Proposed Registration Decision PRD2021-02

Picarbutrazox and VAYANTIS Seed Treatment

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Overview

Proposed registration decision for picarbutrazox

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 Picarbutrazox Technical and VAYANTIS Seed Treatment, containing the technical grade active ingredient picarbutrazox, to control seed rot/pre-emergence damping-off and post-emergence damping-off in corn and soybean.

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 picarbutrazox and VAYANTIS Seed Treatment.

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 Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

Before making a final registration decision on picarbutrazox and VAYANTIS Seed Treatment, Health Canada's PMRA will consider any comments received from the public in response to this

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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."

consultation document.[3] Health Canada will then publish a Registration Decision[4] on picarbutrazox and VAYANTIS Seed Treatment, 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 picarbutrazox?

Picarbutrazox is a new conventional fungicide active ingredient that controls particular economically important diseases of corn and soybean.

Health considerations

Can approved uses of picarbutrazox affect human health?

VAYANTIS Seed Treatment, containing picarbutrazox, is unlikely to affect your health when used according to label directions.

Potential exposure to picarbutrazox may occur through the diet (food and drinking water), when handling and applying the end-use product, or when handling and planting treated seeds. When assessing health risks, two key factors are considered; the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are 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 level at which no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient picarbutrazox was of low acute toxicity via the oral, dermal and inhalation routes. It was minimally irritating to the eyes and non-irritating to the skin. It did not cause an allergic skin reaction.

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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*.

The end-use product VAYANTIS Seed Treatment, containing picarbutrazox, was of low acute toxicity via the oral, dermal, and inhalation routes. It was minimally irritating to the eyes and non-irritating to the skin. It did not cause an allergic skin reaction.

Registrant-supplied short-term and long-term (lifetime) animal toxicity tests were assessed for the potential of picarbutrazox to cause neurotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the liver and thyroid in rats. There was no evidence of increased sensitivity of the young. Thyroid tumours were noted in male and female rats at the highest dose tested, however, there was no evidence to suggest that picarbutrazox damaged genetic material. 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 food and drinking water

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

Animal studies revealed no acute health effects. Consequently, a single dose of picarbutrazox is not likely to cause acute health effects in the general population (including infants and children).

On the strength of the overall information, a threshold approach was considered appropriate for the cancer risk assessment based on the observed thyroid follicular cell adenomas in rats. Overall the endpoints selected for the non-cancer dietary risk assessment are considered protective of these findings.

Aggregate chronic (non-cancer and cancer) dietary intake estimates (food plus drinking water) for the general population and all population subgroups are expected to be less than or equal to 3% 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 constitute a health risk of concern.

Residue trials conducted throughout Canada and the United States using picarbutrazox as a seed treatment on soybean and on field corn, sweet corn and popcorn are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document.

Occupational risks from handling VAYANTIS Seed Treatment

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

Workers treating seeds with VAYANTIS Seed Treatment in commercial facilities or with commercial mobile treaters as well as workers planting treated seeds, may come into direct contact with picarbutrazox residues on the skin and through inhalation. Therefore, the label of VAYANTIS Seed Treatment specifies that treatment must be conducted with a closed-transfer system only. In addition, workers must wear long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, cleaning, bagging, sewing, stacking, as well as during handling and planting of treated seeds. Taking into consideration these label statements, the rate of application and the duration of exposure for handlers and workers, health risks to these individuals are not of concern.

Health risks to bystanders

Bystander risks are not of health concern when VAYANTIS Seed Treatment is used according to the proposed label directions and 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 picarbutrazox is introduced into the environment?

When used according to label directions, the risks associated with the use of picarbutrazox are acceptable from the viewpoint of environmental protection.

Picarbutrazox will remain in the soil for up to 2 to 3 months depending on the soil type and conditions; however, when considering the breakdown-products of picarbutrazox, the combination of picarbutrazox and its breakdown products can remain in the soil for up to a year depending on the soil type and conditions. It will not move from the treatment area into the air and, therefore, will not move to another area by movement through the air. Picarbutrazox is not expected to move downward in the soil, and, therefore, is unlikely to reach groundwater; however, many of its breakdown-products can move downward in the soil and reach groundwater. Picarbutrazox has low potential to move off the treatment area to reach surface waters such as ponds, streams and rivers. If it does enter water, picarbutrazox will move to the sediment where it will not remain for a long period of time. Picarbutrazox is not expected to accumulate in plant or animal tissue.

When picarbutrazox is used in accordance with the label directions and the required precautions, the risk to terrestrial invertebrates, birds, wild mammals, bees, beneficial arthropods, terrestrial plants, aquatic invertebrates (including sediment-dwelling invertebrates), amphibians, fish, algae and vascular aquatic plants from the use of picarbutrazox were determined to be acceptable without the requirement of additional risk mitigation measures.

Value considerations

What is the value of VAYANTIS Seed Treatment?

Picarbutrazox is the active ingredient in VAYANTIS Seed Treatment. The registration of this product will provide Canadian growers with a unique mode of action to manage important fungal diseases in corn and soybean while mitigating the risk of resistance development by causal pathogens to other fungicides that are registered to control the same diseases.

VAYANTIS Seed Treatment is applied to seed of corn and soybean to control seed rot/pre-emergence damping-off and post-emergence damping off that can reduce crop stands.

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 Picarbutrazox Technical and VAYANTIS Seed Treatment to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

To reduce the potential of workers coming into direct contact with picarbutrazox on the skin or through inhalation, workers must wear long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, applying, cleaning, bagging, sewing, stacking, as well as during handling and planting of treated seeds. The label also specifies that commercial seed treatment must be conducted with closed-transfer system only. Furthermore, a standard label statement to protect against drift during application is present on the label.

Environment

- Precautionary statements are required to inform users of the toxicity of picarbutrazox to aquatic organisms.
- Precautionary statements are required for the labeling of treated seed.
- Precautionary statements are required to inform users of the potential for leaching.

Next steps

Before making a final registration decision on picarbutrazox and VAYANTIS Seed Treatment, 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

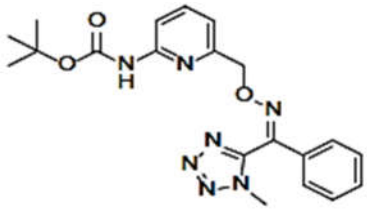
When Health Canada makes its registration decision, it will publish a Registration Decision on picarbutrazox and VAYANTIS Seed Treatment (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection,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

Science evaluation

Picarbutrazox and VAYANTIS Seed Treatment

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Picarbutrazox
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*tert*-butyl (6-{[(*Z*)-(1-methyl-1*H*-5-tetrazolyl) (phenyl)methylene]aminooxymethyl}-2-pyridyl)carbamate
2. Chemical Abstracts Service (CAS)	1,1-dimethylethyl *N*-[6-[[[(*Z*)-[(1-methyl-1*H*-tetrazol-5-yl) phenylmethylene]amino]oxy]methyl]-2-pyridinyl]carbamate
CAS number	500207-04-5
Molecular formula	$C_{20}H_{23}N_7O_3$
Molecular weight	409.44 g/mol
Structural formula	
Purity of the active ingredient	97.5%

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

Technical product—Picarbutrazox technical

Property	Result
Colour and physical state	White solid (crystalline powder)
Odour	None
Melting range	136.6–138.7°C

Property	Result
Boiling point or range	Decomposes at >150°C
Density	1.2541–1.2639 g/cm^3
Vapour pressure at 20°C	$<1.2 \times 10^{-7}$ Pa
Ultraviolet (UV)-visible spectrum	λ_{max} is 221.5 nm in acidic and neutral media (smaller peaks at 291.5 and 272.0 nm in acidic and at 280.5 nm in neutral), and 223.0 nm in basic medium (smaller peak at 282.5 nm).
Solubility in water at 20°C	0.333 mg/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) *n*-Hexane — 0.103 *n*-Heptane — 0.106 *n*-Octanol — 3.32 Ethanol — 15.0 Methanol — 34.8 Xylene — 21.2 Toluene — 49.8 Ethyl acetate — 185 Dichloromethane — >250 Acetone — >250
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 4.16
Dissociation constant (pK_a)	pKa = 2.95
Stability (temperature, metal)	Stable up to 150°C.

End-use product—VAYANTIS seed treatment

Property	Result
Colour	Off-white
Odour	No particular odour
Physical state	Liquid
Formulation type	Flowable concentrate (suspension)
Label concentration	400 g/L
Container material and description	High-density polyethylene (HDPE), 1–1050 L
Density	1.11 g/mL
pH of 1% dispersion in water	6–8
Oxidizing or reducing action	Compatible with oxidizing agents, reducing agents, fire extinguishing agents and water.

Property	Result
Storage stability	Stable in non-fluorinated HDPE packaging under accelerated (54°C for 2 weeks) conditions.
Corrosion characteristics	Not corrosive to its HDPE packaging.
Explodability	Not explosive

1.3 Directions for use

VAYANTIS Seed Treatment is applied to seed of corn (field, sweet, pop, seed) at 2.5–12.5 mL/100 kg seed and to soybean at 2.5–6.25 mL/100 kg seed to control seed rot/pre-emergence damping-off and post-emergence damping-off caused by *Pythium* spp. In corn, the minimum rate is for use in fields with a known low level of pre-emergence damping-off while a mid-rate (for example, 6.25 mL/100 kg seed) is for use in fields with higher levels of pre-emergence damping-off. A rate in the upper end of the range is for use in fields with a known history of post-emergence damping-off. In soybean, the minimum and maximum rates are for use in fields with known low levels and higher levels of damping-off, respectively. VAYANTIS Seed Treatment may be also tank-mixed with other seed treatment fungicides and/or insecticides to broaden disease spectrum and to protect from insect pest damage.

1.4 Mode of action

The mode of action of picarbutrazox is not conclusively known. However, it is known to have a unique mode of action as there is no cross-resistance to other fungicides that are active on the same pathogens. Picarbutrazox is classified as a group U17 fungicide by the Fungicide Resistance Action Committee (FRAC).

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 methods provided for the analysis of the active ingredient in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for residue analysis

High performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes in environmental media, plant matrices (AOAC Official Method 2007.1 and QuEChERS-multiresidue method) and in animal matrices (QuEChERS-multiresidue method).

HPLC-MS/MS Methods 83966 and RES-00155 were developed for the determination of residues of picarbutrazox and metabolites TZ-1E, TZ-2-β-Glc, TZ-5 and TZ-5-Glc, and metabolites TT-1 and TT-3 for data gathering purposes in plant matrices. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation.

Acceptable recoveries (70–120%) were obtained in environmental media and in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Extraction solvents used in the plant and livestock enforcement methods were similar to those used in the plant and livestock metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled plant and animal matrices was not required.

Methods for residue analysis are summarized in Appendix I, Tables 1a and 1b.

3.0 Impact on human and animal health

3.1 Toxicology summary

Picarbutrazox is a tetrazolyloxime fungicide with a new pesticidal mode of action, the details of which have not been fully elucidated.

A detailed review of the toxicology database for picarbutrazox was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies included mechanistic studies examining liver and thyroid toxicity pathways and studies assessing the toxicity of select metabolites of picarbutrazox. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the potential health hazards associated with picarbutrazox.

Metabolism and toxicokinetics following single dose administration in the rat were investigated using picarbutrazox radiolabelled at the phenyl or pyridine ring. Based on the results of a biliary excretion study, picarbutrazox was well absorbed at low dose levels, with peak plasma concentrations occurring between 2 and 6 hours post-dosing. Absorption as a percentage of the administered dose (AD) decreased with increasing dose level, such that absorption was less than 30% of the AD at 100 mg/kg bw. At final sacrifice, which occurred 4 days post-dosing, the highest residues were found in the gut and gut contents, liver, prostate, fat, and adrenal glands. Elimination of orally-administered picarbutrazox was rapid and extensive. The majority of the AD was recovered in the excreta within 48 hours. The major route of excretion was via the feces, representing more than 80% of AD for low dose and more than 93% of AD for high dose. Recovered radiolabel in bile accounted for 77–80% of AD for low dose and 14–23% of AD for high dose. Radiolabel recovery in urine was 8–10% of AD for low dose and 1–2% of AD for high dose.

Radioactivity in tissues 96 hours after single oral dose administration was low and there was no evidence of retention within tissues. The metabolic and toxicokinetic parameters measured were generally comparable between sexes, though high-dose absorption was slightly lower in females than in males.

The phenyl- or pyridine-labelled picarbutrazox assays yielded 11 to 18 identified metabolites in urine, bile, or feces. Unchanged picarbutrazox was not identified in urine or bile, indicating extensive metabolism. The major metabolic transformation routes for picarbutrazox involved hydroxylation, hydrolysis, or a ring closure to form a 5,5-dimethyloxazolidin-2-one group. Glucuronide conjugates were observed for multiple metabolites.

In acute toxicity testing, picarbutrazox was of low acute toxicity via the oral, dermal, and inhalation routes in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. Picarbutrazox was negative for skin sensitization in guinea pigs when tested using the Maximization method.

VAYANTIS Seed Treatment was of low acute toxicity via the oral, dermal, and inhalation routes in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits, and was negative for skin sensitization when tested in mice using the local lymph node assay. In addition, an isolated chicken eye assay showed that the product was non-irritating.

The liver was identified as a target of toxicity for picarbutrazox following repeated dietary exposure in mice and rats. The thyroid was also affected in multiple studies in the rat. In addition to weight changes in these organs, histopathological alterations were observed in several studies. Liver effects observed among mice and rats included increased weight, hepatocyte enlargement, vacuolation, cellular inclusions, eosinophilic foci, fatty change, cystic degeneration, elevated liver enzymes, and clinical chemistry alterations. Thyroid effects included increased weight and follicular cell hypertrophy or hyperplasia in rats in short-term and long-term dietary studies. Thyroid hormone levels were also affected in multiple short-term dosing studies in rats. Other effects observed in mice and rats were usually confined to a single study or at dose levels near the limit dose.

Following repeated oral dietary exposure in dogs, decreases in body weight and body weight gain were observed. Liver weights were increased and hepatocellular hypertrophy was observed. Gallbladder weights were also increased, but without any histopathological correlates. In the 12-month study, alkaline phosphatase and alanine aminotransferase were increased while albumin was decreased. Dogs were found to be less sensitive to picarbutrazox than mice and rats. There was no evidence that longer duration of dosing increased toxicity in dogs.

No systemic toxicity occurred in rats following daily dermal application of picarbutrazox up to the limit dose for 28 days.

In a supplementary 5-day inhalation toxicity study in rats, hepatocellular hypertrophy and thyroid follicular cell hypertrophy were observed at the mid-dose level. At the high-dose level, breathing difficulties were noted as well as increased thyroid and parathyroid weight, tracheal epithelial alteration, macrophage accumulation in the lungs, and decreased body weight over the first two days.

In the rat acute gavage neurotoxicity study, there was no evidence of neurotoxicity up to the limit dose. The short-term rat dietary toxicity studies with functional observational battery components also showed no evidence of selective neurotoxicity in the parameters examined.

There was no evidence of genotoxicity in a battery of in vitro and in vivo genotoxicity studies conducted with picarbutrazox. An increased number of thyroid follicular cell adenomas was observed in both males and females of the high-dose group in the rat combined chronic toxicity/carcinogenicity study. A mode of action (MOA) for the development of the thyroid tumours in rats was proposed by the applicant in conjunction with supplied mechanistic studies to support this proposed MOA. Specifically, the applicant referred to the hypothalamic-pituitary-thyroid axis perturbation MOA commonly associated with phenobarbital. This MOA states that administration of the test substance induces hepatic drug-metabolizing enzymes. These enzymes also clear circulating T4 hormones. The pituitary increases thyroid stimulating hormone (TSH) production to counter this effect which leads to increased thyroid activity and eventually tumours. The provided mechanistic data included plasma thyroid hormone measurements in multiple studies, a thyroid peroxidase activity study, and a hepatic drug metabolizing enzyme induction study. These data, in conjunction with the full toxicity database, were supportive of the proposed MOA, though the low incidences of follicular cell hyperplasia and the lack of reversibility data were noted as limitations. Other possible tumourigenic MOAs were considered inconsistent with the available data, such as the negative results in the genotoxicity battery and a thyroid peroxidase activity study. Although rats have been shown to be considerably more sensitive to the tumour precursor events, this tumourigenic mode of action has not been excluded from being relevant to humans. Overall, the weight of evidence supported the proposed MOA and a threshold approach for risk assessment was considered appropriate. As such, a separate cancer risk assessment was not necessary.

The rat 2-generation dietary reproductive toxicity study with picarbutrazox revealed liver and thyroid toxicity in parents and offspring, consistent with the observations from the short-term toxicity studies. There were no effects on reproductive parameters. In the F2 generation, body weights were decreased during the latter half of the postnatal period and thyroid hypertrophy was observed in weanlings at terminal necropsy. The thyroids of the F1 generation were not subject to histopathological assessment at weaning. There was no evidence of sensitivity of the young.

In the gavage developmental toxicity studies, there was no evidence of sensitivity of the young in either rats or rabbits. Maternal and fetal rats were tested up to the limit dose and no adverse effects were observed. In rabbits, maternal animals showed thin appearance and body weight loss over gestation days 6 to 9, as well as decreased body weight, body weight gain, and food consumption at the limit dose.

Fetal rabbits at the same dose level showed an increased number of ribs and corresponding thoracic vertebrae, along with a decreased number of lumbar vertebrae. This fetal effect was observed in the presence of maternal toxicity and is not considered serious.

The toxicity of select isomers and metabolites of picarbutrazox were investigated to a limited extent in acute, genotoxicity, and short-term dietary toxicity studies. TZ-4 tested positive with a single strain of *S. typhimurium* in a bacterial reverse mutation assay. In acute oral toxicity tests in rats, treatment with TZ-2, TZ-5, or TY-2 resulted in mortalities at 2000 mg/kg bw, whereas dosing with picarbutrazox did not produce mortalities at this dose level in rats. Clinical signs of toxicity were limited to decreased activity following dosing with 300 mg/kg bw of TZ-5, which had cleared by six hours post-dosing. Repeat-dose dietary testing with TZ-5 suggests possible effects on the kidney and nasal epithelia that were not observed in the picarbutrazox studies, but the effect levels in these studies were higher than with picarbutrazox. In a rat 90-day dietary study with TT-3K, body weight and body weight gain were decreased in females at the highest dose level. A 90-day dietary study in rats with TZ-1E produced liver weight effects, hepatocellular hypertrophy, and some clinical chemistry effects. With the limited information available, for the purposes of risk assessment, the isomers and metabolites were considered to be of equivalent toxicity to picarbutrazox.

The identification of select isomers and metabolites is presented in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with picarbutrazox and its associated end-use product are summarized in Appendix I, Tables 3 and 4, respectively. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 5.

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, there was no evidence of increased sensitivity of the fetus or offspring compared to parental animals in either the developmental toxicity or reproductive toxicity studies. In the 2-generation reproductive toxicity study, decreased body weights and increased thyroid hypertrophy were observed in offspring at a higher dose level than increased thyroid weight and thyroid hypertrophy in the parental animals.

