cyclohexane ring forming the ethyl ester of tricarballylic acid is the major photolytic pathway.	Irradiated: ethyl ester of tricarballylic acid = 55.69% (372 hours)	1048198*
		Half-life (continuous irradiation): 2.6 days	Trinexapac-ethyl underwent phototransformation to produce CGA300405, citric-acid and/or iso-citric acid, at least 6 polar components (not further identified) and non-polar	CGA300405, citric acid and/or iso-citric acid	2723423** 2723424** 2931284***

Characteristic	Test substance	Value		Comment	Transformation products	PMRA#
				phototransformation products (not further identified). There was minimal mineralization to CO_2 in the study.		
Biotransformation: • Biotransformation in aerobic soil is an important route of dissipation for trinexapac-ethyl. The parent compound, trinexapac-ethyl, is non-persistent. The transformation product, trinexapac acid (CGA179500), is slightly persistent. • Biotransformation in anaerobic soil is an important route of dissipation for trinexapac-ethyl. The parent compound, trinexapac-ethyl, is slightly persistent. The major transformation products have potential to persist and accumulate and could contaminate ground water. • Non-persistent in anaerobic aquatic systems.						
Biotransformation: Aerobic soil	Trinexapac-ethyl	3−6 hours (trinexapac-ethyl)		Under sterile conditions, trinexapac-ethyl was not transformed. Bound residues increased during the incubation period and accounted for 11−18% of applied at day 90.	CGA-179500 and unidentified polar compound	1048201*
		16−18 days (CGA-179500) = Slightly persistent				
	Trinexapac-ethyl	2.1−4.2 hours (trinexapac-ethyl)			CGA-179500	
		1.1−21.4 days (CGA-179500)				
	Trinexapac-ethyl	**Soil Type**	**DT_{50}**		CGA179500	2723437** 2723438**
		Gartenacker	0.24 hours			
		18 Acres	0.24 hours			
		Capay	17.28 hours			
		Sarpy	8.88 hours			
		East Anglia	3.36 hours			
Biotransformation: Aerobic soil	CGA300405	**Soil Type**	**DT_{50}**		Not determined	2723440** 2723441**
		18 Acres	1.73 hours			

Characteristic	Test substance	Value		Comment	Transformation products	PMRA#
		East Anglia	0.19 hours			
		Gartenacker	1.54 hours			
Biotransformation: Anaerobic soil	Trinexapac-ethyl	10−25 days			CGA179500	1048201*
		12–14.5 days				1048205*
		Soil Type	**DT_{50}**			2723443** 2723444**
		Gartenacker	4.8 hours			
		18 Acres	16.8 hours			
		Capay	48 hours			
		Sarpy	14.4 hours			
Biotransformation: Aerobic water/sediment system	Trinexapac-ethyl	**System**	**DT_{50}**	At 20°C, dark conditions 20°C and at pH = 7.3–8.5	CGA179500	1048207*
		River	3.9 days			
		Pond	5.5 days			
	Trinexapac-ethyl	low dose (20 µg/L)	25.9 days	Natural water	CGA179500	2723445** 2723446** 2931284***
		high dose (91 µg/L)	21.2 days			
		sterile high dose (93 µg/L)	69.9 days			
Biotransformation: Anaerobic water/ sediment system	Trinexapac-ethyl	**Sediment and water from Alice, North Dakota** DT_{50} in water: 3.8 days Half-life/DT_{50} in the entire system: 4.2 days			CGA179500, CO_2	2723448** 2723449**
		Sediment and water from Lake Okeechobee, Florida Half-life/DT_{50} in water: 1.2/0.6 days Half-life/DT_{50} in the entire system: 2.2/1.6 days				

Characteristic	Test substance	Value		Comment	Transformation products	PMRA#
Mobility: • Trinexapac-ethyl is classified as having low to high potential for mobility in soil (McCall *et al*., 1981). • Trinexapac acid (CGA179500) is classified as having low to high potential for mobility in soil (McCall *et al*., 1981). • Adsorption of CGA300405 ((3-ethoxycarbonyl-pentanedioic acid) is very low. • Volatilization will not be an important route of transport.						
Adsorption/ Desorption	Trinexapac-ethyl	**Soil type**	K_{oc}			1048211* 2931284***
		Clay	635			
		Sandy	283			
		Sandy loam	60			
		Loam	143			
	Trinexapac acid	**Soil type**	K_{oc}			1048210* 2931284***
		Clay	581			
		Sandy	609			
		Sandy loam	144			
		Loam	328			
	CGA300405 (3-ethoxycarbonyl-pentanedioic acid)	Inherently too unstable		Higher recoveries observed in the preliminary test indicated that adsorption of CGA300405 is very low.		*2723440*** 2931284***
Volatility	Trinexapac-ethyl	N.A.		No detectable trinexapac-ethyl was found to volatilize from dry or moist soil. All trinexapac-ethyl was found to remain on the sandy soil following the 10-day purging period. Radiocarbon balance ranged from 98.7−112% using 0% humidity nitrogen and 102.7−109% of dose following purging with 100% humidity nitrogen. The humidity of in the purging gas and the soil water contents did not have effect on the volatilization of this compound.		1048203*

Characteristic	Test substance	Value	Comment	Transformation products	PMRA#
Dissipation and accumulation under field conditions: • Trinexapac-ethyl is unlikely to accumulate in soil and carryover to the next growing season. • Trinexapac acid (CGA-179500) is classified as non-persistent to slightly persistent in soil and is unlikely to carry-over to the next growing season. • Leaching is unlikely to occur under field conditions with trinexapac-ethyl and trinexapac acid (CGA-179500). • The major route of dissipation for trinexapac-ethyl under terrestrial field conditions was biotransformation.					
Terrestrial field dissipation	Trinexapac-ethyl	Bare plot: DT_{50}: 1.1 days (0−15 cm layer)		Trinexapac acid (CGA 17500) DT_{50}: 5.1 days (0−15 cm layer)	1050717* 1050718*
Terrestrial field dissipation	Trinexapac-ethyl	Under field conditions: <u>Trinexapac-ethyl</u> DT_{50} = 2.5 days DT_{90} = 8.3 days	Minto, Manitoba/silt loam CGA163935 and CGA179500 dissipated quickly in soil, with concentrations below the LOQ of 10 ppb by Days 9 and 21, respectively. Concentrations of CGA163935 and CGA179500 were exclusively detected in the 0−10 cm soil layer, with the exception of the measurement of CGA179500 just above the LOQ of one 10−25 cm soil depth sample. There is no potential for either compound to carry over into the following season. The major route of dissipation of CGA163935 under terrestrial field conditions was transformation.	<u>CGA179500</u> DT_{50} = 6.4 days DT_{90} = 21.4 days	2723465**
Bioaccumulation: • Trinexapac-ethyl is not expected to bioaccumulate or bioconcentrate. • The bioconcentration of trinexapac-ethyl residues was low.					
Bioconcentration and elimination	Trinexapac-ethyl	BCFs (bluegill sunfish) Edible tissue = 2.5× Non edible tissue = 11× Whole body tissues = 6× Half-life = 1−3 days	Depuration phase was included.		1048243*

Characteristic	Test substance	Value	Comment	Transformation products	PMRA#
Flow-through bioconcentration	Trinexapac-ethyl	BCFs (bluegill sunfish) Edible = 1.9× Non edible = 9.9× Whole body tissues = 5.5×	No depuration phase was included.	Edible and non-edible fish tissues: Trinexapac acid (CGA179500) and 6-cyclo-propyl-6-hydroxyl-2-methyl-4-one-hex-2,5-dienois acid	1048244*

A.R. – applied radioactivity percent of applied amount

* Originally reviewed and published in the Proposed Regulatory Decision PRDD2001-05; *Trinexapac-ethyl*
** New studies submitted
*** Also used in the recent EFSA review

Effects on non-target organisms

Table 12 Effects on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
Invertebrates					
Earthworm (*Eisenia fetida*)	14-day – Acute	Trinexapac-ethyl (Technical; purity: 96.6%)	LC_{50} > 93.1 mg a.i./kg dry weight NOEC = 93.1 mg a.i./kg (equivalent to 209.5 kg a.i./ha)	N.A.	1048217*
	14-day – Acute	CGA179500 (Trinexapac-acid); Trinexapac-ethyl transformation product (purity: 99%)	LC_{50} > 1000 mg a.i./kg dry weight	N.A.	2931263**
	28-day – Chronic (Reproduction)	Trinexapac-ethyl formulation (A11825A; 115 g/L trinexapac-ethyl)	NOEC = 26.5 mg a.i./kg dry weight	N.A.	2723470** 2723471**
Honey bee (*Apis mellifera*)	48-hour − Acute (Contact)	Trinexapac-ethyl (Technical; purity: 96.2%)	LD_{50} = 47 µg a.i./bee	Practically non-toxic	1048219*
	48-hour − Acute (Contact)	Trinexapac-ethyl (Technical; purity: 96.8 %)	LD_{50} > 200 µg/bee	Practically non-toxic	2723477** 2723478** 2931284 and 2931286***
	48-hour − Acute (Oral)	Trinexapac-ethyl (Technical; purity: 96.8 %)	LD_{50} > 200 µg/bee	Practically non-toxic	
	Chronic – Bee Adult (10-day continuous feeding)	Trinexapac-ethyl formulation, (A8587F; 250 g/L trinexapac-ethyl)	NOED = 26.9 µg a.i./bee/day	N.A.	2723474** 2723475** 2931284 and 2931286***
	22-day Repeated exposure – Larva	Trinexapac-ethyl (Technical; purity: 96.8 %)	8-day NOED = 12.6 µg a.i./larva per developmental period	N.A.	2723479** 2723480** 2931284 and 2931286***