In the developmental toxicity study in rats, no fetal toxicological effects were observed. In the developmental toxicity study in rabbits, the mean number of fetal ribs and thoracic vertebrae were increased at the highest dose level. At the same dose level, dams had decreased body weight, body weight gain, and food consumption.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young as effects on the young are well characterized and occurred in the presence of maternal toxicity. Therefore, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold for the current assessment of picarbutrazox.

3.2 Toxicology reference values

3.2.1 Acute reference dose (ARfD)

The only endpoint of concern potentially attributable to a single exposure was observed at a limit dose. Therefore, an acute reference dose is not required.

3.2.2 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, a NOAEL of 2.3 mg/kg bw/day from the 2-year dietary chronic toxicity/carcinogenicity study in the rat was selected. At the LOAEL of 7.8 mg/kg bw/day, effects on the thyroid and liver were observed. 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 onefold. The composite assessment factor (CAF) is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{2.3 mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day of picarbutrazox}$$

The ADI provides a margin of 390 to the NOAEL for thyroid follicular cell adenomas in the rat.

3.2.3 Short- and intermediate-term dermal

For short- and intermediate-term dermal risk assessment, a NOAEL of 1000 mg/kg bw/day from the 28-day dermal toxicity study in rats was selected, which was the highest dose level tested in this study. This study was conducted via the relevant route and was of an appropriate duration of exposure.

The target margin of exposure (MOE) for this scenario is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.2.4 Short- and intermediate-term inhalation

The only repeat-dose inhalation toxicity study available was a supplemental 5-day dose range-finding study; therefore, the use of NOAELs from the oral toxicity studies for these exposure scenarios was appropriate.

For short-term inhalation risk assessment, the NOAEL of 15 mg/kg bw/day from the 28-day dietary rat toxicity study was selected. Toxicity was observed in the form of effects on the liver and thyroid at the LOAEL of 150 mg/kg bw/day.

For intermediate-term inhalation risk assessment, the parental NOAEL of 2.9 mg/kg bw/day from the 2-generation reproductive toxicity study in the rat was selected. Toxicity was observed in the form of effects on the thyroid at the LOAEL of 12 mg/kg bw/day.

The target MOE for all inhalation scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of these studies and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.3 Cancer assessment

There was adequate evidence to support a threshold-based mechanism to the thyroid follicular cell tumours in rats. The ADI and the selected reference values for occupational exposure provide sufficient margins to this tumour.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use product and mitigation measures

The acute hazard assessment indicated that VAYANTIS Seed Treatment is of low acute toxicity via the oral, dermal, and inhalation routes in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits, and was negative for skin sensitization when tested in mice using the local lymph node assay. Based on these acute hazards, a long-sleeved shirt, long pants, socks, shoes, and chemical-resistant gloves are required for workers during mixing, loading, application, clean-up and repair to protect from any acute health hazards of concern.

3.4.2 Occupational exposure and risk assessment

VAYANTIS Seed Treatment is a suspension-formulated product for commercial seed treatment of corn (field, pop, sweet and seed) and soybean in commercial facilities or by mobile treaters.

Workers have the potential for exposure to picarbutrazox while treating seeds in commercial seed treatment facilities or by using commercial mobile treaters, both equipped with a closed-transfer system, as well as during bagging, sewing and stacking bags of treated seeds, and during calibration, cleaning and repair of equipment. Potential exposure can also occur during handling and planting of treated seeds. Occupational exposure to picarbutrazox is expected to occur

predominantly via the dermal and inhalation routes for mixers, loaders, other seed treatment workers, and planters. Exposure duration is characterized as intermediate-term for commercial workers and short-term for planters.

3.4.2.1 Dust-off study

The submitted dust-off study was conducted to compare the dust-off potential of corn and soybean seed untreated or treated with VAYANTIS Seed Treatment, or treated with other seed treatment products, formulated as suspensions. A polymer was added in the slurry of the seed treatment formulations intended for corn seeds. Treated seed samples were measured using a Heubach dust measurement apparatus in grams of dust per 100 kilograms of seeds.

Based on the average dust-off levels measured in this study, the general trend for seed-type effect identified treated corn seeds as being dustier than treated soybean seeds, even when the slurry applied to corn seeds contained a dust-reducing coating polymer. Regarding the formulation effect, treatment with any of the products decreased the dust-off levels from soybean and corn seeds when compared to untreated seeds. Regarding the treatment effects, the dust-off levels for both soybean seeds and corn seeds, when treated with any product, were comparable. Although some limitations were noted, the submitted dust-off study was well conducted and scientifically acceptable.

Based on the submitted dust-off data generated with VAYANTIS Seed Treatment, the use of unit exposure estimates from the selected surrogate passive dosimetry exposure studies is not expected to underestimate occupational exposure of seed treatment workers and planters.

3.4.2.2 Commercial seed treatment exposure and risk assessment

VAYANTIS Seed Treatment can be used for the commercial treatment, including treatment by mobile treaters, of seeds of corn (field, pop, sweet and seed) and soybean.

As chemical-specific unit exposure data were not submitted for VAYANTIS Seed Treatment, surrogate passive dosimetry exposure studies owned by the Agricultural Handlers Exposure Task Force (AHETF), of which the applicant is a member and has full access to the data, were used to estimate the worker exposure.

The choice of the surrogate exposure study was based on results of the dust-off study, and also on various key factors influencing the exposure scenario, such as the formulation type, the seed type, the facility, the mixing/loading and treating equipment, the workers' tasks, the exposure duration, the personal protective equipment (PPE) and engineering controls, as well as the quality of the data, such as the number of replicates, the validation recoveries and the unit exposure results.

To assess the exposure from treating corn and soybean seeds, the AH806 2010 study is the most appropriate. The study was conducted in a commercial facility and separately monitored the treatment of corn and canola seeds. As such, the unit exposure estimates derived from the corn data, based on workers wearing a long-sleeved shirt, long pants and chemical-resistant gloves, were used in the risk assessments for corn and soybean seeds.

Based on the dust-off study results, corn seeds generally produce more dust than soybean seeds. In addition, the dust-off levels for both corn seeds and soybean seeds, when treated with any product, were comparable. Therefore, the use of corn data is not expected to underestimate exposure to workers treating corn or soybean seeds.

For treaters, baggers, sewers and stackers, daily dermal or inhalation exposure was calculated by coupling the dermal or inhalation unit exposure estimates with the amount of active ingredient handled per day obtained from the active ingredient application rate and the amount of seeds treated in a day (in other words, commercial throughput). For cleaners, the exposure estimates were calculated by coupling the dermal or inhalation unit exposure estimates with the active ingredient application rate. The daily dermal and inhalation exposures were normalized to mg/kg bw/day by using the default adult body weight. Dermal and inhalation exposures were not combined since the toxicology reference values are based on different toxicology effects. To assess health risks, exposure estimates were compared to the toxicology reference values presented in Section 3.4.1 to obtain the MOEs. The target MOE for both dermal and inhalation exposure was 100.

As presented in Appendix I, Table 6, the dermal and inhalation MOEs obtained are above the target MOE of 100. Hence, no health risks of concern are expected for commercial seed treatment workers and mobile treaters handling VAYANTIS Seed Treatment provided that they use closed-transfer equipment and wear the required PPE.

Taking into account both the acute toxicity of the end-use product and the risk assessment of picarbutrazox, workers are required to wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and shoes.

3.4.2.3 Exposure and risk assessment for planting seeds commercially treated with VAYANTIS Seed Treatment

Commercially treated seeds are either bagged or stored in bulk. During planting, workers load the treated seeds into a planter from bags or from bulk containers using an auger. As such, workers have the potential for exposure to VAYANTIS Seed Treatment while loading and planting treated seeds.

To assess the exposure scenarios of planting treated corn and soybean seeds, the PMRA selected the AH825 2007 surrogate exposure study, which is owned by the AHETF. This is a well conducted study with no major limitations. It monitored workers opening paper bags of treated corn seeds; manually loading them in the planter; unloading the remaining seeds; planting using a closed-cab tractor and performing small repairs. The use of unit exposure values from this

study is not expected to underestimate exposure to workers loading seeds from bulk containers since the exposure from this scenario is lower than the exposure from loading seeds from bags. Furthermore, as shown in the dust-off study, corn seeds are dustier than soybean seeds and the dust-off levels, when treated with any product, were comparable. Therefore, the use of corn data is not expected to underestimate exposure to workers planting corn or soybean seeds.

Daily dermal or inhalation exposure was estimated by coupling the dermal or inhalation unit exposure values from the AH825 2007 surrogate exposure study with the amount of active ingredient handled per day obtained from the active ingredient application rate and the amount of seeds planted in a day. The daily dermal and inhalation exposures were normalized to mg/kg bw/day by using the default adult body weight. Dermal and inhalation exposures were not combined since the toxicology reference values are based on different toxicology effects. To assess health risks, exposure estimates were compared to the toxicology reference values presented in Section 3.4.1 to obtain the MOEs. The target MOE for both dermal and inhalation exposure was 100.

As presented in Appendix I, Table 7, the dermal and inhalation MOEs obtained are well above the target MOE of 100. Hence, no health risks of concern are expected for planters of VAYANTIS Seed Treatment-treated seeds provided that they use the PPE and engineering controls recommended based on the surrogate exposure study. The unit exposure values derived from AH825 2007 study represented workers wearing a long-sleeved shirt, long pants and chemical-resistant gloves and using closed-cab planters. However, since the calculated MOEs are well above the target MOE of 100, the requirement of closed-cab planters can be waived.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

VAYANTIS Seed Treatment is not a domestic class product; therefore, a residential handler exposure assessment is not required.

3.4.3.2 Postapplication exposure and risk assessment

VAYANTIS Seed Treatment is not a domestic class product and is not for use in residential settings; therefore, a residential postapplication exposure assessment is not required.

3.4.4 Bystander exposure and risk assessment

Bystander exposure should be negligible since the product will be used in commercial seed treatment facilities or by mobile treaters and the likelihood for drift during the treatment of seeds is expected to be minimal. Therefore, bystander exposure and risk are not of health concern.

3.5 Dietary exposure and risk assessment

3.5.1 Residues in drinking water sources

Environmental concentrations of picarbutrazox in potential drinking water sources were estimated using numerical models for the human health risk assessment. Modelling was conducted using the Pesticides in Water Calculator (PWC) version 1.52, using standard PMRA scenarios which take into account regional weather and soil characteristics as well as relevant plant properties.

A subset of use patterns was considered for the modelling, which is intended to represent all labelled uses. The use-pattern selected for the modelling was for seed treatment at a rate of 2.725 g a.i./ha. Modelling inputs for drinking water estimated environmental concentrations (EECs) differ from environmental fate parameters given the residue definition (Table 3.5.1.1 Major fate input parameters for the drinking water modelling.1).

Table 3.5.1.1 Major fate input parameters for the drinking water modelling

Fate parameter	Value (drinking water)
Residues modelled	Picarbutrazox, TZ-1E, TZ-2, TZ-4, TT-3, TZ-5, and TY-2
Adsorption K_d (mL/g)	24.3 for picarbutrazox (20th percentile of 6 K_d values) 7.8 for TZ-2 (20th percentile of 7 K_d values) 0.004 for TT-3 (estimated by EPISuite)
Hydrolysis half-life at pH 7 and 20°C (days)	Stable (assumed)
Photolysis half-life in water at 35°N latitude (days)	4140 (with aqueous phototransformation products)
Aerobic soil biotransformation half-life at 20°C (days)	46 for picarbutrazox 30 for TZ-2 stable for TT-3
Aerobic aquatic biotransformation half-life at 20°C (days)	146 (the longer of two half-lives)
Anaerobic aquatic biotransformation half-life at 20°C (days)	526 (the longer of two half-lives)

For surface water, PWC calculates the amount of pesticide entering the water body by run-off and drift, and the subsequent degradation of the pesticide in the water system. 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. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1 meter of a water table. Estimated concentrations in drinking water sources are presented in Table 3.5.1.2.

Table 3.5.1.2 Level 1 EECs for the combined residue of picarbutrazox in potential sources of drinking water, expressed as picarbutrazox equivalent

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Overall[5]
Seed treatments, modelled as 1 application of 2.725 g a.i./ha per year	2.1	2.1	0.042	0.0086	0.0068

[1] 90th percentile of daily concentrations
[2] 90th percentile of 365-day moving average concentrations
[3] 90th percentile of the highest 1-day average concentration from each year
[4] 90th percentile of yearly average concentrations
[5] Average of all yearly average concentrations

3.5.2 Residues in plant and animal foodstuffs

The residue definition for enforcement in plant products, and enforcement and dietary exposure in animal commodities, is picarbutrazox. The residue definition in plant products for dietary exposure is picarbutrazox and the metabolite TZ-1E. Plant enforcement method, AOAC Official Method 2007.1, and plant and animal enforcement method, QuEChERS-multi residue method, are valid for the quantitation of picarbutrazox residues in crop and animal matrices. Residues of picarbutrazox and the metabolites TZ-1E, TZ-2-β-Glc, TZ-5 and TZ-5-Glc are stable when stored frozen at ≤-18°C in matrices from five crop categories, corn grain and radish (high-starch commodities), leaf lettuce (high-water commodity), dry pinto beans (high-protein commodity), oranges (high-acid commodity), canola seed (high-oil commodity) and wheat straw, for up to 13.4 months. Therefore, residues of picarbutrazox and the metabolites TZ-1E, TZ-2-β-Glc, TZ-5 and TZ-5-Glc are considered stable in all frozen crop matrices and processed crop fractions for up to 13.4 months. Residues of the tetrazole-derived metabolites TT-3 and TT-1 are stable when stored frozen at ≤-18°C in radish root and wheat grain (high-starch commodities), lettuce and radish tops (high-water commodities) and barley straw only, for up to 12 months. The raw agricultural commodities soybean seed and field corn grain were processed, but were not further analyzed due to the lack of quantifiable residues. Quantifiable residues are not expected to occur in animal matrices with the current use pattern. Crop field trials conducted throughout Canada and the United States using end-use products containing picarbutrazox at slightly exaggerated rates in or on soybean seed and corn (field, sweet and pop) seed are sufficient to support the proposed maximum residue limits.

3.5.3 Dietary risk assessment

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

3.5.3.1 Acute dietary exposure results and characterization

No appropriate toxicological reference value attributable to a single dose for the general population (including children and infants) was identified.

3.5.3.2 Chronic dietary exposure results and characterization

The following criteria were applied to the basic chronic (non-cancer and cancer) analysis for picarbutrazox: 100% crop treated, default processing factors (where available), and the proposed Canadian MRLs for all soybean, corn and animal commodities. The basic chronic dietary exposure from all supported picarbutrazox food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 3% of the ADI. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to picarbutrazox from food and drinking water is 0.8% (0.000153 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1–2 years of age at 3% (0.000595 mg/kg bw/day) of the ADI.

3.5.4 Maximum residue limits

Table 3.5.4.1 Recommended maximum residue limits

Commodity	Recommended MRL (ppm)
Dry soybeans; eggs; fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; field corn; milk; popcorn grain; sweet corn kernels plus cob with husks removed	0.01

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

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and chronic dietary risk estimates are summarized in Appendix I, Tables 1b, 8 and 9.

3.6 Aggregate 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). An endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies; therefore, an acute oral aggregate risk assessment is not required. The most relevant toxicology endpoint and assessment factor for the chronic oral aggregate exposure is the same as that selected for the ADI (see Section 3.2.2). Since residential exposure is not expected for picarbutrazox, the aggregate assessment consisted of combining food and drinking water exposure only, which was shown to be acceptable see Section 3.5.3.2).

3.7 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 picarbutrazox. Based on its chemical structure, picarbutrazox has been classified into the Fungicide Resistance Action Committee's Group U17: Tetrazolyloximes. Currently, picarbutrazox is the only member of that class. Outside of the liver and thyroid toxicity linked to hepatic drug-metabolizing enzyme induction, there is no known mammalian toxicity MOA. Overall, for the current evaluation, the PMRA did not identify information indicating that picarbutrazox shares a common mechanism of toxicity with other pest control products. Therefore, no cumulative health risk assessment is required at this time.

3.8 Health incident reports

Picarbutrazox is pending registration for use in Canada, and there are no incident reports in the PMRA database at this time.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Environmental fate properties of picarbutrazox and its transformation products are summarized in Appendix I, Table 10 and 11.

Terrestrial environment: In the terrestrial environment, picarbutrazox is moderately persistent in soil. In aerobic, anaerobic and irradiated laboratory soil studies, TZ-1E, the E-isomer of picarbutrazox, TZ-2, TZ-5 and TT-3 were observed as major transformation products in one or more of the studies. TZ-1E was only observed in the soil phototransformation study. Based on the structural similarity of TZ-1E to picarbutrazox and the results of ecotoxicity studies conducted with TZ-1E, this transformation product was considered toxicologically equivalent to picarbutrazox and was included in the environment modelling residue definition and, therefore, was included in degradation kinetics and carry-over calculations resulting in combined residue

fate parameters. Given that TZ-1E is not produced under non-irradiated laboratory conditions, under those conditions, it was not included in the calculation of fate parameters. Hydrolysis and aerobic biotransformation are anticipated to be the two most significant routes of dissipation (combined residue representative half-lives of 21.1 (pH 7) and 52.2 days, respectively). Phototransformation and anaerobic biotransformation are anticipated to contribute to a lesser degree (half-lives of 89 and 101.5 days, respectively) (Appendix I, Table 11).

Observations from the terrestrial field dissipation study indicated that the combined residue is moderately persistent under field conditions on bare ground plots (DT_{50} range: 55.6 to 105 days) and persistent under field conditions on turfgrass plots (DT_{50} range: 238 to 360 days). The dissipation times suggest that the combined residue may be persistent under field conditions and have the potential to be carried over to the following growing season. However, maximum carry over of the combined residue observed during field trials on bare ground and turf grass were 14.2 and 16.8% AR, respectively, and ranged between 3.8% and 16.8% for all sites in Canadian relevant eco-regions. As such, picarbutrazox is not anticipated to carry-over under field conditions.

Laboratory experiments show that picarbutrazox is immobile in most soils but may demonstrate low mobility in soils with low organic carbon content (K_{oc} values ranged between 1530 and 5849 L/kg). Observations from field dissipation studies indicate that picarbutrazox was confined to the top 30 cm layer. Considering all the information available in a leaching assessment, the PMRA concludes that picarburazox is not likely to reach groundwater. Based on the structural similarity of TZ-1E to picarbutrazox, this transformation product was considered to have the same K_{oc} range and mobility as picarbutrazox. Laboratory experiments conducted with TZ-2 show that this transformation product is more mobile than picarbutrazox (K_{oc} ranged from 426.7 to 5359 L/g). Observations from field dissipation studies however indicate that TZ-2 was also confined to the top 30 cm layer. Considering all the information available in a leaching assessment, the PMRA concludes that TZ-2 is not likely to reach groundwater. Fewer data were available to assess the leaching potential of the remaining major transformation products. K_{oc} values for these transformation products were estimated using Episuite software which suggest that the major soil transformation products TZ-5 and TT-3 may have high mobility in soil and therefore the potential to leach to groundwater. As a result, precautionary label statements will be required to inform users of the leaching potential.