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
Predators					
Green lacewing (*Chrysoperla carnea*)	Extended laboratory	Trinexapac-ethyl formulation (A11825A)	NOEC = 400 g a.i./ha (equivalent to 3.31 L product/ha)	N.A.	2723481** 2723482** 2931284 and 2931286***
Predatory mite (*Typhlodromus pyri*)	Dose response toxicity (Laboratory) – exposed on glass plates	Trinexapac-ethyl formulation (A11825A)	LR_{50} = 314.3 g a.i./ha (equivalent to 2.60 L a.i./ha)	N.A.	2723483** 2723484**
Predatory soil mite (*Hypoaspis aculeifer*)]	14-day study – Reproduction	CGA300405 (3-ethoxycarbonyl-pentanedioic acid) – Trinexapac-ethyl transformation product	Mortality and reproduction NOEC (mortality and reproduction) = 1000 mg a.i./kg soil dry weight (the highest concentration tested)	N.A.	2723485** 2723486**
Parasitoids					
Rove beetle (*Aleochara bilineata*)	Chronic – extended laboratory test	Trinexapac-ethyl formulation (A11825A)	ER_{50} > 400 g a.i./ha	N.A.	2723487** 2723488**
Aphid parasitoid *(Aphidius rhopalosiphi*)	48-hour − Acute	Trinexapac-ethyl formulation (A11825A)	LR_{50} = 441.8 g a.i./ha (equivalent to 3.66 L a.i./ha)	N.A.	2723489** 2723490**
Other Terrestrial Invertebrates					
Springtails (*Folsomia candida*)	28-day – Reproduction	CGA300405 (3-ethoxycarbonyl-pentanedioic acid) Trinexapac-ethyl transformation product	NOEC (mortality and reproduction) = 1000 mg/kg soil dry weight EC_{10}, EC_{20} and EC_{50} (reproduction) > 1000 mg a.i./kg soil dry weight	N.A.	2723491** 2723492** 2931284 and 2931286***
Birds					
Bobwhite quail (*Colinus virginianus*)	Acute − Dietary	Trinexapac-ethyl (Technical; purity: 96.6%)	LC_{50} > 5200 mg a.i./kg dw	Practically non-toxic	1048247*
	Chronic − Reproduction	Trinexapac-ethyl (Technical; purity: 96.6%)	NOEC = 200 mg a.i./kg dw	N.A.	1048249*
Northern bobwhite (*Colinus virginianus*)	Acute − Oral	Trinexapac-ethyl (Technical; purity 93.7%)	LD_{50} > 2250 mg/kg bw	Practically non-toxic	2723523** 2723524** 2931284 and 2931286***
Mallard duck (*Anas platyrhynchos*)	Acute − Oral	Trinexapac-ethyl (Technical; purity: 96.6%)	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	1048246* 2931284 and 2931286***
	Acute − Dietary	Trinexapac-ethyl (Technical; purity: 96.6%)	LC_{50} > 5200 mg a.i./kg dw	Practically non-toxic	1048248*
	22-week − Reproduction	Trinexapac-ethyl (Technical; purity: 96.6%)	NOEC = 600 mg a.i./kg dw	N.A.	1048251*
Zebra finch (*Taeniopygia guttata*)	14-day − Acute (Oral)	Trinexapac-ethyl (Technical; purity: 95.8%)	LD_{50} = 1684 mg a.i./kg bw	Slightly toxic	2723526** 2723527**

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
Mammals					
Rat (*Rattus norvegicus)*	Acute − Oral	Trinexapac-ethyl (Technical; purity: 96.6%)	LD_{50}: 4210 mg/kg bw (♀) 4610 mg/kg bw (♂) 4460 mg/kg bw (sexes combined)	Slightly toxic	1048309* 2931284 and 2931286***
	90-day − Dietary	Trinexapac-ethyl (Technical; purity: 96.6%)	NOAEL: Males: 500 ppm (equal to 34 mg/kg bw/d) Females: 5000 ppm (equal to 395 mg/kg bw/d)	N.A.	1048315* 1048316*
	Reproduction	Trinexapac-ethyl (Technical; purity: 96.2%)	Parental NOAEL = 1000 ppm (60 mg /kg bw/d ♂ and 76 mg /kg bw/d ♀) Offspring NOAEL = 10 000 ppm (594 mg /kg bw/d for ♂ and 751 mg /kg bw/d ♀) Reproductive NOAEL = 20 000 ppm (1 212 mg a.i./kg bw/d ♂ and 1 484 mg /kg bw/d ♀)	N.A.	1048152* 1048153* 1048159* 1048160* 1048346*
Mouse (*Mus musculus*)	90-day − Dietary	Trinexapac-ethyl (Technical; purity: 96.6%)	NOAEL = 10 000 mg a.i./kg dw (equal to 1 552 and 1 970 mg/kg bw/d in males and females, respectively)	N.A.	1051388*
Vascular plants					
Vascular plant	Seedling emergence	Trinexapac-ethyl (Technical; purity: 93.7%)	NOEC = 841 g a.i./ha for all species	N.A.	1048262* 1048263* 2931284 and 2931286***
	Vegetative vigour	Trinexapac-ethyl (Technical; purity: 93.7%)	EC_{25} = 299 g a.i./ha on carrot plant dry weight	N.A.	1048261*

[1] Atkins et al. (1981) for bees and USEPA classification for others, where applicable; N.A. - not applicable.
* Originally reviewed and published in the Proposed Regulatory Decision PRDD2001-05; *Trinexapac-ethyl*
** New studies submitted
*** Also used in the recent EFSA review

Table 13 Effects on aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA
Freshwater species					
Invertebrates					
Water flea (*Daphnia magna*)	48-hour – Acute (Static-renewal)	Trinexapac-ethyl (Technical; purity: 96.6%)	EC_{50} > 142.5 mg a.i./L (immobilization) NOEC = 29 mg a.i./L Mortality, immobilization, floating at water surface, erratic swimming	Practically non-toxic	1048231* 2931284 and 2931286***
	48-hour – Acute (Static)	CGA179500 (Trinexapac-acid); Trinexapac-ethyl transformation product (purity: 99%)	EC_{50} = 111 mg a.i./L NOEC = 58 mg a.i./L	Practically non-toxic	1048233* 2931284 and 2931286***
	48-hour – Acute (Static)	CGA300405 (3-ethoxycarbonyl-pentanedioic acid); Trinexapac-ethyl transformation product (purity: 97%)	EC_{50} > 100 mg a.i./L NOEC = 100 mg a.i./L	Practically non-toxic	2723494** 2723495** 2931284 and 2931286***
	21-day – Chronic (Flow-through conditions)	Trinexapac-ethyl (Technical; purity: 93.8%)	NOEC = 2.4 mg a.i./L Reduction in adult daphnid length	N.A.	1048235* 2931284 and 2931286***
	21-day – Chronic (semi-static)	Trinexapac-ethyl (Technical; purity: 95.7%)	EC_{50} > 10 mg a.i./L (reproduction) NOEC = 3.2 mg a.i./L	Moderately toxic	2723499** 2723500**
Fish					
Rainbow trout (*Oncorhynchus mykiss*)	96-hour – Acute (Static renewal)	Trinexapac-ethyl (Technical; purity: 96.6%)	LC_{50} = 68 mg a.i./L NOEC = 30 mg a.i./L	Slightly toxic	1048224* 2931284 and 2931286***
	96-hour – Acute (Static)	CGA179500 (Trinexapac-acid); Trinexapac-ethyl transformation product (purity: 99%)	LC_{50} > 100 mg/L NOEC = 100 mg/L Mortality, immobilization, erratic swimming, sluggish reaction to stimuli	Practically non-toxic	1048226* 2931284 and 2931286***
Bluegill sunfish *(Lepomis macrochirus)*	96-hour – Acute (Static renewal)	Trinexapac-ethyl (Technical; purity: 96.6%)	LC_{50} > 130.1 mg a.i./L NOEC = 46.6 mg a.i./L	Practically non-toxic	1048228* 2931284 and 2931286***

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA
			Immobilization and sluggish reaction to stimuli		
Fathead minnow (*Pimephales promelas*)	Early life stage – Chronic	Trinexapac-ethyl (Technical; purity: 92.2%)	NOEC = 0.89 mg a.i./L NOEC = 0.41 mg a.i./L (Second study)	N.A.	1048242* 2931284 and 2931286***
Carp (*Cyprinus carpio*)	96-hour – Acute	Trinexapac-ethyl (Technical; purity: 92.2%)	LC_{50} = 57 mg a.i./L NOEC = 32 mg a.i./L Mortality, darkened pigmentation	Slightly toxic	1048237* 2931284 and 2931286***
	96-hour – Acute	CGA179500 (Trinexapac-acid); Trinexapac-ethyl transformation product (purity: 99%)	LC_{50} > 100 mg a.i./L NOEC = 100 mg a.i./L	Practically non-toxic	1048239* 2931284 and 2931286***
Channel catfish (*Ictalurus punctatus*)	96-hour – Acute	Trinexapac-ethyl (Technical; purity: 92.2%)	LC_{50} = 35 mg a.i./L NOEC = 20 mg a.i./L Mortality, erratic swimming, loss of equilibrium	Slightly toxic	1048240* 2931284 and 2931286***
Freshwater algae					
Diatom (*Navicula pelliculosa*)	5-day – Chronic	Trinexapac-ethyl (Technical; purity: 92.2%)	EC_{50} (Cell density) = 42 mg a.i./L NOEC = 6.2 mg a.i./L	N.A.	1048253*
	96-hour – Acute	CGA179500 (Trinexapac-acid); Trinexapac-ethyl transformation product (purity: 99%)	EC_{50} > 100 mg/L NOEC = 100 mg/L	N.A.	1048254*
Bluegreen algae (*Anabaena flos-aquae*)	5-day – Chronic	Trinexapac-ethyl (Technical; purity: 92.2%)	EC_{50} = 0.35 mg a.i./L (cell density) NOEC = 0.11 mg a.i./L	N.A.	1048255*
Blue algae (*Microcystis aeruginosa*)	96-hour – Acute	CGA179500 (Trinexapac-acid); Trinexapac-ethyl transformation product (purity: 99%)	EC_{50} = 72 mg a.i./L NOEC = 28 mg a.i./L	N.A.	1048257*
Green algae (*Selenastrum capricornutum/ Pseudokirchneriella subcapitata*)	5-day – Chronic	Trinexapac-ethyl (Technical; purity: 92.2%)	EC_{50} = 9.4 mg a.i./L (cell density) NOEC = 3 mg a.i./L	N.A.	1048256*
	96-hour – Acute	Trinexapac-ethyl (Technical; purity: 95.8%)	EC_{50} = 14.5 mg a.i./L (cell density)	N.A.	2723533** 2723534** 2931284 and 2931286***