Aquatic environment: In the aquatic environment, picarbutrazox is slightly persistent to moderately persistent. Laboratory studies show that hydrolysis, phototransformation and aerobic/anaerobic biotransformation contribute to the overall dissipation (Appendix I, Table 11). In laboratory studies, TZ-1E, TZ-2, TZ-3E, TZ-4, TZ-4-1, TZ-5, TY-2, TY-3, TY-4, TY-5, TY-6, TY-8, TY-9 (pH 9 only), TT-1 and TT-3 were observed as major transformation products. TZ-1E was only observed in phototransformation studies. Aquatic degradation kinetics were calculated based on the combined residue of picarbutrazox and the transformation product TZ-1E. Hydrolysis half-lives of the combined residue were 4.8, 21.1 and 24.3 days at pH 4, 7 and 9, respectively. Under irradiation, aquatic phototolysis half-lives of the combined residue were 3.0 days in distilled water, 3.8 days in natural water and 1.7 days in pH 9 buffer solution. In aerobic water/sediment systems, picarbutrazox partitioned to the sediment with water layer DT_{50}s of 10.5

to 10.9 days. For the total system, the combined residue was slightly to moderately persistent with total system DT_{50s} of 33.5 to 53.2 days. In anaerobic water/sediment systems, picarbutrazox also partitioned to the sediment with water layer DT_{50s} of 9.33 to 25.3 days. For the total system, the combined residue was slightly persistent with total system DT_{50s} of 20.9 to 31.7 days.

Air: Picarbutrazox has low solubility in water, low vapour pressure and low Henry's law constant. The intrinsic physico-chemical properties suggest that picarbutrazox is not likely to volatilize from moist soil or water surfaces under field conditions. Picarbutrazox, therefore, has a low potential for transport in the atmosphere.

Bioaccumulation: The log K_{ow} of 3.77 for picarbutrazox suggests a potential for bioaccumulation. However, results from a bioconcentration study conducted with rainbow trout showed a growth corrected, lipid-normalized kinetic bioconcentration factor of 314 for whole fish indicating that the potential for bioaccumulation is low. The depuration half-life of picarbutrazox from rainbow trout was 1.5 days. Picarbutrazox is therefore not expected to bioaccumulate.

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 EECs with concentrations at which adverse effects occur. 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. 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 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). A summary of endpoints for terrestrial and aquatic organisms is presented in Appendix I, Table 12 and 13, respectively.

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 exanple, direct application at a maximum cumulative application rate) and the most sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate effects metric, 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 arthropod test species). 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, further characterization of the risk is conducted by taking into consideration more realistic exposure scenarios and effects metrics. These consideration may include additional exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

The potential risk from the use of VAYANTIS Seed Treatment was assessed at the following application rates:

- Seed treatment: maximum seed treatment rate of 5.0 g a.i./100 kg seed for corn and 2.5 g a.i./100 kg seed for soybean. For non-target terrestrial and aquatic organisms, the most conservative EECs were determined based on the soybean rate which corresponds to 2.725g a.i./ha based on the planting of soybean seed. For birds and mammals, the highest exposure estimates resulted from the corn seed application rate.

The screening level risk assessment and further characterization of risk for picarbutrazox, its end-use product and transformation products are summarized in Appendix I, Table 15, Table 16, and Table 17 for seed treatment application.

4.2.1 Risks to terrestrial organisms

For the acute exposure risk assessment for terrestrial organisms, effects metrics used when calculating RQs include an uncertainty factor of 1/2 for terrestrial invertebrates and 1/10 for birds and mammals applied to an EC_{50} or LC_{50} and compared to an LOC of 1. For pollinators, the effects metric does not include an uncertainty factor and is compared to an LOC of 0.4. For the chronic exposure risk assessment, the effects metrics do not include an uncertainty factor. A summary of available terrestrial toxicity data for picarbutrazox, its formulated end-use product and its transformation products is presented in Appendix I, Table 12 Picarbutrazox is classified as practically nontoxic to bees, birds and mammals.

A summary of the effects metrics used in the risk assessment is presented in Appendix I, Table 14 The screening level risk assessment for picarbutrazox is presented in Appendix I, Table 15 and Table 16 for seed treatment.

In summary, when used according to the proposed label directions, risks associated with the use of picarbutrazox as a seed treatment are acceptable for the following terrestrial organisms:

- Earthworms
- Beneficial arthropods
- Pollinators
- Birds and mammals
- Terrestrial plants

Earthworms

Earthworms may be exposed to picarbutrazox through contact of residues in soil. The soil EEC of 0.0012 mg a.i./kg soil was calculated based on the proposed seed treatment rate of 2.5 g a.i./100 kg seed for soybean seed, a seeding rate of 109 kg soybean seed/ha and accounting for soil degradation using the 90^{th} upper percentile on the mean of the aerobic soil representative half-lives of 64 days. This concentration was calculated assuming that the product is evenly distributed in the top 0 to 15 cm depth of soil with a bulk density of 1.5 g/cm^3. EECs for

transformation products were calculated conservatively assuming that 100% of the applied picarbutrazox active ingredient was instantly transformed into the transformation product on a molecular weight/weight basis. Mortality and reproductive effects of picarbutrazox, TZ-1E, TZ-2 and TZ-5 on earthworms were determined in laboratory soil studies and the results were compared to the screening level soil EEC. The resulting RQ did not exceed the LOC, therefore, risks to earthworms from picarbutrazox and its transformation products TZ-1E, TZ-2 and TZ-5 are acceptable when label directions are followed.

Beneficial predatory and parasitic arthropods

Picarbutrazox is not expected to be present on plant and soil surfaces when used as a seed treatment, as such, exposure of surface dwelling beneficial arthropods to picarbutrazox is not anticipated from the proposed use pattern. The risks to surface dwelling beneficial arthropods from the use of picarbutrazox as a seed treatment are therefore acceptable when label directions are followed.

Soil dwelling predatory mites may be exposed to residues of picarbutrazox in soil resulting from treated seed. The soil EEC of 0.0012 mg a.i./kg soil for picarbutrazox, as described under the earthworm section, was used to assess risk to soil dwelling predatory mites. The reproductive effects of picarbutrazox, TZ-1E, TZ-2 and TZ-5 on the soil dwelling predatory mite, *Hypoaspis geolaelaps aculeifer*, were determined in laboratory soil studies and the results were compared to the screening level soil EEC of 0.0012 mg a.i./kg soil. The resulting RQs did not exceed the LOC. The chronic reproductive risks to soil dwelling beneficial predatory arthropods from the use of picarbutrazox as a seed treatment are acceptable when label directions are followed.

Pollinators

The primary route of exposure for pollinators from seed treatment products is through the diet via systemic transport of pesticide residues (including picarbutrazox and transformation products) from the seed into the pollen and nectar of the plant. Minimal systemic transport of picarbutrazox residues through the plant from treated seed is anticipated, therefore, exposure of pollinators is expected to be minimal. Pollinators can be exposed to pesticide residues in dust generated during the planting of treated seeds. Dust reduction best management practices and awareness is likely to reduce this exposure route. In addition, picarbutrazox is practically non-toxic to pollinators. When considering all the evidence, the acute and chronic risks to adult honeybees and honeybee larva from the use of picarbutrazox as a seed treatment are acceptable when label directions are followed.

Birds and mammals

Birds and mammals may be exposed to picarbutrazox residues by the consumption of treated seed. Screening level estimated daily exposures (EDEs) were calculated based on the proposed seed treatment rate of 5.0 g a.i./100 kg seed for corn seed and a seeding rate of 31.5 kg corn seed/ha. Corn seed was selected for the screening level risk assessment as treated corn seed resulted in higher exposure values to birds and mammals than treated soybean seed.

The EDE is calculated as follows

(FIR/BW) × EEC, where: FIR = Food Ingestion Rate and BW = Body weight

The screening level EDEs and RQ calculations for birds and mammals are presented in Appendix I, Table 16.

The RQs for birds and mammals resulting from both acute oral exposure and reproductive exposure did not exceed the LOC at the screening level. The risks to birds and mammals from the use of picarbutrazox as a seed treatment are acceptable when label directions are followed.

Non-target terrestrial plants

Non-target terrestrial plants are not anticipated to be exposed to picarbutrazox from the planting of treated seed. The risks to non-target terrestrial plants from the use of picarbutrazox as a seed treatment are acceptable when label directions are followed.

4.2.2 Risks to aquatic organisms

A risk assessment of picarbutrazox, the transformation products, TZ-1E, TZ-2, TZ-4, TZ-5, TY-3 and the end-use product VAYANTIS seed treatment was conducted for freshwater and marine aquatic organisms based on available toxicity data.

Table For the acute exposure risk assessment, effects metrics used when calculating RQs include an uncertainty factor of 1/2 for aquatic plants and invertebrates and 1/10 for fish and amphibians applied to an EC_{50} or LC_{50}. For the chronic exposure risk assessment, the effects metrics do not include an uncertainty factor. A summary of aquatic toxicity data for picarbutrazox, its formulated end-use product and its transformation products is presented in Appendix I, Table 13 Picarbutrazox is classified as highly toxic to freshwater invertebrates, freshwater fish, marine invertebrates and marine fish. Label statements are required to inform users of the potential toxicity to aquatic organisms.

A summary of the effects metrics used in the risk assessment are presented in Appendix I, Table 14. A summary of the results of the aquatic risk assessment are presented in Appendix I, Table 17.

The screening level risk from the use of picarbutrazox as a seed treatment was assessed based upon the maximum seed treatment rate of 2.5 g a.i./100 kg seed for soybean and a seeding rate of 109 kg soybean seed/ha. The maximum corresponding rate of active ingredient per hectare was determined to be 2.725g a.i./ha. The resulting EECs were calculated assuming that 100% of the active ingredient was instantaneously and completely introduced and mixed within the water body.

In summary, when used according to the proposed label directions, risks associated with picarbutrazox are acceptable for the following aquatic organisms:

- Freshwater vascular plants and algae, and marine algae
- Freshwater and marine invertebrates
- Freshwater and marine fish
- Amphibians

4.3 Environmental incident reports

Picarbutrazox is pending registration for use in Canada, and there are no incident reports in the PMRA database at this time.

5.0 Value

The registration of VAYANTIS Seed Treatment will provide Canadian growers with a unique fungicide mode of action to manage important diseases in corn and soybean while mitigating the risk of resistance development by causal pathogens to other fungicides that are registered to control the same diseases.

The efficacy of VAYANTIS Seed Treatment for control of seed rot/pre-emergence damping-off and post-emergence damping-off was assessed at multiple rates in 14 field and controlled environment studies conducted on field corn. Data for stand counts (number of plants/area) demonstrated that VAYANTIS Seed Treatment applied at 2.5–12.5 mL/100 kg seed can be expected to protect corn seed and seedlings from seed rot/pre-emergence damping-off and post-emergence damping-off caused by *Pythium* spp. It was determined that application of the lowest rate was most appropriate for fields with historically low levels of pre-emergence damping-off while 6.25 mL/100 kg seed rate was more effective on fields with known higher levels of damping-off. It was also demonstrated that VAYANTIS Seed Treatment applied at 12.5 mL/100 kg seed may improve stand count to a greater extent than lower rates under conditions favouring the development of post-emergence damping-off.

The efficacy of VAYANTIS Seed Treatment for control of seed rot/pre-emergence damping-off and post-emergence damping-off caused by *Pythium* spp. was assessed in three field and two controlled environment studies conducted on soybean. Stand count data demonstrated that VAYANTIS Seed Treatment applied at 2.5 to 6.25 mL/100 kg seed protected soybean seed rot/pre-emergence damping-off and post-emergence damping-off caused by *Pythium* spp. The higher rate is most appropriate for fields with historically higher levels of damping-off.

VAYANTIS Seed Treatment did not cause injury to either corn or soybean.

The data collectively support the efficacy claims summarized in Appendix I, Table 21 for VAYANTIS Seed Treatment.

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, picarbutrazox and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that picarbutrazox and its transformation products do not meet all of the TSMP Track 1 criteria. Please refer to Appendix I, Table 20 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.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations, including the Toxic Substances Management Policy[1] and Formulants Policy,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol).

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

6 SI/2005-114, last amended on June 25, 2008. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*

7 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

8 DIR2006-02, Formulants Policy and Implementation Guidance Document

7.0 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 Picarbutrazox Technical and VAYANTIS Seed Treatment, containing the technical grade active ingredient picarbutrazox, to control seed rot/pre-emergence damping-off and post-emergence damping-off in corn and soybean.

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

Additional information being requested

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

List of abbreviations

↑	increased
↓	decreased
♂	male
♀	female
µg	microgram(s)
µm	Micrometer
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
A:G	albumin/globulin ratio
AHETF	Agricultural Handler Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ARfD	acute reference dose
AST	aspartate aminotransferase
atm	atmosphere
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm	centimetres
CR	chemical-resistant
DF	dry flowable
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_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	Estimated Daily Exposure
EEC	Estimated Environmental Concentration
ER_{25}	effective rate for 25% of the population
F1	first generation
F2	second generation
fc	food consumption
fe	food efficiency
FIR	Food ingestion rate

FOB	functional observational battery
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GD	gestation day
GGT	gamma-glutamyl transpeptidase
GLP	good laboratory practices
ha	hectare(s)
HDT	highest dose tested
HDPE	high-density polyethylene
Hg	mercury
HPLC	high performance liquid chromatography
ICE	isolated chicken eye
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score
MIS	maximum irritation score
M/L	mixing and loading
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
No	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content

OM	organic matter content
P	parental generation
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
rel.	relative
RSD	relative standard deviation
S9	mammalian metabolic activation system
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TP	Transformation product
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TSH	thyroid stimulating hormone
UAN	urea ammonium nitrate
UDP-GT	uridine diphosphate glucuronyltransferase
UF	uncertainty factor
UV	ultraviolet
v/v	volume per volume dilution
wt	weight

Appendix I Tables and figures

Table 1a Residue analysis in environmental media

Matrix	Method type	Analyte	LOQ	Reference
Fish – edible and inedible tissue	HPLC-MS/MS	Parent, TZ-1E, TZ-2	0.024 mg/kg	PMRA# 2809362, 2809363
Soil	HPLC-MS/MS	Parent, TZ-1E, TZ-2	0.01 mg/kg	PMR # 2809344, 2809345
Sediment – artificial and natural	HPLC-MS/MS	Parent	0.05 mg/kg	PMRA# 2809346, 2809347
Water – surface	HPLC-MS/MS	Parent, TZ-1E	0.05 µg/L	PMRA# 2809358, 2809359, 2809360, 2809361
	HPLC-MS/MS	TZ-2	0.1 µg/L	PMRA# 2809358, 2809359, 2809360, 2809361
Water – fresh (well)	HPLC-MS/MS	Parent, TZ-1E	15 µg/L	PMRA# 2809502, 2809503
Water – salt	HPLC-MS/MS	Parent, TZ-1E	15 µg/L	PMRA# 2809502, 2809503
Water – laboratory well water	HPLC-MS/MS	TZ-2, TZ-4, TY-3, TZ-5	0.1 µg/L	PMRA# 2809474, 2809475, 2809476, 2809477, 2809478, 2809479, 2809480, 2809481
Water – fortified well water	HPLC-MS/MS	TZ-2, TZ-4, TY-3, TZ-5	0.1 µg/L	PMRA# 2809474, 2809475, 2809476, 2809477, 2809478, 2809479, 2809480, 2809481
Water – algal assay medium	HPLC-MS/MS	TZ-2, TZ-4, TY-3, TZ-5	0.1 µg/L	PMRA# 2809474, 2809475, 2809476, 2809477, 2809478, 2809479, 2809480, 2809481

Table 1b Residue analysis in plant and animal matrices

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ	Reference
Animal commodities					
ILV of Enforcement Method	Milk, egg, and bovine meat and liver	Picarbutrazox	QuEChERS-multiresidue method	0.01 ppm	PMRA# 2935712
Radiovalidation	Radiovalidation data were not provided. QuEChERS-multiresidue method uses similar extraction solvents (acetonitrile based) as those used in the livestock metabolism studies. In the metabolism studies, the majority of the radioactive residues in poultry liver, eggs, goat muscle, fat, kidney, liver and milk demonstrated good extractability (≥72%). Therefore, radiovalidation data are not required.				
Plant commodities					
Enforcement Method	Cucumber, orange, canola, corn grain, dry beans and wheat straw	Picarbutrazox and metabolites TZ-1E and TZ-5	AOAC Official Method 2007.1/ LC-MS/MS	0.005 ppm per analyte, all matrices	PMRA# 2808240
	Cucumber, orange and corn grain		QuEChERS-multiresidue method/ LC-MS/MS	0.005 ppm per analyte, all matrices	
Data-Gathering Method	Cucumber, corn grain, wheat straw, canola seed, radish root, dry pinto beans and orange fruit.	Picarbutrazox and metabolites TZ-1E, TZ-2-β-Glc, TZ-5, and TZ-5-Glc	Method 83966/ LC-MS/MS	0.005 ppm per analyte, all matrices	PMRA# 2808238

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ	Reference
ILV of Enforcement Method	Cucumber, orange, canola, corn grain, dry beans and wheat straw	Picarbutrazox and metabolites TZ-1E and TZ-5	AOAC Official Method 2007.1/ LC-MS/MS	0.005 ppm per analyte, all matrices	PMRA# 2808244
	Cucumber, orange and corn grain		QuEChERS-multiresidue method/ LC-MS/MS		
Radiovalidation	Residues of picarbutrazox and the metabolites in metabolism studies, analytical method 83966 and QuEChERS-multiresidue method were extracted using acetonitrile. AOAC Official Method 2007.1 also uses extraction solvents acetonitrile + 1% acetic acid. Extraction efficiencies from all crop matrices (lettuce, cucumber, corn forage), all labels (PH, PY and TTZ) in the metabolism studies were >80%. Therefore, radiovalidation data are not required.				