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA
	96-hour – Acute	CGA300405 (3-ethoxycarbonyl-pentanedioic acid); Trinexapac-ethyl transformation product (purity: 97%)	EC_{50} = 33 mg a.i./L	N.A.	2723535** 2723536**
			NOEC = 3.2 mg a.i./L	N.A.	
	72-hour – Acute	CGA179500 (Trinexapac-acid); Trinexapac-ethyl transformation product (purity: 99%)	EC_{50} > 97.6 mg a.i./L	N.A.	1048258*
			NOEC = 97.6 mg a.i./L		
Plants					
Duckweed (*Lemna gibba*)	14-day – Chronic	Trinexapac-ethyl (Technical; purity: 96.6%)	EC_{50} = 0.19 mg a.i./L (frond density)	N.A.	1048265*
			NOEC = 0.018 mg a.i./L		
	7-day – Chronic (Static)	Trinexapac-ethyl (Technical; purity: 98.4%)	NOEC = 1.0 mg a.i./L Yield (frond number) and Growth rate (frond number)	N..A.	2931279**
	48-hour – Acute (Static)	CGA179500 (Trinexapac acid) (Trinexapac-ethyl transformation product; purity: 99%)	EC_{50} = 111 mg a.i./L	N.A.	1048233*
	7-day – Chronic (Static)	CGA179500 (Trinexapac acid) (Trinexapac-ethyl transformation product; purity: 99 ± 1%)	NOEC = 0.30 mg a.i./L (frond number)	N..A.	2931280**
	7-day – Chronic (Static)	CGA300405 (3-ethoxycarbonyl-pentanedioic acid); (Trinexapac-ethyl transformation product; purity: 97%)	EC_{50} > 100 mg a.i./L (yield)	N.A.	2723549** 2723550** 2931284 and 2931286***
			EC_{50} > 100 mg a.i./L (growth rate)		
Eurasian watermilfoil (*Myriophyllum spicatum*)	14-day – Chronic (Semi-static)	Trinexapac-ethyl (Technical; purity: 95.4%)	EC_{50} (Yield) = 0.20 mg a.i./L	N.A.	2931284 and 2931286***
Marine species					
Invertebrates					
Mysid shrimp *(Americamysis bahia)*	96-hour – Acute	Trinexapac-ethyl (Technical; purity: 92.2%)	LC_{50} = 6.5 mg a.i./L	Moderately toxic	1048221* 2931284 and 2931286***
			NOEC < 3.4 mg a.i./L		
			Mortality, erratic swimming, darkened pigmentation, lethargy		
Mollusk Eastern oyster	96-hour – Acute	Trinexapac-ethyl (Technical; purity:	EC_{50} = 89 mg a.i./L (shell deposition)	Slightly toxic	1048222* 2931284 and

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA
(Crassostrea virginica)		96.6%)	NOEC < 8.4 mg a.i./L		2931286***
Fish					
Sheepshead minnow (*Cyprinodon variegatus*)	96-hour – Acute	Trinexapac-ethyl (Technical; purity: 92.2%)	LC_{50} = 180 mg a.i./L	Practically non-toxic	1048229*
			NOEC < 60 mg a.i./L		
			Erratic swimming, loss of equilibrium, darkened pigmentation, lethargy		
Algae					
Marine diatom *(Skeletonema costatum)*	5-day – Chronic	Trinexapac-ethyl (Technical; purity: 92.2%)	EC_{50} = 16 mg a.i./L (cell density)	N.A.	1048260*
			NOEC = 3.7 mg a.i./L		

[1] USEPA classification, where applicable; N.A. - not applicable
* Originally reviewed and published in the Proposed Regulatory Decision PRDD2001-05; *Trinexapac-ethyl*
** New studies submitted
*** Also used in the recent EFSA review

Risk assessment on non-target species

Table 14 Screening level risk assessment of trinexapac-ethyl, formulated end-use product and transformation product for non-target terrestrial species other than birds and mammals

Organism	Exposure/test substance[1]	Endpoint value[2]	EEC[3]	RQ[7]	Level of concern[8]
Invertebrates					
Earthworm (*Eisenia fetida*)	Acute – Technical Grade Active Ingredient	LC_{50}/2: > 46.55 mg a.i./kg soil	0.056 mg a.i./kg soil[4]	0.001	Not exceeded
	Chronic – Trinexapac-ethyl formulation; A11825A	NOEC = 26.5 mg a.i./kg soil	0.056 mg a.i./kg soil[4]	0.002	Not exceeded
Honeybee (*Apis mellifera*)	Acute oral, adults – Technical Grade Active Ingredient	LD_{50} = > 200 µg a.i./bee	3.625 µg a.i./bee[5]	0.002	Not exceeded
	Acute contact, adults – Technical Grade Active Ingredient	LD_{50} = 47 µg a.i./bee	0.3 µg a.i./bee[5]	0.006	Not exceeded
	Chronic oral, adults – Trinexapac-ethyl formulation; A8587F	NOED = 26.9 µg a.i./bee	3.625 µg a.i./bee[5]	0.135	Not exceeded
	Chronic oral, larvae – Technical Grade Active Ingredient	8-day NOED = 12.6 µg a.i./bee	1.5 µg a.i./bee[5]	0.119	Not exceeded
Predators					
Green lacewing (*Chrysoperla carnea*)	Extended laboratory toxicity test – Trinexapac-ethyl formulation; A11825A	NOEC = 400 g a.i./ha	125 g a.i./ha[6]	0.313	Not exceeded

Organism	Exposure/test substance[1]	Endpoint value[2]	EEC[3]	RQ[7]	Level of concern[8]
Predatory mite (*Typhlodromus pyri*)	Contact, glass plates – Trinexapac-ethyl formulation; A11825A	LR_{50} = 314.3 g a.i./ha	125 g a.i./ha[6]	0.398	Not exceeded
Predatory soil mite (*Hypoaspis aculeifer*)	14-day study – CGA300405 (3-ethoxycarbonyl-pentanedioic acid); Trinexapac-ethyl transformation product	NOEC = 1000 mg/kg soil dry weight	0.056 mg a.i./kg soil[4]	0.000056	Not exceeded
Parasitoids					
Rove beetle (*Aleochara bilineata*)	Chronic - extended laboratory test – Trinexapac-ethyl formulation; A11825A	ER_{50} >400 g a.i./ha	125 g a.i./ha[6]	< 0.313	Not exceeded
Aphid parasitoid *(Aphidius rhopalosiphi*)	Contact, glass plates – Trinexapac-ethyl formulation; A11825A	LR_{50} = 441.8 g a.i./ha	125 g a.i./ha[6]	0.283	Not exceeded
Other Terrestrial Invertebrates					
Springtails (*Folsomia candida*)	28-day Reproduction – CGA300405 (3-ethoxycarbonyl-pentanedioic acid); (Trinexapac-ethyl transformation product	EC_{50} /2: >500 mg a.i./kg soil dry weight	0.056 mg a.i./kg soil[4]	< 0.0001	Not exceeded
Vascular plants					
Vascular plant	Seedling emergence – Technical Grade Active Ingredient	NOEC = 841 g a.i./ha for all species (highest rate tested)	125 g a.i./ha[6]	0.149	Not exceeded
	Vegetative vigour – Technical Grade Active Ingredient	EC_{25} = 299 g a.i./ha on carrot plant dry weight	125 g a.i./ha[6]	0.418	Not exceeded

[1] CGA300405 – 3-ethoxycarbonyl-pentanedioic acid; A11825A and A8587F – Trinexapac-ethyl formulations

[2] For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used in modifying the toxicity values for terrestrial invertebrates when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints.

[3] EEC = Estimated Environmental Concentration.

[4] For earthworm and springtails: The EEC is 0.056 mg a.i./kg soil. This is the EEC of trinexapac-ethyl in soil, calculated assuming that the concentration of trinexapac-ethyl at the maximum environmental rate is 125 g a.i./ha, that the product is evenly distributed in the 0−15 cm depth of the soil and that the bulk density of the soil is 1.5 g/cm^3.

[5] For pollinators:

The exposure estimate for the contact exposure route for pollinators (adult) = application rate (kg a.i./ha) × adjustment factor = 0.125 kg a.i./ha × 2.4 µg a.i./bee per kg a.i./ha = 0.3 µg a.i./bee.

The exposure estimate for the adult oral exposure for pollinators (adult) = application rate (kg a.i./ha) × adjustment factor = 0.125 kg a.i./ha × 29 µg a.i./bee per kg a.i./ha) = 3.625 µg a.i./bee.

The exposure estimate for the adult oral exposure for pollinators (larva) = application rate (kg a.i./ha) × adjustment factor = 0.125 kg a.i./ha × 12 µg a.i./bee per kg a.i./ha) = 1.5 µg a.i./bee.

[6] For other terrestrial organisms and non-target terrestrial vascular plants: The EEC is based on the maximum environmental rate for trinexapac-ethyl is 125 g a.i./ha calculated using the proposed use on winter wheat: one application at 125 g a.i./ha.