Table 2 Identification of select isomers and metabolites of picarbutrazox

Code	Chemical name
TZ-1E	*tert*-butyl (6-{[(*E*)-(1-methyl-1*H*-5-tetrazolyl)(phenyl)methylene]-aminooxymethyl}-2-pyridyl)carbamate
TZ-2	(*Z*)-*O*-[(6-amino-2-pyridyl)methyl](1-methyl-1*H*-5-tetrazolyl)(phenyl)methanone oxime
TZ-2E	(*E*)-*O*-[(6-amino-2-pyridyl)methyl](1-methyl-1*H*-5-tetrazolyl)(phenyl)methanone oxime
TY-2	(6-amino-2-pyridyl)methanol
TZ-4	(1-methyl-1*H*-5-tetrazolyl)(phenyl)methanone
TZ-5	(1-methyl-1*H*-5-tetrazolyl)(phenyl)methanol
TT-3K	Potassium 1-methyl-1-*H*-tetrazole-5-carboxylate
BPOH-NF-171	*tert*-butyl{6-[(6-{[(*Z*)-(1-methyl-1*H*-5-tetrazolyl) (phenyl)methylene]amino oxy}methyl-2-pyridyl) carbamoyloxy]methyl-2-pyridyl}carbamate
Me-NF-171	methyl N-[(6-{[(*Z*)-(1-methyl-1*H*-5-tetrazolyl) (phenyl)methylene]amino oxymethyl}-2-pyridyl)] carbamate

Table 3 Toxicity profile of technical picarbutrazox

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

Study type/animal/PMRA#	Study results
Toxicokinetic studies	
Absorption, distribution, toxicokinetics, metabolism and excretion study following single gavage doses (low and high) Sprague-Dawley rats PMRA# 2809304	Absorption, distribution, metabolism and excretion were investigated with [phenyl-U-^{14}C] labelled picarbutrazox. Single doses were administered by gavage at 1 or 100 mg/kg bw. Some rats were bile duct-cannulated to assess biliary excretion. **Absorption:** Absorption was higher at 1 mg/kg bw than at 100 mg/kg bw and bile was an important route of excretion. The total absorbed radiolabel was 86–91% of the administered dose (AD) at 1 mg/kg bw and 15–25% of the AD at 100 mg/kg bw. **Excretion:** Most of the radioactivity (>90%) was eliminated in urine and feces within 48 hours post-dosing. Excretion was mainly via the feces. Urinary excretion was slightly higher at 1 mg/kg bw than at 100 mg/kg bw. At 96 hours, urinary excretion in the 1 mg/kg bw group accounted for 11% and 9% of the AD and fecal excretion accounted for 82% and 84% of the AD in males and females, respectively. Recovered radiolabel in bile accounted for 77–80% of the AD for low dose and 14–23% of the AD for high dose. Overall excretion of radioactivity was rapid with >90% of the AD excreted during the first 48 hours for both sexes and both dose levels. **Kinetic Parameters:** Plasma and whole-blood sampling of animals showed the rate and extent of systemic exposure at 100 mg/kg bw increased in comparison to the 1 mg/kg bw group, but in a less than dose-proportionate manner consistent with the observed differences in absorption between dose levels. The whole blood to plasma ratios suggested a relatively even distribution of radioactivity between plasma and red blood cells. **Distribution:** In general, concentrations of radioactivity in the tissues were similar in males and females. Concentrations of radioactivity in tissues were highest in the liver for both sexes and dose levels. Overall, tissue retention was low with low or no detectable levels of the radioactivity retained in tissues at 96 hours post-dosing (<1% of the AD). In the 1 mg/kg bw group, peak

Study type/animal/PMRA#	Study results
	tissue concentrations generally occurred at 2 hours post-dosing and were higher in females than males. At 6 hours, tissue concentrations had generally declined, but were higher for males than females in the majority of tissues. At 2 hours, the highest concentrations of radioactivity (excluding gastrointestinal tract) were in the liver. At 6 hours in the 100 mg/kg bw group, the highest concentrations of radioactivity were in the liver, prostate, fat, and adrenal glands. Concentrations of radioactivity in tissues declined over time.
Study type/animal/PMRA#	**Study results**
	Metabolites: There were no major sex differences in the profile of radioactive components. Unchanged picarbutrazox accounted for a maximum of 78.3% of the 100 mg/kg bw dose (in the feces). Other components detected in the feces were TZ-7-3 (maximum of 25.4% of the AD), TZ-7 (maximum of 6.2% of the AD) and TZ-8-3/TZ-1-23 (maximum of 12.9% of the AD). Minor metabolites TZ-9 and TZ-2-3 accounted for no greater than 6.0% of the AD. The major metabolite in bile (maximum of 38.1% of the AD) was identified as an unstable glucuronide conjugate of TZ-7-3. One other major component was seen at a maximum of 10.4% of the AD in bile of females at the low dose level and was identified as an unstable conjugate of TZ-8-3/TZ-1-23 (intramolecular ester transition of TZ-1-23 to TZ-8-3 occurs readily). All other metabolites detected in bile accounted for no greater than 7.1% of the AD. In urine, the highest concentration metabolite was a glucuronide conjugate of TZ-3 (maximum of 5.2% of the AD). No other metabolite in urine accounted for greater than 5% of the dose. Unchanged picarbutrazox was not detected in urine or bile. The following compounds were identified: TZ-1-2, TZ-2-3, TZ-7, TZ-7-3, TZ-8-3/TZ-1-23, TZ-9 and TZ-3. At 2 hours after a single dose at 1 mg/kg bw, the major metabolites identified in plasma were TZ-7 and TZ-8-3/TZ-1-23. Most of the metabolites of picarbutrazox identified in excreta were also detected in tissues.
Absorption, distribution, toxicokinetics, metabolism and excretion study following single gavage doses (low) Sprague-Dawley rats	Absorption, distribution, metabolism and excretion were investigated with [pyridine-4-^{14}C] labelled picarbutrazox. A single oral dose of 1 mg/kg bw was administered by gavage. **Absorption and Excretion:** Most of the radioactivity (>90% of the AD) was eliminated in urine (9-12% of the AD) and feces (86–82% of the AD) within 48 hours post-dosing. Excretion was mainly via the feces. Total recovery was 96 and 95% of the AD for

Study type/animal/PMRA#	Study results
PMRA# 2809311	male and female groups, respectively. **Kinetic Parameters:** Plasma and whole-blood sampling of animals showed that the rate and extent of exposure was higher in females than in males. The whole blood to plasma ratios indicated similar concentrations of radioactivity in plasma and red blood cells. **Distribution:** In general, concentrations of radioactivity in tissues were similar in males and females. Concentrations of radioactivity in tissues were highest in the liver for both sexes. Overall tissue retention after single oral doses was low, with low or no detectable levels of the radioactivity retained in tissues at 96 hours post-dosing (<1% of the AD). **Metabolites:** There were no major sex differences in the profile of radioactive components. Unchanged picarbutrazox accounted for a maximum of 3.9% of the AD (in feces). Metabolites detected in the feces were TZ-7-3 (maximum of 25.3% of the AD), TZ-8-3 (maximum of 7.8% of the AD), TZ-2-3 (maximum of 2.2% of the AD), TZ-1-23 (maximum of 4.5% of the AD), TZ-7 (maximum of 4.9% of the AD), and TZ-9 (maximum of 4.4% of the AD) were also detected. In urine, the primary metabolite was TY-7 (maximum of 4.3% of the AD). No other metabolite in urine accounted for greater than 3% of the AD. Unchanged picarbutrazox was not detected in urine. Unidentified compounds represented approximately 6% and 21% of the AD in urine and feces, respectively. Metabolites identified were: TZ-2-3, TZ-7, TZ-7-3, TZ-1-23, TZ-8-3, TZ-9 in the feces and TZ-7-3, TZ-9 and TY-7 in the urine.
Acute toxicity studies	
Acute Oral Toxicity (gavage) Sprague-Dawley rats PMRA# 2809142	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low acute toxicity
Acute Dermal Toxicity Sprague-Dawley rats PMRA# 2809168	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low acute toxicity

Study type/animal/PMRA#	Study results
Acute Inhalation Toxicity Sprague-Dawley rats PMRA# 2809170	LC_{50} > 5.20 mg/L (♂/♀) Clinical signs at 5.20 mg/L included wet fur and test substance staining Low acute toxicity
Eye Irritation Japanese White rabbits PMRA# 2809175	MAS = 0.2/110, MIS = 5/110 at 1 hour Minimally irritating
Dermal Irritation Japanese White rabbits PMRA# 2809177	MAS = 0/8, MIS = 0/8 Non-irritating
Skin Sensitization, Maximization Method Hartley guinea pigs PMRA# 2809179	Negative
Short-term toxicity studies	
5-Day Inhalation Sprague-Dawley rats PMRA# 2809172	Supplemental – range-finding, non-guideline, non-GLP NOAEC and LOAEC not established Effects at and above 1.00 mg/L (261 mg/kg bw/day): ↑ liver wt and hepatocellular hypertrophy (♂/♀); ↑ thyroid follicular cell hypertrophy (♀) Effects at 5.2 mg/L (1364 mg/kg bw/day): Exposure-related breathing difficulties, ↑ thyroid/parathyroid wt, ↑ epithelial alteration at the tracheal bifurcation (♂/♀); ↑ centriacinar foamy alveolar macrophage accumulation (♂); ↓ bw first two days (♀)
28-Day Oral Toxicity (diet) CD-1 mice PMRA# 2809214	Supplemental – range-finding, non-GLP NOAEL and LOAEL not established Effects at and above 96/125 mg/kg bw/day: ↑ hepatocellular hypertrophy (♂/♀); ↑ hepatocellular cytoplasmic inclusion bodies, ↑ hepatocellular vacuolation, ↓ total protein, ↓ albumin and A:G ratio (♂) Effects at 1010/1233 mg/kg bw/day: ↑ ALT (♂/♀); ↑ liver wt, ↓

Study type/animal/PMRA#	Study results
	bilirubin, ↑ AST, ↑ prothrombin time (♂); ↓ rel. kidney wt, ↑ hepatocellular cytoplasmic inclusion bodies, ↑ eosinophil count, ↑ phosphorus (♀)
90-Day Oral Toxicity (diet) CD-1 mice PMRA# 2809200	NOAEL not established LOAEL = 25/33 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ hepatocellular fatty vacuolation (♂/♀)
28-Day Oral Toxicity (diet) Sprague-Dawley rats PMRA# 2809212	NOAEL = 15/16 mg/kg bw/day (♂/♀) LOAEL = 150/163 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ liver wt, thyroid wt, ↑ centrilobular hepatocellular hypertrophy, ↑ pituitary gland basophilic cell hypertrophy, ↑ thyroid follicular cell hypertrophy, ↑ prothrombin time, ↑ APTT (♂/♀)
90-Day Oral Toxicity (diet) Sprague-Dawley rats PMRA# 2809193	NOAEL = 10/12 mg/kg bw/day (♂/♀) LOAEL = 34/40 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ thyroid wt, ↑ liver wt, ↑ thyroid follicular cell hypertrophy, ↑ total protein, ↑ GGT, ↑ calcium, ↓ urine pH (♂/♀); ↑ APTT, ↑ cholesterol (♂); ↓ A:G ratio, ↑ platelet count, ↑ TSH (♀) No treatment-related FOB findings
90-Day Oral Toxicity (diet) Sprague-Dawley rats PMRA# 2809196	NOAEL = 12/14 mg/kg bw/day (♂/♀) LOAEL = not established/70 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ liver wt, ↑ thyroid wt, ↑ adrenal wt, ↑ peripheral fatty change in liver, ↑ centrilobular hepatocellular hypertrophy, ↑ thyroid follicular cell hypertrophy, ↑ hypertrophy of pituitary basophilic cells, ↑ fatty change in adrenal cortex, ↑ platelet count, ↑ fibrinogen concentration, ↑ prothrombin time, ↑ APTT, ↓ mean corpuscular hemoglobin, ↓ mean corpuscular volume, ↑ GGT, ↓ A:G ratio, ↑ total protein, ↑ urea nitrogen, ↑ calcium, ↓ bilirubin (♀) No treatment-related FOB findings
28-Day Dermal Toxicity Sprague-Dawley rats PMRA# 2809226	NOAEL = 1000 mg/kg bw/day (♂/♀)

Study type/animal/PMRA#	Study results
28-Day Oral Toxicity (diet) Beagle dogs PMRA# 2809223	Supplemental – range-finding NOAEL and LOAEL not established Effects at 742/581 mg/kg bw/day: ↓ bw, ↓ bwg (bw loss overall in high dose ♂ and all ♀ groups without dose-response), ↑ liver wt, ↑ hepatocellular hypertrophy (♂/♀); ↑ gallbladder wt without microscopic correlates (♂)
90-Day Oral Toxicity (diet) Beagle dogs PMRA# 2809208	NOAEL = 13/14 mg/kg bw/day (♂/♀) LOAEL = 133/130 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg (♂/♀)
1-Year Oral Toxicity (diet) Beagle dogs PMRA# 2809210	NOAEL = 40/43 mg/kg bw/day (♂/♀) LOAEL = 327/298 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ liver wt, ↑ gallbladder wt, ↑ hepatocellular hypertrophy, ↑ ALP, ↑ ALT, ↓ albumin (♂/♀)
Chronic Toxicity/Oncogenicity Studies	
18-Month Oral Toxicity (diet) CD-1 mice PMRA# 2809229	NOAEL = 3.4/23 mg/kg bw/day (♂/♀) LOAEL = 21/134 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ liver wt, ↑ hepatocellular hypertrophy, ↑ hepatocellular vacuolation (♂/♀); ↑ cytoplasmic inclusion bodies in liver (♂); ↑ portal inflammatory cell infiltration (♀) No evidence of tumourigenicity
2-Year Oral Toxicity with 1-Year Satellite Group (diet) Sprague-Dawley rats PMRA# 2809231	NOAEL = 2.3/3.0 mg/kg bw/day (♂/♀) LOAEL = 7.8/10 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ thyroid follicular cell hypertrophy, ↑ hepatocellular vacuolation, ↑ hepatocellular hypertrophy (♂/♀); ↑ thyroid wt, ↑ eosinophilic foci in liver (♂); ↑ cholesterol, ↓ triglycerides, ↑ cystic degeneration in liver (♀) Tumour incidences (in %) Thyroid follicular cell adenomas incidences (in %) at 0, 2.3, 7.8, and 27 mg/kg bw/day (♂) were 3, 5, 3, and 16; and at 0, 3.0, 10, and 35 mg/kg bw/day (♀) were 3, 3, 0, and 16 Evidence of tumourigenicity

Study type/animal/PMRA#	Study results
Developmental/Reproductive Toxicity Studies	
1-Generation Reproductive Toxicity (diet) Sprague-Dawley rats PMRA# 2809235	Supplemental – range-finding NOAEL and LOAEL not established Parental Effects at and above 12/15 mg/kg bw/day: ↑ hepatocellular hypertrophy (F1), ↑ thyroid follicular cell hypertrophy (F1) (♂/♀); ↑ thyroid wt (P), ↑ thyroid follicular cell hypertrophy (P), ↓ fc (F1) (♀) Effects at 45/58 mg/kg bw/day: ↑ liver wt, ↑ thyroid wt, ↑ hepatocellular hypertrophy (P) (♂/♀); ↓ fc, ↑ thyroid follicular cell hypertrophy (P) (♂) Reproductive No reproductive adverse effects observed Offspring No offspring adverse effects observed No evidence of sensitivity of the young
2-Generation Reproductive Toxicity (diet) Sprague-Dawley rats PMRA# 2809237	Parental NOAEL = 2.9/4.0 mg/kg bw/day (♂/♀) Parental LOAEL = 12/16 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ thyroid wt (F1), ↑ thyroid hypertrophy (♂/♀), ↑ TSH (P), ↑ kidney wt (F1♂), ↑ hepatocellular hypertrophy (F1♂), ↓ T4 (♀) Reproductive NOAEL = 46/63 mg/kg bw/day Reproductive LOAEL not established Offspring NOAEL = 16 mg/kg bw/day Offspring LOAEL = 63 mg/kg bw/day Effects at the LOAEL: ↓ bw PND 14 and 21 (F2), ↑ thyroid hypertrophy (F2), ↑ liver wt, ↑ pups with purple, black, and/or pale areas on the head, body, or tail (F1), ↓ spleen wt (F2♀) No evidence of sensitivity of the young

Study type/animal/PMRA#	Study results
Developmental Toxicity (gavage) Sprague-Dawley rats PMRA# 2809242	Supplemental – range-finding NOAEL and LOAEL not established No maternal or developmental adverse effects observed up to 1000 mg/kg bw/day
Developmental Toxicity (gavage) Sprague-Dawley rats PMRA# 2809244	Maternal NOAEL = 1000 mg/kg bw/day Maternal LOAEL not established No maternal adverse effects observed Developmental NOAEL = 1000 mg/kg bw/day Developmental LOAEL not established No developmental adverse effects observed No evidence of sensitivity of the young
Developmental Toxicity (gavage) New Zealand White rabbits PMRA# 2809246	Supplemental – range-finding NOAEL and LOAEL not established Effects at 300 mg/kg bw/day: ↓ bwg (GD 6-9 and 9-12), ↓ fc (GD 6-18) No developmental adverse effects observed up to 300 mg/kg bw/day
Developmental Toxicity (gavage) New Zealand White rabbits PMRA# 2809248	Maternal NOAEL = 500 mg/kg bw/day Maternal LOAEL = 1000 mg/kg bw/day Effects at the LOAEL: Thin appearance, bw loss (GD 6-9), ↓ bwg (corrected for gravid uterine wt) (GD 6-29), ↓ bw (GD 25-29), ↓ fc, ↑ rel. liver wt, scant feces Developmental NOAEL = 500 mg/kg bw/day Developmental LOAEL = 1000 mg/kg bw/day Effects at the LOAEL: ↑ mean number ribs and corresponding thoracic vertebrae related to ↓ mean number lumbar vertebrae No evidence of sensitivity of the young

Study type/animal/PMRA#	Study results
Genotoxicity Studies	
Bacterial reverse mutation assay S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA/pKM101 PMRA# 2809251	Negative ± metabolic activation Tested up to a limit concentration
Chromosome aberration Chinese hamster lung (CHL/IU) in vitro PMRA# 2809297	Negative ± metabolic activation Tested up to a cytotoxic concentration
Gene mutation Mouse lymphoma L5178Y cells in vitro PMRA# 2809289	Negative ± metabolic activation Tested up to a precipitating concentration
Micronucleus Mouse bone marrow in vivo ♂ CD-1 mice PMRA# 2809300	Negative No mortality or clinical signs of toxicity Tested up to a limit dose
Neurotoxicity studies	
Acute Neurotoxicity (gavage) Sprague-Dawley rats PMRA# 2809239	NOAEL = 2000 mg/kg bw (♂/♀) LOAEL not established No adverse effects were observed No evidence of neurotoxicity
Mechanistic studies	
Hepatic Drug-Metabolizing Enzyme Induction Study (diet) Sprague-Dawley rats (♂)	Supplemental – non-guideline NOAEL and LOAEL not established Effects at and above 5.6 mg/kg bw/day: ↑ gene amplification of UGT1A1 (7 days) Effects at and above 62 mg/kg bw/day: ↓ T3 (14 days), ↑ TSH (7

Study type/animal/PMRA#	Study results
Groups were 7 days, 14 days, or 14 days + 14 days of recovery PMRA# 2809313	days), ↑ hepatic microsomal protein (7 days, 14 days), ↑ UDP-GT activity (7 days), ↑ liver and thyroid wt (7 days), ↑ thyroid follicular cell hypertrophy (7 days, 14 days), ↑ hepatocellular hypertrophy (7 days, 14 days) Effects at 191 mg/kg bw/day: ↓ bwg day 1 (7 days), ↓ T3 (7 days), ↓T4 (7 days, 14 days), ↑ TSH (14 days) , ↑ liver and thyroid wt (14 days, 14+14 days), ↑ hypertrophy of basophilic cells in pituitary (7 days, 14 days) Recovery of effects was observed following cessation of treatment, though the liver and kidney weights had not completely returned to control levels
Thyroid Peroxidase Activity Wistar rat thyroid tissue in vitro PMRA# 2809315	Supplemental – non-guideline Negative for thyroid peroxidase activity inhibition
Metabolites and isomers	
Bacterial reverse mutation assay TZ-1E S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA/pKM101 PMRA# 2809256	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay TZ-2 S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA PMRA# 2809259	Negative ± metabolic activation Tested up to a limit concentration

Study type/animal/PMRA#	Study results
Bacterial reverse mutation assay TZ-2E S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA PMRA# 2809262	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay TY-2 S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA PMRA# 2809268	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay TZ-4 S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA/pKM101 PMRA# 2809272	Positive in TA1535 ± S9 Negative ± metabolic activation in other strains Tested up to a limit concentration
Bacterial reverse mutation assay TZ-5 S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA/pKM101 PMRA# 2809275	Negative ± metabolic activation Tested up to a limit concentration

Study type/animal/PMRA#	Study results
Bacterial reverse mutation assay BPOH-NF-171 S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA PMRA# 2809280	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay Me-NF-171 S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA PMRA# 2809283	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay TT-1 S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA PMRA# 3082017	Negative ± metabolic activation Tested up to a limit concentration
Bacterial reverse mutation assay TT-3K S. typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strains WP2uvrA PMRA# 3082007	Negative ± metabolic activation Tested up to a limit concentration

Study type/animal/PMRA#	Study results
Micronucleus Mouse bone marrow in vivo ♂ CD-1 mice PMRA# 2809302	Negative No mortality or clinical signs of toxicity Tested up to a limit dose
Acute Oral Toxicity (gavage) Fixed dose method TZ-1E ♀ Sprague-Dawley rats PMRA# 2809144	LD_{50} > 2000 mg/kg bw (♀) Low toxicity
Acute Oral Toxicity (gavage) Fixed dose method TZ-2 ♀ Sprague-Dawley rats PMRA# 2809146	LD_{50} between 300 and 2000 mg/kg bw (♀) Moderate toxicity (low overall when combined with PMRA# 2809148)
Acute Oral Toxicity (gavage) Toxic class method TZ-2 ♀ Sprague-Dawley rats PMRA# 2809148	LD_{50} > 2000 mg/kg bw (♀) Low toxicity
Acute Oral Toxicity (gavage) Toxic class method TZ-2E ♀ Sprague-Dawley rats PMRA# 2809150	LD_{50} > 2000 mg/kg bw (♀) Low toxicity

Study type/animal/PMRA#	Study results
Acute Oral Toxicity (gavage) Toxic class method TZ-4 ♀ Sprague-Dawley rats PMRA# 2809155	LD_{50} > 2000 mg/kg bw (♀) Low toxicity
Acute Oral Toxicity (gavage) Toxic class method TZ-5 ♀ Sprague-Dawley rats PMRA# 2809160	LD_{50} between 300 and 2000 mg/kg bw (♀) Two mortalities out of three tested at 2000 mg/kg bw, none at 300 mg/kg bw Moderate toxicity
Acute Oral Toxicity (gavage) Toxic class TY-2 ♀ Sprague-Dawley rats PMRA# 2809162	LD_{50} between 300 and 2000 mg/kg bw (♀) Three mortalities out of three tested at 2000 mg/kg bw, none at 300 mg/kg bw Moderate toxicity
Acute Oral Toxicity (gavage) Toxic class method BPOH-NF-171 ♀ Sprague-Dawley rats PMRA# 2809164	LD_{50} > 2000 mg/kg bw (♀) Low toxicity
Acute Oral Toxicity (gavage) Toxic class method Me-NF-171 ♀ Sprague-Dawley rats PMRA# 2809166	LD_{50} > 2000 mg/kg bw (♀) Low toxicity

Study type/animal/PMRA#	Study results
Acute Oral Toxicity (gavage) Toxic class method TT-1 ♀ Sprague-Dawley rats PMRA# 3082012	LD_{50} > 2000 mg/kg bw (♀) Low toxicity
Acute Oral Toxicity (gavage) Toxic class method TT-3K ♀ Sprague-Dawley rats PMRA# 3082006	LD_{50} > 2000 mg/kg bw (♀) Low toxicity
90-Day Oral Toxicity (diet) TZ-1E Sprague-Dawley rats PMRA# 2809203	NOAEL = 34/39 mg/kg bw/day (♂/♀) LOAEL = 68/77 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ hepatocellular hypertrophy, ↑ liver wt, ↑ potassium (♂); ↓ bw, ↓ bwg, ↑ abs liver wt, ↑ T3, ↑ T4, ↑ cholesterol, ↓ A:G ratio (♀) No treatment-related FOB findings
28-Day Oral Toxicity (diet, ♂/♀) and 29- or 79-Day Oral Toxicity (diet, lower dose levels than 28-day study, ♂ only, histopathology was limited to kidneys) TZ-5 Sprague-Dawley rats PMRA# 2809220	Supplemental – range-finding, non-GLP NOAEL and LOAEL not established Effects at and above 74/85 mg/kg bw/day (28-day study): ↑ cellular infiltration and granular casts in the outer stripe of the outer medulla of the kidneys (♂), ↑ basophilic tubules and tubular dilatation in kidney (♂), ↑ rel. kidney wt (♂) Effects at and above 212/240 mg/kg bw/day (28-day study): ↑ rel. liver wt, ↑ centrilobular hepatocellular hypertrophy (♂/♀); ↓ bw, ↓ bwg, ↓ fc, ↓ fe, ↑ blood urea nitrogen, ↑ platelet count, ↓ reticulocyte count and ratio (♂) Effects at 723/829 mg/kg bw/day (28-day study): ↑ abs liver wt, ↑ thyroid follicular cell hypertrophy, ↑ total protein, ↓ GGT (♂/♀); ↑ rel. thyroid wt, ↑ rel. adrenal wt, ↑ vacuolation in adrenal, ↑ total cholesterol, ↓ bilirubin, ↑ α2u-globulin (♂); ↓ bw, ↓ bwg, ↓ fc, ↓ fe (♀)

Study type/animal/PMRA#	Study results
	Effects at and above 2 mg/kg bw/day (29-day study): ↑ eosinophilic bodies in kidneys, related to α2u-globulin (♂) Effects at and above 23 mg/kg bw/day (29-day study): ↑ basophilic tubules and tubular dilatation in kidneys (♂) Effects at 74 mg/kg bw/day (29-day study): ↑ pale kidney (♂), ↑ granular casts in kidneys (♂) Effects at and above 24 mg/kg bw/day (28-day study): ↑ eosinophilic bodies in kidneys (♂) Effects at and above 2 mg/kg bw/day (79-day study): ↑ eosinophilic bodies in kidneys, related to α2u-globulin (♂) Effects at and above 6 mg/kg bw/day (79-day study): ↑ basophilic tubules in kidneys (♂) Effects at and above 19 mg/kg bw/day (79-day-study): ↑ cellular infiltration and granular casts in the outer stripe of the outer medulla of the kidneys (♂) Effects at 62 mg/kg bw/day (79-day study): ↑ pale kidney (♂)
90-Day Oral Toxicity (diet) TZ-5 Sprague-Dawley rats PMRA# 2809206	NOAEL = 36/46 mg/kg bw/day (♂/♀) LOAEL = 122/154 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ degeneration and hyperplasia of olfactory epithelium (♂/♀); ↓ A:G ratio, ↓ glucose, ↑ blood urea nitrogen, ↑ GGT, ↓ urinary pH (♂); ↓ bwg, ↑ hepatocellular hypertrophy, ↑ rel. kidney wt (♀) No treatment-related FOB findings
28-Day Oral Toxicity (diet) TT-3K Sprague-Dawley rats PMRA# 3082014	NOAEL = 1754/1805 mg/kg bw/day (♂/♀) LOAEL not established

Study type/animal/PMRA#	Study results
90-Day Oral Toxicity (diet) TT-3K Sprague-Dawley rats PMRA# 3082015	NOAEL = 1263/283 mg/kg bw/day (♂/♀) LOAEL not established/1433 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg (♀)

Table 4 Toxicity profile of the end-use product VAYANTIS Seed Treatment, containing picarbutrazox

Study type/animal/PMRA #	Study results
Acute Oral Toxicity (gavage) Wistar rats PMRA# 2808534	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low acute toxicity
Acute Dermal Toxicity Wistar rats PMRA# 2808536	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low acute toxicity
Acute Inhalation Toxicity Wistar rats PMRA# 2808538	LC_{50} > 3.04 mg/L (♂/♀) Clinical signs at 3.04 mg/L included red-brown fur staining, slight laboured and/or noisy respiration, and slightly ↓ activity Low acute toxicity
Eye Irritation NZW rabbits PMRA# 2808540	MAS = 2/110, MIS = 11/110 at 1 hour Minimally irritating
Eye Irritation Isolated chicken eyes PMRA# 2808542	ICE Class I Minimally irritating

Study type/animal/PMRA #	Study results
Dermal Irritation NZW rabbits PMRA# 2808544	MAS = 0/8, MIS = 0/8 Non-irritating
Skin Sensitization, Local Lymph Node Assay CBA/Ca mice PMRA# 2808547	Negative

Table 5 Toxicology reference values for use in health risk assessment for picarbutrazox

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Not required as an endpoint of concern attributable to a single exposure was only identified at the limit dose in the oral toxicity studies		
Repeated (chronic) dietary	2-year dietary toxicity in the rat	NOAEL = 2.3 mg/kg bw/day Liver and thyroid effects	100
	ADI = 0.02 mg/kg bw/day		
Short and intermediate-term dermal	28-day dermal toxicity in the rat	NOAEL = 1000 mg/kg bw/day No adverse effects	100
Short-term inhalation[2]	28-day oral toxicity in the rat	NOAEL = 15 mg/kg bw/day Liver, thyroid, and pituitary gland effects	100
Intermediate-term inhalation[2]	2-generation reproductive toxicity in the rat	Parental NOAEL = 2.9 mg/kg bw/day Thyroid effects	100
Aggregate	Due to the absence of residential uses, potential aggregation involves food and drinking water exposure only. Use of the ADI in this scenario is appropriate.		
Cancer	Cancer risk (threshold) was addressed through the selected toxicology reference values.		

[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, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 Exposure and risk estimates for commercial workers treating corn and soybean seeds with VAYANTIS Seed Treatment

Tasks	Unit Exposure [1]			Rate (g a.i./ 100 kg seed)	Commercial Throughput[2] (kg seed/day)	Daily Exposure (mg/kg bw/ day)[3,4]		Calculated MOE	
	Dermal	Inhalation	Units			Dermal	Inhalation	Dermal[5]	Inhalation[6]
Corn seeds – using corn unit exposures from the AH806 2010 study; PPE[7]: single layer + CR gloves; closed M/L									
Treaters	256	3.72	µg/kg a.i. handled	5	125 000	2.00×10^{-2}	2.91×10^{-4}	50 000	9980
Baggers/ sewers/ stackers	238	18.7	µg/kg a.i. handled	5	125 000	1.86×10^{-2}	1.46×10^{-3}	53 800	1990
Cleaners	127	24.1	µg/g a.i./ 100 kg seeds	5	N/A	7.94×10^{-3}	1.51×10^{-3}	126 000	1930
Soybean seeds – using corn unit exposures from the AH806 2010 study; PPE: single layer + CR gloves; closed M/L									
Treaters	256	3.72	µg/kg a.i. handled	2.5	63 000	5.04×10^{-3}	7.32×10^{-5}	198 000	39600
Baggers/ sewers/ stackers	238	18.7	µg/kg a.i. handled	2.5	63 000	4.69×10^{-3}	3.68×10^{-4}	213 000	7880
Cleaners	127	24.1	µg/g a.i./ 100 kg seed	2.5	N/A	3.97×10^{-3}	7.53×10^{-4}	252 000	3850

[1] Dermal and inhalation unit exposure values (arithmetic means) are from the specified surrogate exposure study (AH806 2010). Unit exposure values for mixers/loaders and baggers/sewers/stackers are in µg/kg a.i. handled, while unit exposure values for cleaners are in µg/g a.i./100 kg seeds.
[2] Commercial throughput values are from the PMRA's memo "Commercial Seed Treatment Throughput Values".
[3] For mixers/loaders and baggers/sewers/stackers: dermal/inhalation daily exposure (mg/kg bw/day) = [dermal/inhalation unit exposure (µg/kg a.i. handled) × Rate (g a.i./100 kg seed) ÷ 100 × Commercial Throughput (kg seed/day)] / [80 kg bw × 1000 µg/mg].
[4] For cleaners: dermal/inhalation daily exposure (mg/kg bw/day) = [dermal/inhalation unit exposure (µg/g a.i. /100 kg seed) × application rate in g a.i./100 kg seed] / [80 kg bw × 1000 µg/mg].
[5] Based on the short- to intermediate-term dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 100.
[6] Based on the intermediate-term oral NOAEL of 2.9 mg/kg bw/day and a target MOE of 100.
[7] PPE: personal protective equipment; CR: chemical-resistant; M/L: mixing and loading.

Table 7 Exposure and risk estimates for workers handling and planting corn and soybean seeds treated with VAYANTIS Seed Treatment

Crop	Unit Exposure[1] (µg/kg ai handled)		Rate (g a.i./ 100 kg seed)	Seed Planted[2] (kg seed/day)	Daily Exposure (mg/kg bw/ day)[3]		Calculated MOE	
	Dermal	Inhalation			Dermal	Inhalation	Dermal[4]	Inhalation[5]
Using corn unit exposures from the AH825 2007 study (bagged seeds); PPE[6]: Single layer + CR gloves; closed-cab[7]								
Corn	1515	82.83	5	1350	1.28×10^{-3}	6.99×10^{-5}	782000	215000
Soybean	1515	82.83	2.5	9000	4.26×10^{-3}	2.33×10^{-4}	235000	64400

[1] Dermal and inhalation unit exposure values (arithmetic means) are from the specified surrogate exposure study (AH825 2007).
[2] The amounts of seed planted per day (kg seed/day) are from the PMRA's 'Seed Treated Planted Per Day-2018' table.
[3] Dermal/inhalation daily exposure (mg/kg bw/day) = [dermal/inhalation unit exposure (µg/kg a.i. handled) × Rate (g a.i./100 kg seed) ÷ 100 × Seed Planted (kg seed/day)] / [80 kg bw × 1000 µg/mg].
[4] Based on the short- to intermediate-term dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 100.
[5] Based on the short-term oral NOAEL of 15 mg/kg bw/day and a target MOE of 100.
[6] PPE: personal protective equipment; CR: chemical-resistant
[7] Since the calculated MOEs are well above the target MOE of 100, the requirement of closed-cab planters can be waived.

Table 8 Integrated food residue chemistry summary

NATURE OF THE RESIDUE IN LAYING HEN		PMRA # 2809320
Species and Numbers	6 laying hens (White Star)	
Radiolabel position	[Phenyl-U-^{14}C]-picarbutrazox (specific activity: 3.02 MBq/mg [81.62 µCi/mg]) [Pyridine-4-^{14}C]-picarbutrazox (specific activity: 3.01 MBq/mg [81.35 µCi/mg])	
Average dose	[Phenyl-U-^{14}C]-picarbutrazox: 12.635 mg/kg corresponding to 0.858 mg picarbutrazox equivalents/kg body weight. [Pyridine-4-^{14}C]-picarbutrazox: 11.018 mg/kg corresponding to 0.793 mg picarbutrazox equivalents/kg body weight. **Equivalent to 1102–1263× the calculated dietary burden for poultry.**	
Treatment Regimen	Orally by gelatin capsule once daily	
Study period	14 consecutive days	
Collection time	Eggs: twice a day (morning and evening); Excreta: once a day	
Tissues collected	Liver, fat, skin with fat, muscle, gastrointestinal (GI) tract and its contents, blood, carcass and bile.	
Interval from last dose to sacrifice	11 hours	
Plateau of residues in eggs	The TRR in egg yolk reached a plateau of approximately 0.009 mg/kg (phenyl) and 0.020 mg/kg (pyridine) after 7 days and 9 days (168 – 216 hours) dosing, respectively.	
Extraction solvents	acetonitrile:water (4:1 – 1:1, v/v) ± hexane	

Matrices	**Phenyl-^{14}C-label**		**Pyridine-^{14}C-label**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Excreta	--	100	--	93.7
Cage Wash	--	5.3	--	4.2
GI Tract and Contents	--	<0.1	--	<0.1
Pooled Egg Yolk (Day 8–14)	0.011	<0.1	0.014	<0.1
Pooled Egg White (mean of Day 8–14)	0.009	<0.1	0.021	<0.1
Liver	0.040	<0.1	0.034	<0.1
Fat	0.002-0.004	<0.1	0.004–0.005	<0.1
Muscle	0.001	<0.1	<0.001–0.002	<0.1

Summary of Major Identified Metabolites in Hen Matrices	
Radiolabel Position	**[Phenyl-^{14}C], [Pyridine-^{14}C]**
Metabolites Identified	Major Metabolites
Liver	TZ-9
Egg yolks	TZ-9 TZ-7
Egg whites	TZ-9 TZ-7

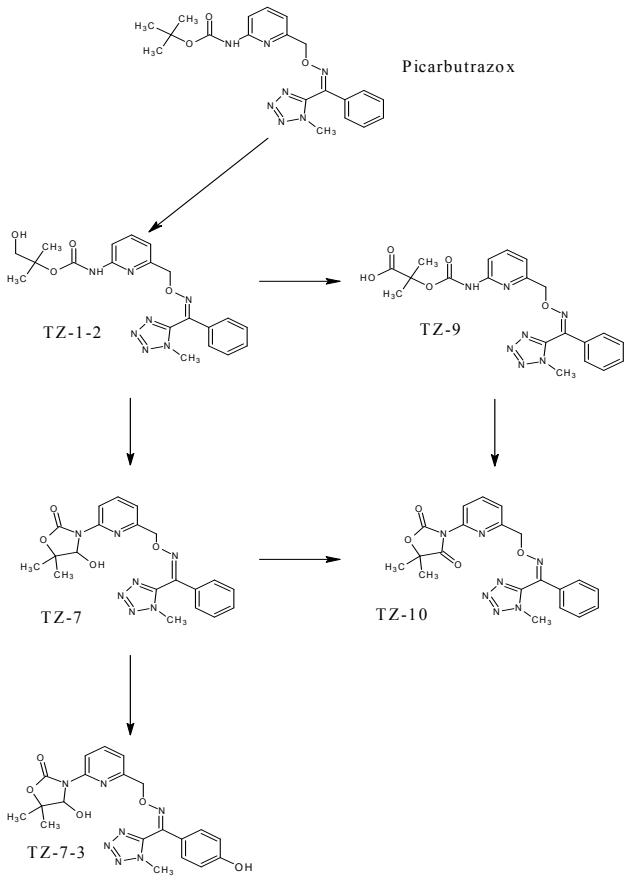
Nature Of The Residue In Lactating Goat	**PMRA# 2809322**
Species and Numbers	2 lactating goats (one per label) (Toggenburg)
Radiolabel position	[Phenyl-U-^{14}C]-picarbutrazox (specific activity: 3.02 MBq/mg [81.62 µCi/mg]) [Pyridine-4-^{14}C]-picarbutrazox (specific activity: 3.01 MBq/mg [81.35 µCi/mg])
Average dose	[Phenyl-U-^{14}C]-picarbutrazox: 20.322 mg/kg corresponding to 0.858 mg picarbutrazox equivalents/kg body weight. [Pyridine-4-^{14}C]-picarbutrazox: 22.580 mg/kg corresponding to 0.793 mg picarbutrazox equivalents/kg body weight. **Equivalent to ~1016–1129× the calculated dietary burden for dairy cattle.**
Treatment Regimen	Orally by gelatin capsule once daily
Study period	7 consecutive days
Collection time	Milk: twice a day (morning and evening); Excreta: once a day
Tissues collected	Liver, kidney, fat, muscle, gastrointestinal (GI) tract and its contents, and bile
Interval from last dose to sacrifice	12 hours
Plateau of residues in milk	The TRR in milk reached a plateau at the end of dosing: 0.1% of the TRR (both labels; 0.019 ppm).
Extraction solvents	acetonitrile: water (4:1-1:1, v/v) ± hexane

Matrices	**Phenyl-^{14}C-label**		**Pyridine-^{14}C-label**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Urine	--	11.8	--	8.0
Feces	--	56.8	--	67.8
Cage Wash	--	1.3	--	2.7
GI Tract & Contents	--	15.1	--	10.2
Milk (120 hour sample)	0.280	0.3	0.018	0.1
Liver	0.280	0.3	0.619	0.5

Kidney	0.090	<0.1	0.118	<0.1
Fat	0.086	<0.03	0.123	<0.4
Muscle	0.013	<0.02	0.033	<0.02

Summary of Major Identified Metabolites in Goat Matrices	
Radiolabel Position	**[^{14}C-Phenol], [^{14}C-Pyidine]**
Metabolites Identified	**Major Metabolites**
Muscle	Picarbutrazox TZ-1-2 TZ-7
Fat	Picarbutrazox TZ-7
Kidney	TZ-9
Liver	TZ-7 TZ-9 TZ-10
Milk	TZ-9

Proposed Metabolic Scheme in Livestock



FREEZER STORAGE STABILITY IN ANIMAL MATRICES
Freezer storage stability data was not required as livestock feeding studies were not submitted or required in support of the current petition.