[7] RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the endpoint value (RQ = EEC/endpoint value).

[8] LOC = Level of concern. The RQ is then compared to the level of concern (LOC = 1 for most species; 2 for beneficial arthropods, 0.4 for acute risk to pollinators; 1 for chronic risk to pollinators). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary.

Table 15 Screening level risk assessment of trinexapac-ethyl for birds and mammals

	Toxicity[1] (mg a.i./kg bw/d)	Feeding guild (Food item)[2]	EDE[3] (mg a.i./kg bw)	Risk quotient[4]	Level of concern[5]
Birds					
Small Sized Bird (0.02 kg)					
Acute (1/10 LD_{50})	168.4	Insectivore (Small insects)	10.17	0.06	Not exceeded
Reproduction (NOEC)	200	Insectivore (Small insects)	10.17	0.05	Not exceeded
Medium Sized Bird (0.1 kg)					
Acute (1/10 LD_{50})	168.4	Insectivore (Small insects)	7.94	0.05	Not exceeded
Reproduction	200	Insectivore (Small insects)	7.94	0.04	Not exceeded
Large Sized Bird (1 kg)					
Acute (1/10 LD_{50})	168.4	Herbivore (Short range grass)	5.13	0.03	Not exceeded
Reproduction (NOEC)	200	Herbivore (Short range grass)	5.13	0.03	Not exceeded
Mammals					
Small Sized Mammal (0.015 kg)					
Acute (1/10 LD_{50})	421	Insectivore (Small insects)	5.85	0.01	Not exceeded
Reproduction (NOAEL)	1 212	Insectivore (Small insects)	5.85	0.005	Not exceeded
Medium Sized Mammal (0.035 kg)					
Acute (1/10 LD_{50})	421	Herbivore (Short range grass)	11.35	0.03	Not exceeded
Reproduction (NOAEL)	1 212	Herbivore (Short range grass)	11.35	0.01	Not exceeded
Large Sized Mammal (1 kg)					
Acute (1/10 LD_{50})	421	Herbivore (Short range grass)	6.06	0.01	Not exceeded
Reproduction (NOAEL)	1 212	Herbivore (Short range grass)	6.06	0.01	Not exceeded

[1] Endpoints were divided by an uncertainty factor to account for varying protection goals (in other words, protection at the community, population, or individual level).

For acute toxicity studies, the uncertainty factor of 1/10 the LD_{50} was used in modifying the toxicity values for birds and mammals when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints.

The lowest acute LD_{50} value of 1684 mg a.i./kg bw obtained from the study with the use of trinexapac-ethyl on zebra finch (*Taeniopygia guttata*) was conservatively used in the screening level risk assessment. As the risk quotients for birds resulting from acute oral exposure to trinexapac-ethyl did not exceed the level of concern at the screening level, further refinement is not required.

The lowest acute LD_{50} value of 4210 mg/kg bw obtained from the study with the use of trinexapac-ethyl on rats (*Rattus norvegicus*) was conservatively used in the screening level risk assessment. As the risk quotients for

mammals resulting from acute oral exposure to trinexapac-ethyl did not exceed the level of concern at the screening level, further refinement is not required.

[2] Specialized feeding guilds are considered for each category of animal weights to help determine exposure (herbivore, frugivore, insectivore and granivore).

[3] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where: FIR: Food Ingestion Rate . For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$

All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$

BW: Generic Body Weight

[4] RQ = Risk Quotient. The on-field RQ is calculated by dividing the EDE by the endpoint value (RQ = EDE/endpoint value).

RQs are based on estimated environmental concentrations (EEC): For birds and mammals, the EEC takes into account the maximum seasonal cumulative rate on vegetation and is calculated using PMRA standard methods based on the Hoerger and Kenaga nomogram as modified by Fletcher (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

[5] LOC = Level of Concern. The RQ is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary.

Table 16 Screening level risk assessment of trinexapac-ethyl for non-target aquatic species*

Organism	Exposure/test substance[1]	Endpoint value[2] (mg a.i./L)	EEC[3] (mg a.i./L)	Risk quotient[4]	Level of concern[5]
Freshwater species					
Water flea (*Daphnia magna*)	Acute – Technical Grade Active Ingredient	NOEC = 29	0.0156	0.001	Not exceeded
	Chronic – Technical Grade Active Ingredient	NOEC = 2.4	0.0156	0.007	Not exceeded
Channel catfish (*Ictalurus punctatus*)	Acute – Technical Grade Active Ingredient	$LC_{50}/10 = 3.5$	0.0156	0.004	Not exceeded
Carp (*Cyprinus carpio*)	Acute – Technical Grade Active Ingredient	$LC_{50}/10 = 5.7$	0.0156	0.003	Not exceeded
Fathead minnow (*Pimephales promelas)*	Early life stage – Technical Grade Active Ingredient	NOEC = 0.41	0.0156	0.038	Not exceeded
Amphibians (using fish data as a surrogate)	Acute – Technical Grade Active Ingredient	$LC_{50}/10 = 3.5$	0.0834	0.024	Not exceeded
	Acute – Technical Grade Active Ingredient	$LC_{50}/10 = 5.7$	0.0834	0.015	Not exceeded
	Chronic – Technical Grade Active Ingredient	NOEC = 0.41	0.0834	0.203	Not exceeded
Freshwater alga	Acute – Technical Grade Active Ingredient	$EC_{50}/2 = 0.175$	0.0156	0.089	Not exceeded