LIVESTOCK FEEDING – Dairy cattle

A feeding study was not required based on the low dietary burden. Therefore, the goat metabolism study was used to estimate the anticipated residues in the relevant livestock matrices.

Matrices	Residue Definition	Dietary Burden (ppm)	Anticipated Residues (ppm)
Dairy/Beef Cattle			
Whole milk	Picarbutrazox	0.010	0
Fat			0
Liver			0
Kidney			0
Muscle			0
Swine			
Fat	Picarbutrazox	0.006	0
Liver			0
Kidney			0
Muscle			0

LIVESTOCK FEEDING – Laying hens

A feeding study was not required based on the low dietary burden. Therefore, the poultry metabolism study was used to estimate the anticipated residues in the relevant livestock matrices.

Matrices	Residue Definition	Dietary Burden (ppm)	Anticipated Residues (ppm)
Eggs	Picarbutrazox	0.006	0
Fat			0
Liver			0
Muscle			0

NATURE OF THE RESIDUE IN LETTUCE - Phenyl and Pyridinyl labels	PMRA # 2809324
Radiolabel Position	[Phenyl-U-^{14}C]-picarbutrazox (specific activity: 3.02 MBq/mg) [Pyridine-4-^{14}C]-picarbutrazox (specific activity: 3.01 MBq/mg)
Treatment	
Test Site	Lettuce plants were grown in a greenhouse setting in 5m^2 plot boxes.
Treatment	Three broadcast foliar applications performed with a 5-day retreatment interval at BBCH 44, 45 and 46 at 108–113 g a.i./ha.
Total Rate	328–338 g a.i./ha
Formulation	Suspension concentrate (SC) formulation: 10% picarbutrazox.

Harvest	Samples of lettuce leaves were harvested just prior to the second application and at 2, 7 and 14 days after the third application.		
Extraction solvents	Acetonitrile:water (1:1, v/v) and acetonitrile		
Matrices	**PHI (days)**	**[^{14}C- Phenyl] TRR (ppm)**	**[^{14}C- Pyridine] TRR (ppm)**
Harvest 1 – leaves	Prior to 2nd application	1.484	1.001
Harvest 2 – leaves	2	2.835	4.084
Harvest 3 – leaves	7	3.075	3.091
Harvest 4 – leaves	14	2.471	1.634
SUMMARY OF MAJOR IDENTIFIED METABOLITES IN PLANT MATRICES – Lettuce			
Radiolabel Position	**[^{14}C- Phenyl], [^{14}C- Pyridine]**		
Metabolites Identified	**Major Metabolites**		
Harvest 1	Picarbutrazox		
Harvest 2	Picarbutrazox		
Harvest 3	Picarbutrazox		
Harvest 4	Picarbutrazox		
NATURE OF THE RESIDUE IN LETTUCE – Tetrazole label		**PMRA # 3082003**	
Radiolabel Position	[Tetrazole-5-^{14}C]-picarbutrazox (specific activity: 17.64 MBq/ml)		
Treatment			
Test Site	Lettuce plants grown from seed were cultivated in a glass greenhouse under controlled environmental conditions.		
Treatment	Three foliar treatments, at 7-day intervals, 7, 14 and 21 days before the first sampling at rates equivalent to 100.67-105.93 g a.i./ha. Applications to lettuce seedlings were initiated approximately 5 days post-transplant.		
Total Rate	300 g a.i./ha		
Formulation	Not indicated in the study.		
Harvest	Lettuce leaves were collected 7 and 14 days after the final spray application.		
Extraction solvents	Acetonitrile: water (1:1; v/v) and acetonitrile		
Matrices	**PHI (days)**	**[^{14}C- Tetrazole] TRR (ppm)**	
Harvest 1 – leaves	7	5.9389	
Harvest 2 – leaves	14	1.9793	
SUMMARY OF MAJOR IDENTIFIED METABOLITES IN LETTUCE			
Radiolabel Position	**[^{14}C- Tetrazole]**		
Metabolites Identified	**Major Metabolites**		
Harvest 1 - 7-day PHI	Picarbutrazox TZ-1E		
Harvest 2 - 14-day PHI	Picarbutrazox TZ-1E		

NATURE OF THE RESIDUE IN CUCUMBER – Phenyl and Pyridinyl labels			**PMRA# 2809326**
Radiolabel Position	[Phenyl-U-^{14}C]-picarbutrazox (specific activity: 3.02 MBq/mg) [Pyridine-4-^{14}C]-picarbutrazox (specific activity: 3.01 MBq/mg)		
Treatment			
Test Site	Cucumber plants were grown outdoor in 1m^2 wooden box plots.		
Treatment	Three broadcast foliar applications performed with a 5-day retreatment interval at BBCH 69–70, 72 and 73 at 95–119 g a.i./ha.		
Total Rate	326-330 g a.i./ha		
Formulation	SC formulation: 10% picarbutrazox.		
Harvest	Samples of cucumber fruit were harvested just prior to the second application and at 0 and 14 days after the third application.		
Extraction solvents	Acetonitrile:water (1:1, v/v) and acetonitrile.		
Matrices	**PHI (days)**	**TRR (ppm)**	
		[^{14}C- Phenyl]	**[^{14}C- Pyridine]**
Harvest 1 – cucumber	Prior to 2nd application	0.004	0.001
Harvest 2 – cucumber	0	0.001	NA
Harvest 3 – cucumber	10	0.021	0.008

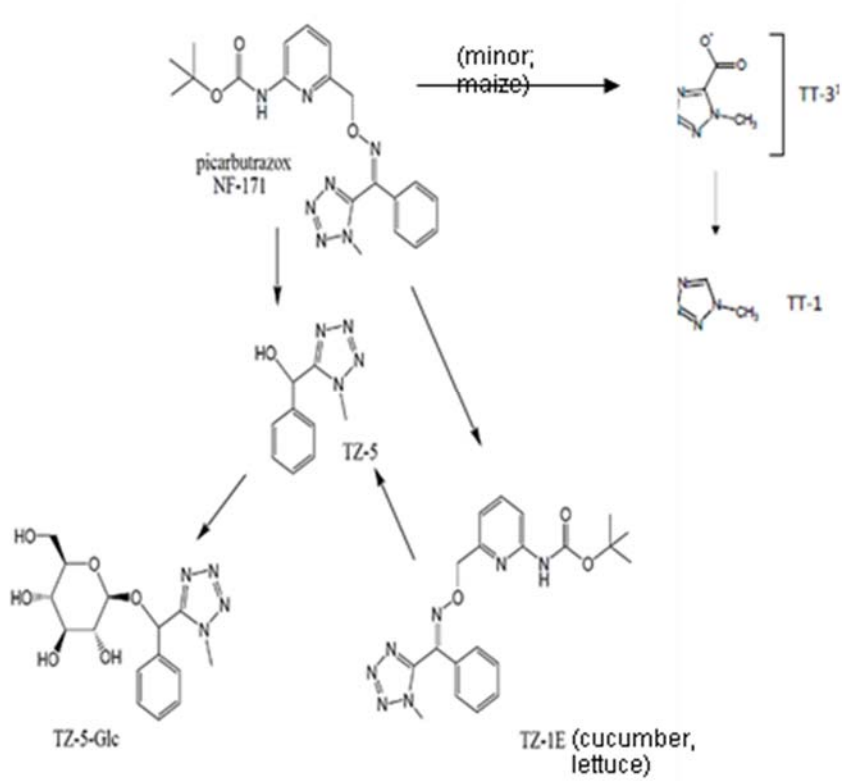
SUMMARY OF MAJOR IDENTIFIED METABOLITES IN CUCUMBER	
Radiolabel Position	**[^{14}C- Phenyl], [^{14}C- Pyridine]**
	Major Metabolites
Harvest 1 – prior to 2nd application	Picarbutrazox TZ-1E
Harvest 2 - 0-day PHI	Picarbutrazox TZ-1E
Harvest 2 - 10-day PHI	Picarbutrazox TZ-1E TZ-5

NATURE OF THE RESIDUE IN CUCUMBER – Tetrazole label		**PMRA # 3082002**
Radiolabel Position	[Tetrazole-5-^{14}C]-picarbutrazox (specific activity: 17.64 MBq/ml)	
Treatment		
Test Site	Treated plants were cultivated in a glass greenhouse under controlled environmental conditions.	
Treatment	Cucumber plants grown in pots from seed received three foliar treatments, at 7-day intervals, 1, 8 and 15 days before the first sampling at rates equivalent to 99.05-102.93 g a.i./ha.	
Total Rate	300 g a.i./ha	
Formulation	Not indicated in the study.	

Harvest		Fruit and leaf samples were collected 1, 7 and 14 days after the final spray application; however, only the fruit samples were further analysed.	
Extraction solvents		Acetonitrile: water (1:1; v/v) and acetonitrile	
Matrices	**PHI (days)**	**[^{14}C- Tetrazole]**	
		TRR (ppm)	
Harvest 1 - cucumber	1	0.1457	
Harvest 2 - cucumber	8	0.0258	
Harvest 3 - cucumber	15	0.0145	
SUMMARY OF MAJOR IDENTIFIED METABOLITES IN LETTUCE			
Radiolabel Position		**[^{14}C- Tetrazole]**	
Metabolites Identified		**Major Metabolites**	
Harvest 1 - 1-day PHI		Picarbutrazox	
Harvest 2 - 8-day PHI		Picarbutrazox TZ-1E	
Harvest 2 - 15-day PHI		Picarbutrazox TZ-1E	
NATURE OF THE RESIDUE IN CORN – Phenyl and Pyridinyl labels			**PMRA # 2809329**
Radiolabel Position		[Phenyl-U-^{14}C]-picarbutrazox (specific activity: 3.02 MBq/mg) [Pyridine-4-^{14}C]-picarbutrazox (specific activity: 3.01 MBq/mg)	
Treatment			
Test Site		Corn seeds were grown to maturity in a glasshouse setting.	
Treatment		Seed treatment	
Total Rate		17.8 g a.i./100 kg seed or 18.6 g a.i./100 kg seed for the phenyl and pyridine label, respectively.	
Formulation		Not indicated.	
Harvest		Samples of corn forage were harvested at 35-day PHI (BBCH 14), immature corn stalks (stover), cobs and grain samples were harvested at 152-day PHI (BBCH 79) and mature corn stalks (stover), cobs and grain samples were harvested at 168-day PHI (BBCH 89).	
Extraction solvents		Acetonitrile:water (1:1 and 8:2 v/v)	
Matrices	**PHI (days)**	**[^{14}C- Phenyl]**	**[^{14}C- Pyridine]**
		TRR (ppm)	**TRR (ppm)**
Forage	35	0.007	0.003
Immature stalks	152	0.002	0.001
Immature cobs	152	<LOD	<LOD
Immature grain	152	<LOD	<LOD

Mature stalks	168	0.003	0.001
Mature cobs	168	0.001	<LOD
Mature grain	168	0.001	0.001
SUMMARY OF MAJOR IDENTIFIED METABOLITES IN CORN			
Radiolabel Position		**[^{14}C- Phenyl], [^{14}C- Pyridine]**	
Metabolites Identified		**Major Metabolites**	
Forage		TZ-5 TZ-5-Glc	
NATURE OF THE RESIDUE IN CORN – Tetrazole label			**PMRA # 3082031**
Radiolabel Position		[Tetrazole-5-^{14}C]-picarbutrazox (specific activity: 5.2 MBq/ml)	
Treatment			
Test Site		The seeds were sown in sandy loam soil in pots and plants were grown to maturity in a glasshouse under controlled environmental conditions.	
Treatment		Seeds treated with [tetrazole-^{14}C]-picarbutrazox at a rate of 23.3 g a.i./100 kg seed.	
Formulation		Not indicated in the study.	
Harvest		Forage was harvested 28 days after emergence, 35 days after the seed treatment (in other words, a 35-day preharvest interval [PHI]) at growth stage BBCH 32. Immature stalks, cobs and grain were harvested at growth stages BBCH 75-77, at a 98-day PHI, and mature stover, cobs and grain were harvested at BBCH 89, at a PHI of 131 days.	
Extraction solvents		Acetonitrile:water combinations.	
Matrices	**PHI (days)**	**[^{14}C- Tetrazole]**	
		TRR (ppm)	
Forage	35	0.002	
Immature stalks	98	0.001	
Immature cobs	98	<0.001	
Immature grain	98	0.001	
Mature stover	131	0.003	
Mature cobs	131	0.001	
Mature grain	131	0.001	
SUMMARY OF MAJOR IDENTIFIED METABOLITES IN LETTUCE			
Radiolabel Position		**[^{14}C- Tetrazole]**	
Metabolites Identified		**Major Metabolites**	
Forage		TZ-5	

Proposed Metabolic Scheme in Plants



FREEZER STORAGE STABILITY IN PLANT MATRICES			**PMRA# 2808246 and 3082016**	
Tested Matrices	**Analytes**	**Tested Intervals (months)**	**Demonstrated Stability & Temperature (°C)**	**Category**
Corn grain; radish root	Picarbutrazox and the metabolites TZ-1E, TZ-2-β-Glc, TZ-5 and TZ-5-Glc	0, 1, 3, 6, 9, 12 and 13.4-14 months	14 months at -20°C	High-starch
Leaf lettuce			13.4 months at -20°C	High-water
Dry pinto beans			13.4 months at -20°C	High-protein
Orange fruit			13.4 months at -20°C	High-acid
Canola seed			13.5 months at -20°C	High-oil
Wheat straw			12.2 months at ≤-18ºC	Dry commodities
Radish root; wheat grain	Tetrazole-derived metabolites TT-1	0, 1, 3, 6, and ~12 months	12.0–12.2 months at ≤-18ºC	High-starch

Lettuce; radish tops	and TT-3		12.4 months at ≤-18ºC	High-water
Barley straw		0, 1, 3, 6, and 12.4 months	14 months at -20°C	Dry commodities

The freezer storage stability data indicate that residues of picarbutrazox and the metabolites TZ-1E, TZ-2-β-Glc, TZ-5 and TZ-5-Glc are stable at -20°C for 13.4 months in the five OECD crop commodity categories. Therefore, these residues are stable in all crops and processed commodities for up to 13.4 months in frozen storage.

The freezer storage stability data for the tetrazole-derived metabolites indicate that TT-1 and TT-3 are stable at ≤-18ºC for 12.0 months in high-starch (radish root and wheat grain), high-water (lettuce and radish tops) and dry commodities (barley straw) in frozen storage.

CROP FIELD TRIALS AND RESIDUE DECLINE ON SOYBEAN **PMRA# 2809334**

Field trials were conducted in 2015–2016 in Canada and the United States. Trials were conducted in growing Regions 2 (2 trials), 4 (3 trials), and 5 (16 trials) for a total of 21 trials. Picarbutrazox FS, a flowable suspension containing 400 g a.i./L, was applied to soybean seeds.

Commodity	Total Application Rate (g a.i./100 kg seed)	PHI (days)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Forage	8.932–12.986	19–55	Picarbutrazox	21	<0.005	<0.005	0.005	0.005	0
Hay		46–73		21	<0.005	<0.005	0.005	0.005	0
Seed		92–154		21	<0.005	<0.005	0.005	0.005	0

n = number of independent trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON CORN (FIELD, SWEET AND POPCORN) **PMRA # 2809336**

Field trials were conducted in 2015–2016 in Canada and the United States. Three popcorn trials were conducted in the Growing Regions 5 (2 trials) and 8 (1 trial). Five sweet corn trials were conducted in Growing Regions 1 (1 trial), 3 (1 trial), 10 (1 trial), 11 (1 trial), and 12 (1 trial). Nineteen field corn trials were conducted in Growing Regions 1 (1 trial), 2 (1 trial), 5 (16 trials), and 6 (1 trial). Picarbutrazox FS (A20597B), a flowable suspension containing 400 g a.i./L, was applied to field corn, sweet corn and popcorn seeds.

Commodity	Total Application Rate (g a.i./100 kg seed)	PHI (days)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Sweet Corn (including Simulated Sweet Corn)									
Forage	8.932–12.986	71–95	Picarbutrazox	21	<0.005	<0.005	0.005	0.005	0
Hay		91–110		21	<0.005	<0.005	0.005	0.005	0
Seed		60–90		21	<0.005	<0.005	0.005	0.005	0
Field Corn									
Forage	8.9–11.9	84–140	Picarbutrazox	19	<0.005	<0.005	0.005	0.005	0
Grain		118–154		19	<0.005	<0.005	0.005	0.005	0
Stover				19	<0.005	<0.005	0.005	0.005	0

Popcorn									
Grain	10.7–11.1	127–147	Picarbutrazox	3	<0.005	<0.005	0.005	0.005	0
Stover				3	<0.005	<0.005	0.005	0.005	0

PROCESSED FOOD AND FEED - SOYBEANS	**PMRA# 3164948**
Processing studies were conducted in 2 growing regions using Picarbutrazox FS (A20597B; guarantee: 400 g a.i./L/flowable suspension) at 29.420 & 30.237 g a.i./100 kg seed (~12-fold of proposed maximum seed treatment use rate) in/on soybean seed. Adequate storage stability data are available on diverse crop types to support the storage intervals of the samples. Samples were analyzed using a validated analytical method. Picarbutrazox residues were all <LOQ (<0.005 ppm) in bulk soybean seed. As such, no processing was initiated.	