Organism	Exposure/test substance[1]	Endpoint value[2] (mg a.i./L)	EEC[3] (mg a.i./L)	Risk quotient[4]	Level of concern[5]
Vascular plant	Dissolved – Technical Grade Active Ingredient	$EC_{50}/2 = 0.095$	0.0156	0.164	Not exceeded
Marine species					
Crustacean: Mysid shrimp *(Americamysis bahia)*	Acute – Technical Grade Active Ingredient	$LC_{50}/2 = 3.25$	0.0156	0.005	Not exceeded
Mollusk: Eastern oyster *(Crassostrea virginica)*	Acute – Technical Grade Active Ingredient	$EC_{50}/2 = 44.5$	0.0156	0.0004	Not exceeded
Salmonid: Sheepshead minnow *(Cyprinodon variegatus)*	Acute – Technical Grade Active Ingredient	$LC_{50}/10 = 18$	0.0156	0.0009	Not exceeded
Marine alga: Marine diatom *(Skeletonema costatum)*	Chronic – Technical Grade Active Ingredient	NOEC = 3.7	0.0156	0.004	Not exceeded

[*] The toxicity of the transformation products were lower than the parent thus, the risk assessments were not completed for the transformation products.

[1] Endpoints were divided by an uncertainty factor to account for varying protection goals (in other words, protection at the community, population, or individual level). For acute toxicity studies, uncertainty factors of 1/2 the EC_{50} and 1/10 the LC_{50} are typically used in modifying the toxicity values for aquatic organisms when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints.

[2] EEC = Estimated Environmental Concentration. The EEC of trinexapac-ethyl in water bodies 80-cm and 15-cm deep are 0.0156 mg a.i./L and 0.0834 mg a.i./L, respectively, calculated assuming that the concentration of trinexapac-ethyl at the maximum environmental rate is 125 g a.i./ha and that the water density is 1 g/mL.

[3] RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the endpoint value (RQ = EEC/endpoint value)

[4] LOC = Level of Concern. The RQ is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary.

Table 17 Toxic substances management policy considerations – comparison to TSMP track 1 criteria

TSMP track 1 criteria	TSMP track 1 criterion value		Endpoints	
			Trinexapac-ethyl	Transformation products
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	Laboratory studies	
			0.05–0.79 days	Trinexapac-acid (CGA: 16−18 days CGA300405: 0.008–0.072 days
	Water	Half-life ≥ 182 days	5.3 days	Not available

TSMP track 1 criteria	TSMP track 1 criterion value		Endpoints	
			Trinexapac-ethyl	Transformation products
	Sediment	Half-life ≥ 365 days	3.9−25.9 days	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilization is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (1.03×10^{-3} Pa at 20°C and 2.16×10^{-3} Pa at 25°C) and Henry's law constant (5.27×10^{-10} atm m^3/mole at pH 5.5 and 2.54×10^{-10} atm m^3/mole at pH 8.2).	Not applicable
Bioaccumulation[4]	Log $K_{ow} \geq 5$		1.60 ± 0.22 at pH 5.3 and 25°C	1.8 at pH 2 and 25°C
	BCF ≥ 5000		11×	Not available
	BAF ≥ 5000		Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act* (CEPA) 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] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix II Supplemental maximum residue limit information—international situation and trade implications

Trinexapac-ethyl is an active ingredient that is concurrently being registered in Canada for use as a plant growth regulator on wheat, barley and oats.

Table 1 compares the MRLs proposed for trinexapac-ethyl in Canada with corresponding American tolerances and Codex MRLs.[9] 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 canadian MRLs, american tolerances and Codex MRLs (where different)

Food commodity	Canadian MRL (ppm)	American tolerance (ppm)	Codex MRL (ppm)
Wheat bran	4	6	8
Wheat	3	4	3
Barley	3	2	3
Barley bran	Covered by the MRL of 3 ppm for barley	2.5	6
Oats	3	4	3
Meat byproducts of cattle, goats, hogs, horses, poultry and sheep	0.02	0.04 Meat byproducts of cattle, goats, hog, horse and sheep	0.1 Edible offal of mammals
Eggs; milk; fat and meat of cattle, goats, hogs, horses, poultry and sheep	0.01	0.02 Fat and meat of cattle, goats, hog, horse, sheep	0.01 Mammalian fats (except milk fats) Meat (from mammals other than marine mammals) 0.05 Edible offal of poultry 0.005 Milks 0.01 Eggs; poultry fats; poultry meat

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

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

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