PROCESSED FOOD AND FEED – FIELD CORN	**PMRA# 2809336**
Processing studies were conducted in 2 growing regions using Picarbutrazox FS (A20597B; guarantee: 400 g a.i./L/flowable suspension) at 27.967-38.818 g a.i./100 kg seed (~5.6-7.8-fold of proposed maximum seed treatment use rate) in/on corn seed. Adequate storage stability data are available on diverse crop types to support the storage intervals of the samples. Samples were analyzed using a validated analytical method. Picarbutrazox residues were all <LOQ (<0.005 ppm) in bulk field corn seed. As such, no processing was initiated.	

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, radish and wheat	**PMRA# 2808252**
Radiolabel Position	[Phenyl-U-^{14}C]-picarbutrazox (specific activity: 3.02 MBq/mg) [Pyridine-4-^{14}C]-picarbutrazox (specific activity: 3.01 MBq/mg)
Treatment	
Test Site	All plants were grown outdoors in above ground wooden boxes.
Soil Type	Sandy loam
Treatment	Bare soil was treated at a rate of 1033 g a.i./ha. Lettuce, radish and wheat were planted at PBIs of 30, 120 and 275 days.
Formulation	10% suspension concentrate (SC)
Extraction solvents	Acetonitrile:water (1:1, v/v) and acetonitrile

Matrices	**PBI (days)**	**[^{14}C-Phenyl] TRR (ppm)**	**[^{14}C-Pyridine] TRR (ppm)**
Immature lettuce	30	0.349	0.037
	120	0.090	0.040
	275	0.067	0.012
Mature lettuce	30	0.173	0.036
	120	0.069	0.025
	275	0.049	0.008
Radish tops	30	0.989	0.089
	120	0.063	0.008
	275	0.051	0.017
Radish roots	30	0.157	0.144
	120	0.033	0.035
	275	0.016	0.017

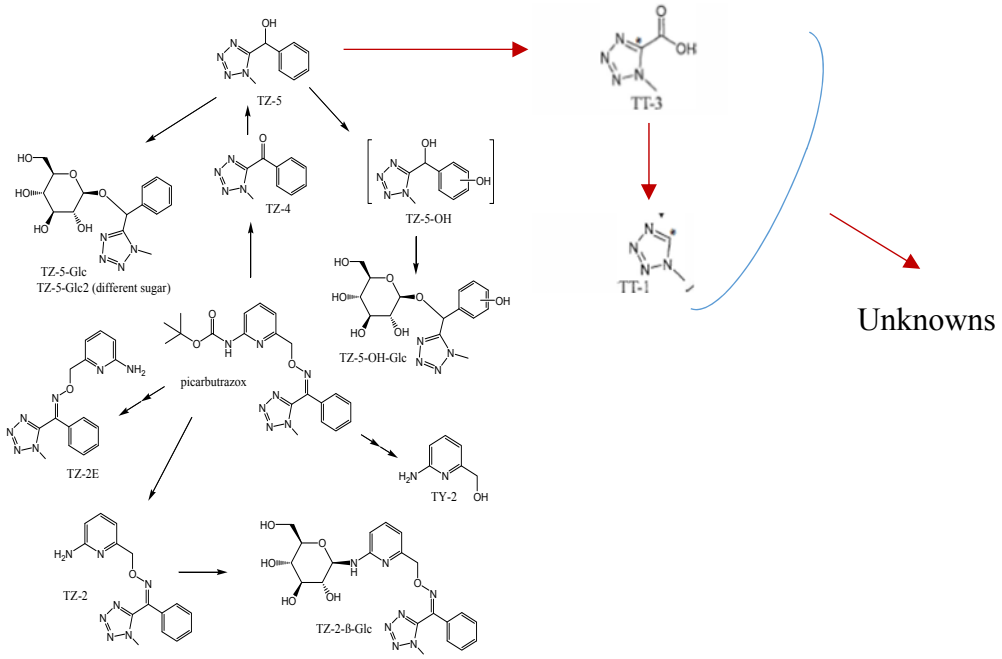
Wheat forage	30	1.019	0.210
	120	0.251	0.027
	275	0.051	0.027
Wheat hay	30	1.750	0.735
	120	0.273	0.091
	275	0.203	0.062
Wheat straw	30	1.646	0.838
	120	0.523	0.129
	275	0.377	0.088
Wheat grain	30	0.070	0.039
	120	0.045	0.028
	275	0.036	0.022

Summary of Major Identified Metabolites in Rotated Crops			
Plant-back Intervals (PBI)	**1st Rotation (30-day PBI)**	**2nd Rotation (120-day PBI)**	**3rd Rotation (375-day PBI)**
Radiolabel Position	**[^{14}C-Phenyl], [^{14}C-Pyridine]**		
Metabolites Identified	**Major Metabolites**		
Immature lettuce	TZ-5 TZ-5-Glc TZ-5-Glc2 TZ-2-β-Glc	TZ-5 TZ-5-Glc	TZ-5 TZ-5-Glc TZ-5-Glc2
Mature lettuce	TZ-5 TZ-5-Glc TZ-5-Glc2	TZ-5 TZ-5-Glc TZ-5-Glc2	TZ-5 TZ-5-Glc TZ-5-Glc2
Radish tops	TZ-5 TZ-5-Glc TZ-2-β-Glc	TZ-5	TZ-5
Radish roots	None	TZ-5	None
Wheat forage	TZ-5 TZ-5-Glc TZ-2-β-Glc	TZ-5 TZ-5-Glc	TZ-5 TZ-5-Glc
Wheat hay	TZ-5 TZ-5-Glc TZ-2-β-Glc	TZ-5 TZ-5-Glc	TZ-5 TZ-5-Glc
Wheat straw	TZ-5 TZ-5-Glc	TZ-5	TZ-5 TZ-5-Glc
Wheat grain	TZ-5	None	None
CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, radish and wheat			**PMRA# 3082004**
Radiolabel Position	[Tetrazole-5-^{14}C]picarbutrazox (specific activity 1.98-2.23 MBq/mg)		
Treatment			
Test Site	Rotational crops were grown outdoors in wooden boxes (1 m^2).		
Soil Type	Sandy loam		

Treatment	Bare soil was treated at a rate of 1.023–1.118 kg a.i./ha. Lettuce, radish and wheat were planted at PBIs of 30, 120 and 275 days.		
Formulation	10% suspension concentrate (SC)		
Extraction solvents	Acetonitrile:water (1:1, v/v) and acetonitrile		
Matrices	**PBI (days)**	**[^{14}C-Tetrazole] TRR (ppm)**	
Immature lettuce	30	1.021	
	120	0.776	
	275	0.198	
Mature lettuce	30	0.549	
	120	0.613	
	275	0.107	
Radish tops	30	0.711	
	120	0.489	
	275	0.255	
Radish roots	30	0.555	
	120	0.375	
	275	0.313	
Wheat forage	30	2.738	
	120	1.762	
	275	0.693	
Wheat hay	30	5.073	
	120	4.299	
	275	3.240	
Wheat straw	30	5.165	
	120	3.501	
	275	1.524	
Wheat grain	30	2.376	
	120	2.097	
	275	1.262	
Summary of Major Identified Metabolites in Rotated Crops			
Plant-back Intervals (PBI)	**1st Rotation (30 day PBI)**	**2nd Rotation (120 day PBI)**	**3rd Rotation (375 day PBI)**
Radiolabel Position	**[^{14}C-Tetrazole]**		
Metabolites Identified	**Major Metabolites**		
Immature lettuce	TT-3	TT-3	TT-1 TT-3
Mature lettuce	TT-3	TT-3	TT-3
Radish tops	TT-3 TZ-5 UKC	TT-3 UKA	TT-3 UKA
Radish roots	TT-3	TT-3 UKA	TT-3 UKA RT20.5

Wheat forage	TT-3	TT-3 UKA	TT-3 UKA
Wheat hay	TT-1 TT-3	TT-3 UKA RT39.5-39.8	TT-1
Wheat straw	TT-1 TT-3	TT-1 TT-3 UKA RT39.2-39.8	TT-1 TT-3 UKA RT39.2-39.8
Wheat grain	TT-3 UKA	TT-1 TT-3 UKA	TT-3 UKA RT21.8

Proposed Metabolic Scheme in Rotational Crops



RESIDUE DATA IN ROTATIONAL CROPS	**PMRA # 2808254**

Eighteen trials (six each for radish, lettuce and wheat) were conducted during the 2015 and 2016 growing seasons in growing regions 1, 2, 10 and 11. One broadcast application was made to bare soil with NF-171 10 SC at a rate of 0.272–0.307 g a.i./ha. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.

Commodity	Total Application Rate (kg a.i./ha)	PBI (days)	Residue Levels (ppm picarbutrazox equivalents)					
			n	LAFT	HAFT	Median	Mean	SDEV
Picarbutrazox								
Lettuce leaves	0.272-0.303	28	2	<0.005	<0.005	0.005	0.005	NA
		115–119	2	<0.005	<0.005	0.005	0.005	NA
		357–364	2	<0.005	<0.005	0.005	0.005	NA
Radish tops	0.279-0.307	28	2	<0.005	<0.005	0.005	0.005	NA
		115–119	2	<0.005	<0.005	0.005	0.005	NA
		357–364	2	<0.005	<0.005	0.005	0.005	NA
Radish roots		28	2	<0.005	<0.005	0.005	0.005	NA
		115–119	2	<0.005	<0.005	0.005	0.005	NA
		357–364	2	<0.005	<0.005	0.005	0.005	NA
Wheat forage	0.273–0.305	28	2	<0.005	<0.005	0.005	0.005	NA
		115–119	2	<0.005	<0.005	0.005	0.005	NA
		357–364	2	<0.005	<0.005	0.005	0.005	NA
Wheat hay		28	2	<0.005	<0.005	0.005	0.005	NA
		115–119	2	<0.005	<0.005	0.005	0.005	NA
		357–364	2	<0.005	<0.005	0.005	0.005	NA
Wheat Straw		28	2	<0.005	<0.005	0.005	0.005	NA
		115–119	2	<0.005	<0.005	0.005	0.005	NA
		357–364	2	<0.005	<0.005	0.005	0.005	NA
Wheat Grain		28	2	<0.005	<0.005	0.005	0.005	NA
		115–119	2	<0.005	<0.005	0.005	0.005	NA
		357–364	2	<0.005	<0.005	0.005	0.005	NA

TZ-2-β-Glc								
Lettuce leaves	0.272-0.303	28	2	<0.004	<0.004	0.004	0.004	NA
		115–119	2	<0.004	<0.004	0.004	0.004	NA
		357–364	2	<0.004	<0.004	0.004	0.004	NA
Radish tops	0.279-0.307	28	2	<0.004	<0.004	0.004	0.004	NA
		115–119	2	<0.004	<0.004	0.004	0.004	NA
		357–364	2	<0.004	<0.004	0.004	0.004	NA
Radish roots		28	2	<0.004	<0.004	0.004	0.004	NA
		115–119	2	<0.004	<0.004	0.004	0.004	NA
		357–364	2	<0.004	<0.004	0.004	0.004	NA
Wheat forage	0.273–0.305	28	2	<0.004	<0.004	0.004	0.004	NA
		115–119	2	<0.004	<0.004	0.004	0.004	NA
		357–364	2	<0.004	<0.004	0.004	0.004	NA
Wheat hay		28	2	<0.004	<0.004	0.004	0.004	NA
		115–119	2	<0.004	<0.004	0.004	0.004	NA
		357–364	2	<0.004	<0.004	0.004	0.004	NA
Wheat Straw		28	2	<0.004	<0.004	0.004	0.004	NA
		115–119	2	<0.004	<0.004	0.004	0.004	NA
		357–364	2	<0.004	<0.004	0.004	0.004	NA
Wheat Grain		28	2	<0.004	<0.004	0.004	0.004	NA
		115–119	2	<0.004	<0.004	0.004	0.004	NA
		357–364	2	<0.004	<0.004	0.004	0.004	NA
TZ-5								
Lettuce leaves	0.272–0.303	28	2	<0.011	<0.011	0.011	0.011	NA
		115–119	2	<0.011	<0.011	0.011	0.011	NA
		357–364	2	<0.011	<0.011	0.011	0.011	NA

Radish tops	0.279–0.307	28	2	<0.011	<0.011	0.011	0.011	NA
		115–119	2	<0.011	<0.011	0.011	0.011	NA
		357–364	2	<0.011	<0.011	0.011	0.011	NA
Radish roots		28	2	<0.011	<0.011	0.011	0.011	NA
		115–119	2	<0.011	<0.011	0.011	0.011	NA
		357–364	2	<0.011	<0.011	0.011	0.011	NA
Wheat forage	0.273–0.305	28	2	<0.011	<0.011	0.011	0.011	NA
		115–119	2	<0.011	<0.011	0.011	0.011	NA
		357–364	2	<0.011	<0.011	0.011	0.011	NA
Wheat hay		28	2	<0.011	<0.011	0.011	0.011	NA
		115–119	2	<0.011	<0.011	0.011	0.011	NA
		357–364	2	<0.011	<0.011	0.011	0.011	NA
Wheat Straw		28	2	<0.011	<0.011	0.011	0.011	NA
		115–119	2	<0.011	<0.011	0.011	0.011	NA
		357–364	2	<0.011	<0.011	0.011	0.011	NA
Wheat Grain		28	2	<0.011	<0.011	0.011	0.011	NA
		115–119	2	<0.011	<0.011	0.011	0.011	NA
		357–364	2	<0.011	<0.011	0.011	0.011	NA
TZ-5-Glc								
Lettuce leaves	0.272-0.303	28	2	<0.006	<0.006	0.006	0.006	NA
		115–119	2	<0.006	<0.006	0.006	0.006	NA
		357–364	2	<0.006	<0.006	0.006	0.006	NA
Radish tops	0.279-0.307	28	2	<0.006	<0.006	0.006	0.006	NA
		115–119	2	<0.006	<0.006	0.006	0.006	NA
		357–364	2	<0.006	<0.006	0.006	0.006	NA

Radish roots		28	2	<0.006	<0.006	0.006	0.006	NA
		115–119	2	<0.006	<0.006	0.006	0.006	NA
		357–364	2	<0.006	<0.006	0.006	0.006	NA
Wheat forage	0.273–0.305	28	2	<0.006	<0.006	0.006	0.006	NA
		115–119	2	<0.006	<0.006	0.006	0.006	NA
		357–364	2	<0.006	<0.006	0.006	0.006	NA
Wheat hay		28	2	<0.006	<0.006	0.006	0.006	NA
		115–119	2	<0.006	<0.006	0.006	0.006	NA
		357–364	2	<0.006	<0.006	0.006	0.006	NA
Wheat Straw		28	2	<0.006	<0.006	0.006	0.006	NA
		115–119	2	<0.006	<0.006	0.006	0.006	NA
		357–364	2	<0.006	<0.006	0.006	0.006	NA
Wheat Grain		28	2	<0.006	<0.006	0.006	0.006	NA
		115–119	2	<0.006	<0.006	0.006	0.006	NA
		357–364	2	<0.006	<0.006	0.006	0.006	NA

Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ.
n = number of independent field trials. NA = Not applicable

RESIDUE DATA IN ROTATIONAL CROPS **PMRA # 2809338/2808252**

Eighteen trials (six each for radish, lettuce and winter wheat) were conducted during the 2015 growing season in growing regions 1, 5, 10, and 11. One broadcast application was made to bare soil with Picarbutrazox FS (containing 400 g a.i./L) at a rate of 0.019–0.021 kg a.i./ha. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.

Commodity	Total Application Rate (kg a.i./ha)	PBI (days)	Residue Levels (ppm picarbutrazox equivalents)					
			n	LAFT	HAFT	Median	Mean	SDEV
Picarbutrazox								
Lettuce leaves	0.019–0.021	0	3	<0.005	<0.005	0.005	0.005	0
		28–31	3	<0.005	<0.005	0.005	0.005	0
Radish tops	0.019–0.021	0	3	<0.005	<0.005	0.005	0.005	0
		28–31	3	<0.005	<0.005	0.005	0.005	0
Radish roots		0	3	<0.005	<0.005	0.005	0.005	0

		28–31	3	<0.005	<0.005	0.005	0.005	0
Wheat forage	0.01–0.021	0	3	<0.005	<0.005	0.005	0.005	0
		28–31	3	<0.005	<0.005	0.005	0.005	0
Wheat hay		0	3	<0.005	<0.005	0.005	0.005	0
		28–31	3	<0.005	<0.005	0.005	0.005	0
Wheat straw		0	3	<0.005	<0.005	0.005	0.005	0
		28–31	3	<0.005	<0.005	0.005	0.005	0
Wheat grain		0	3	<0.005	<0.005	0.005	0.005	0
		28–31	3	<0.005	<0.005	0.005	0.005	0
TZ-2-β-Glc								
Lettuce leaves	0.019–0.021	0	3	<0.004	<0.004	0.004	0.004	0
		28–31	3	<0.004	<0.004	0.004	0.004	0
Radish tops	0.019–0.021	0	3	<0.004	<0.004	0.004	0.004	0
		28–31	3	<0.004	<0.004	0.004	0.004	0
Radish roots		0	3	<0.004	<0.004	0.004	0.004	0
		28–31	3	<0.004	<0.004	0.004	0.004	0
Wheat forage	0.019-0.021	0	3	<0.004	<0.004	0.004	0.004	0
		28–31	3	<0.004	<0.004	0.004	0.004	0
Wheat hay		0	3	<0.004	<0.004	0.004	0.004	0
		28–31	3	<0.004	<0.004	0.004	0.004	0
Wheat straw		0	3	<0.004	<0.004	0.004	0.004	0
		28–31	3	<0.004	<0.004	0.004	0.004	0
Wheat grain		0	3	<0.004	<0.004	0.004	0.004	0
		28–31	3	<0.004	<0.004	0.004	0.004	0
TZ-5								
Lettuce leaves	0.019–0.021	0	3	<0.011	<0.011	0.011	0.011	0
		28–31	3	<0.011	<0.011	0.011	0.011	0
Radish tops	0.019–0.021	0	3	<0.011	<0.011	0.011	0.011	0
		28–31	3	<0.011	<0.011	0.011	0.011	0
Radish roots		0	3	<0.011	<0.011	0.011	0.011	0
		28–31	3	<0.011	<0.011	0.011	0.011	0
Wheat forage	0.019–0.021	0	3	<0.011	<0.011	0.011	0.011	0
		28–31	3	<0.011	<0.011	0.011	0.011	0
Wheat hay		0	3	<0.011	<0.011	0.011	0.011	0
		28–31	3	<0.011	<0.011	0.011	0.011	0
Wheat straw		0	3	<0.011	<0.011	0.011	0.011	0
		28–31	3	<0.011	<0.011	0.011	0.011	0
Wheat grain		0	3	<0.011	<0.011	0.011	0.011	0
		28–31	3	<0.011	<0.011	0.011	0.011	0
TZ-5-Glc								
Lettuce leaves	0.019–0.021	0	3	<0.006	<0.006	0.006	0.006	0
		28-31	3	<0.006	<0.006	0.006	0.006	0
Radish tops	0.019–0.021	0	3	<0.006	<0.006	0.006	0.006	0

		28-31	3	<0.006	<0.006	0.006	0.006	0
Radish roots		0	3	<0.006	<0.006	0.006	0.006	0
		28–31	3	<0.006	<0.006	0.006	0.006	0
Wheat forage	0.019–0.021	0	3	<0.006	<0.006	0.006	0.006	0
		28–31	3	<0.006	<0.006	0.006	0.006	0
Wheat hay		0	3	<0.006	<0.006	0.006	0.006	0
		28–31	3	<0.006	<0.006	0.006	0.006	0
Wheat straw		0	3	<0.006	<0.006	0.006	0.006	0
		28–31	3	<0.006	<0.006	0.006	0.006	0
Wheat grain		0	3	<0.006	<0.006	0.006	0.006	0
		28–31	3	<0.006	<0.006	0.006	0.006	0

Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ.
n = number of independent field trials.

RESIDUE DATA IN ROTATIONAL CROPS **PMRA # 3082033**

Eight trials (two trials on leafy vegetables, and three trials each on root vegetables and cereal grains) were conducted during the 2019 growing season in growing regions 4 (2 trials), 7 (3 trials), and 11 (trials). One broadcast application was made to bare soil with Picarbutrazox FS (containing 400 g a.i./L) at a rate of 0.020 kg a.i./ha. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.

Commodity	Total Application Rate (kg a.i./ha)	PBI (days)	Residue Levels (ppm picarbutrazox equivalents)					
			n	LAFT	HAFT	Median	Mean	SDEV
TT-1								
Lettuce and spinach; and wheat grain	0.020	26–31	2	<0.024	<0.024	0.024	0.024	NA
Radish and turnip root and tops; and wheat forage	0.020	26–31	3	<0.024	<0.024	0.024	0.024	0
Wheat hay	0.020	26–31	2	<0.024	<0.028	0.026	0.026	NA
Wheat straw	0.020	26–31	2	<0.024	<0.024	0.024	0.024	NA
TT-3								
Lettuce and spinach; and wheat grain	0.020	26–31	2	<0.016	<0.016	0.016	0.016	NA

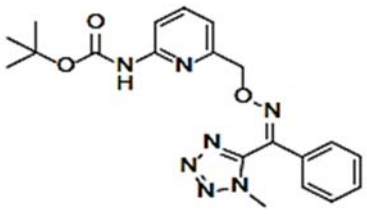
Radish and turnip root and tops; and wheat forage	0.020	26–31	3	<0.016	<0.016	0.016	0.016	0
Wheat hay	0.020	26–31	2	<0.016	0.042	0.029	0.029	NA
Wheat straw	0.020	26–31	2	<0.016	0.023	0.020	0.020	NA
Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ. n = number of independent field trials. NA = Not applicable								
Based on the results of the field accumulation studies, a plant-back interval of 30 days is required for all other crops that are not on the VAYANTIS Seed Treatment label.								

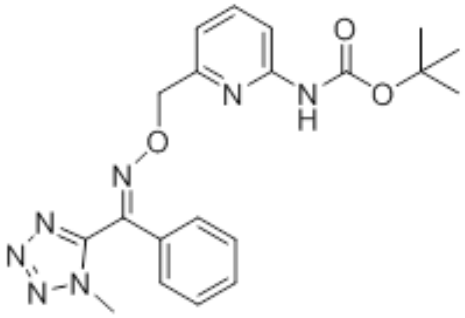
Table 9 Food residue chemistry overview of metabolism studies and risk assessment

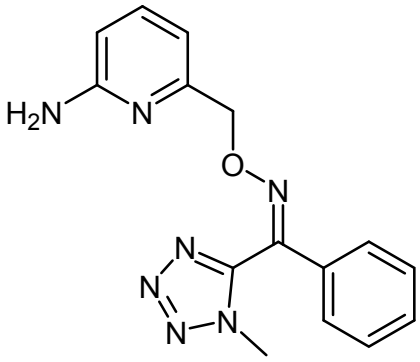
PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (cucumber (foliar treatment), lettuce (foliar treatment) and corn (seed treatment))** **Rotational crops (lettuce, radish, wheat, spinach, turnip)**	Picarbutrazox
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**	Picarbutrazox and TZ-1E Picarbutrazox and TZ-5
METABOLIC PROFILE IN DIVERSE CROPS	Similar in cucumber and lettuce (foliar applications) and corn (seed treatment).
ANIMAL STUDIES	
ANIMALS	**Ruminant and Poultry**
RESIDUE DEFINITION FOR ENFORCEMENT	Picarbutrazox
RESIDUE DEFINITION FOR RISK ASSESSMENT	Picarbutrazox
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	The metabolic profile is similar in the animals investigated.
FAT SOLUBLE RESIDUE	Yes

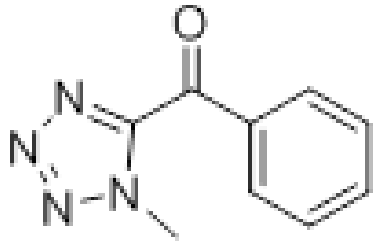
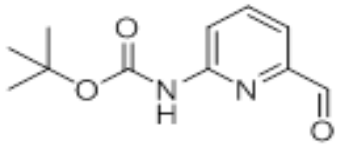
DIETARY RISK FROM FOOD AND DRINKING WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Drinking Water**
Basic chronic (cancer and non-cancer) dietary exposure analysis **ADI = 0.02 mg/kg bw/day** **Estimated chronic drinking water concentration = 2.1 µg a.i. L**	**All infants < 1 year**	0.9	1.7
	Children 1–2 years	2.7	3.0
	Children 3 to 5 years	1.6	1.9
	Children 6–12 years	1.0	1.1
	Youth 13–19 years	0.5	0.7
	Adults 20–49 years	0.4	0.6
	Adults 50+ years	0.4	0.5
	Females 13-49 years	0.3	0.6
	Total population	0.6	0.8

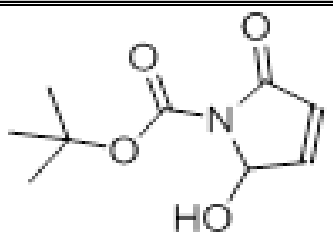
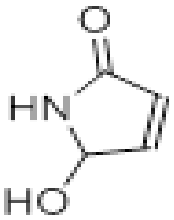
Table 10 Picarbutrazox and its environmental transformation products identified in laboratory and field dissipation studies

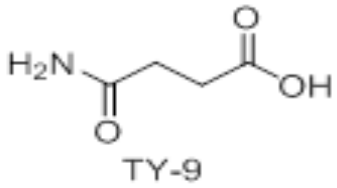
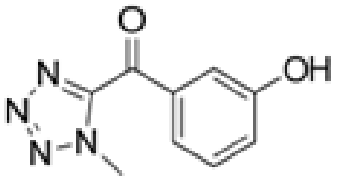
Chemical structure and chemical name	**Study type**		**Maximum %AR (day)**	**Final %AR by study end (study length in days)**
Picarbutrazox (technical grade active ingredient) 	Hydrolysis (pH 4, 7 and 9)		**102% (0)**	**40.7% (30)**
	Soil photolysis		**106.1% (0)**	**63.8% (27.83)**
	Aqueous photolysis	Water	**101.9% (0)**	0.4% (30)
		pH 9	**101.9% (0)**	0.3% (26.9)

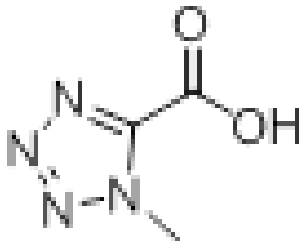
Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
CAS# 500207-04-5 CAS or chemical name: Carbamic acid, N-[6-[[[(Z)-[(1-methyl-1H-tetrazol-5-yl)phenylmethylene]amino]oxy]methyl]-2-pyridinyl]-, 1,1-dimethylethyl ester Common name: Picarbutrazox Synonyms: NF-171, DS-7097	Aerobic soil		**98.5% (0)**	**25.8% (120)**
	Anaerobic soil		**98.3% (0)**	**38.5 (120)**
	Aerobic aquatic		**99.2% (1)**	**33.7% (100)**
	Anaerobic aquatic		**98.1% (0)**	**11.0% (100)**
	Field studies		**78.2% (0)**	**16.8% (366)** Combined picarbutrazox & TZ-1E **11.3%** (731) Combined picarbutrazox & TZ-1E
	K_{OC}		**3741±1550 (1530 - 5849)**	
MAJOR (>10%) TRANSFORMATION PRODUCTS				
TZ-1E (E-Isomer of picarbutrazox)  CAS# 1253511-94-2 CAS or chemical name: Carbamic acid, *N*-[6-[[[(*E*)-[(1-methyl-1*H*-tetrazol-5-yl)phenylmethylene]amino]oxy]methyl]-	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		**35.6% (29.9)**	**35.6% (29.9)**
	Aqueous Photolysis	Water	**76.3% (0.75)**	1.9% (30)
		pH 9	**76.8% (0.34)**	1.0% (26.9)
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected

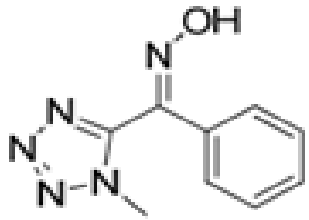
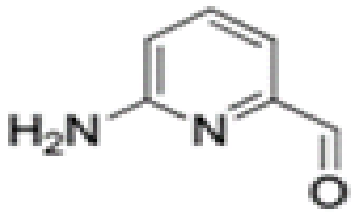
Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
2-pyridinyl]-, 1,1-dimethylethyl ester Common name: Unknown / unavailable Synonyms: E-Isomer of Picarbutrazox	Field studies		**29.8% (7)**	**16.8% (366)** Combined picarbutrazox & TZ-1E **11.3%** (731) Combined picarbutrazox & TZ-1E
	K_{OC}		**3741±1550 (1530 - 5849)**	
TZ-2  CAS# 500206-79-1 CAS or chemical name: Methanone, (1-methyl-1H-tetrazol-5-yl)phenyl-, O-[(6-amino-2-pyridinyl)methyl]oxime, (Z)- Common name: Unknown / unavailable Synonyms: Unknown / unavailable	Hydrolysis (pH 4, 7 and 9)		**100.9% (7)**	**100.9% (7)**
	Soil photolysis		**21.0% (5.5)**	6.7% (29.9)
	Aqueous Photolysis	Water	5.3% AR (0)	0.8% (30)
		pH 9	0.4% (0)	< LOQ (26.9)
	Aerobic soil		**46.3% (62)**	**44.9% (120)**
	Anaerobic soil		**60.3% (60)**	**58.5% (120)**
	Aerobic aquatic		**26.7% (100)**	**26.7% (100)**
	Anaerobic aquatic		**22.0% (63)**	**15.0% (100)**
	Field studies		**14.9% (270)**	4.5% (731)
	Vapour Pressure		< 1.0x 10^{-5} Pa at 50ºC	
	K_{OC}		1713.19±2058.77 (426.7 - 5359)	
TZ-4	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		Not detected	Not detected
	Aqueous photolysis	Water	34.1% (9)	6.5% (30)

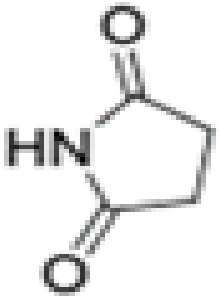
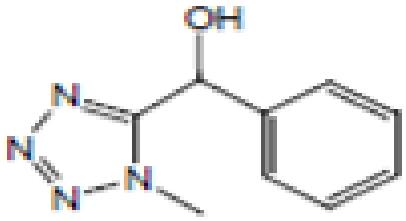
Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
 CAS# 33452-25-4 CAS or chemical name: Methanone, (1-methyl-1H-tetrazol-5-yl)phenyl Common name: Unknown/not available Synonyms: Unknown/not available		pH 9	**67.0% (0.25)**	**15.6%** **(26.9)**
	Aerobic soil		8.2% (120)	8.2% (120)
	Anaerobic soil		6.0% (0)	1.2% (120)
	Aerobic aquatic		9.6% (14)	5.6% (100)
	Anaerobic aquatic		8.5% (32)	3.8% (101)
	Field studies		<10.0%	<10.0%
	K_{OC}		No data	
TY-3  CAS# 956523-98-1 CAS or chemical name: Carbamic acid, N-(6-formyl-2-pyridinyl)-, 1,1-dimethylethyl ester Common name: Unknown/not available Synonyms: Unknown/not available	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous Photolysis	Water	**19.5%** **(9)**	2.4% (30)
		pH 9	**26.6%** **(3)**	0.2% (30)
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	K_{OC}		No data	
TY-5	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected

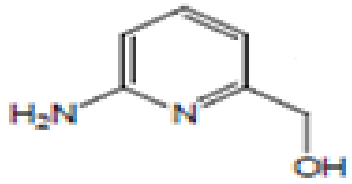
Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
 CAS# 1011716-08-7 CAS or chemical name: 1H-Pyrrole-1-carboxylic acid, 2,5-dihydro-2-hydroxy-5-oxo-, 1,1-dimethylethyl ester Common name: Unknown/not available Synonyms: Unknown/not available	Aqueous Photolysis	Water	**17.0% (9)**	5.7% (30)
		pH 9	**20.0% (9)**	1.2% (30)
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	K_{OC}		No data	
TY-6  CAS# 34085-09-1 CAS or chemical name: 2H-Pyrrol-2-one, 1,5-dihydro-5-hydroxy Common name: Isosuccinimide Synonyms: Unknown/not available	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous Photolysis	Water	**55%** **(30)**	**55%** **(30)**
		pH 9	**47.1%** **(30)**	**47.1%** **(30)**
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	K_{OC}		No data	

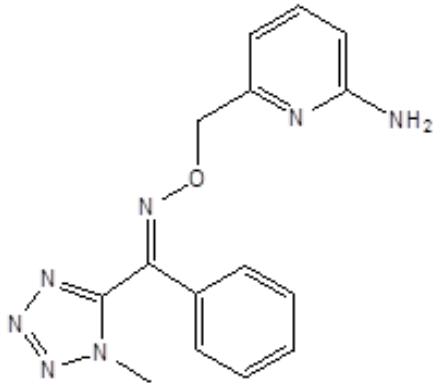
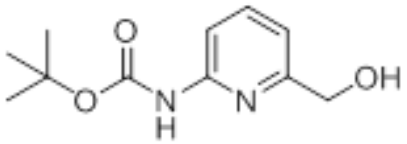
Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
TY-9  TY-9 CAS# 638-32-4 CAS or chemical name: Butanoic acid, 4-amino-4-oxo Common name: Succinamic acid Synonyms: Butanedioic acid monoamide, 4-Amino-4-oxobutanoic acid, 4-Oxo-4-aminobutyric acid, Succinic monoamide	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Phototransformation		Not detected	Not detected
	Aqueous Phototrans -formation	Water	Not detected	Not detected
		pH 9	**20.4%** **(30)**	**20.4%** **(30)**
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	K_{OC}		No data	
TZ-4-1  CAS# Not registered CAS or chemical name:	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous photolysis	Water	**26.4%** **(30)**	**26.4%** **(30)**
		pH 9	Not detected	Not detected
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected

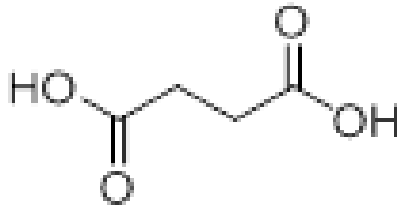
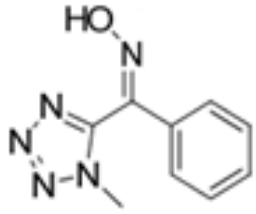
Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
Unknown/not available Common name: Unknown/not available Synonyms: Unknown/not available	*K*OC		No data	
TT-3  CAS# 77689-87-3 CAS or chemical name: 1-Methyl-1H-tetrazole-5-carboxylic acid Common name: Unknown/not available Synonyms: Unknown/not available	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous photolysis	Water	**36.6%** **(30)**	**36.6%** **(30)**
		pH 9	**33.7%** **(30)**	**33.7%** **(30)**
	Aerobic soil		**40.1%** **(120)**	**40.1%** **(120)**
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	*K*OC		No data	
TT-1  CAS# 16681-77-9 CAS or chemical name: 1-Methyltetrazole	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous photolysis	Distilled water	**15.0%** (30)	**15.0%** (30)
		Natural Water	**17.7%** (30)	**17.7%** (30)
		pH 9 Buffer	**28.2% (30)**	**28.2% (30)**
	Aerobic soil		No data	No data

Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
Common name: Unknown/not available Synonyms: 1-Methyl-1h-Tetrazole	Anaerobic soil		No data	No data
	Aerobic aquatic		No data	No data
	Anaerobic aquatic		No data	No data
	Field studies		No data	No data
	*K*OC		No data	
TZ-3E  CAS# 1456696-38-0 CAS or chemical name: Methanone, (1-methyl-1H-tetrazol-5-yl)phenyl-, oxime, (1E)- Common name: Unknown/not available Synonyms: Unknown/not available	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous photolysis	Distilled water	**14.1% (21)**	7.9 - 8.9% (30)
		Natural Water	3.0% (9)	< LOQ (30)
		pH 9 Buffer	Not detected	Not detected
	Aerobic soil		No data	No data
	Anaerobic soil		No data	No data
	Aerobic aquatic		No data	No data
	Anaerobic aquatic		No data	No data
	Field studies		No data	No data
	*K*OC		No data	
TY-4  CAS# 332884-35-2 CAS or chemical name: 6-amino-2-pyridyl carbaldehyde	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous photolysis	Distilled water	**12.3%** (21)	3.6% (30)
		Natural Water	3.8 % (21)	2.2% (30)
		pH 9 Buffer	Not detected	Not detected
	Aerobic soil		No data	No data
	Anaerobic soil		No data	No data

Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
Common name: Unknown/not available Synonyms: 2-Amino-6-Pyridine Carboxaldehyde, 6-Aminopicolinaldehyde	Aerobic aquatic		No data	No data
	Anaerobic aquatic		No data	No data
	Field studies		No data	No data
	*K*OC		No data	
TY-8  CAS# 123-56-8 CAS or chemical name: 2,5-Pyrrolidinedione Common name: Succinimide Synonyms: Many	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil Photolysis		Not detected	Not detected
	Aqueous photolysis	Water	**23%** **(30)**	**23%** **(30)**
		pH 9	Not detected	Not detected
	Aerobic soil		No data	No data
	Anaerobic soil		No data	No data
	Aerobic aquatic		No data	No data
	Anaerobic aquatic		No data	No data
	Field studies		No data	No data
	*K*OC		No data	
TZ-5  CAS# 33452-21-0 CAS or chemical name: 1H-Tetrazole-5-methanol, 1-methyl-α-phenyl-	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		Not detected	Not detected
	Aqueous photolysis	Water	Not detected	Not detected
		pH 9	Not detected	Not detected
	Aerobic soil		9.9% (120)	9.9% (120)
	Anaerobic soil		**17.6%** **(120)**	**17.6%** **(120)**
	Aerobic aquatic		**47.6%** **(100)**	**47.6%** **(100)**
	Anaerobic aquatic		**77.4%** **(60)**	**73.1** **(101)**

Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
Common name: Unknown/not available Synonyms: Unknown/not available	Field studies		<10.0%	
	K_{OC}		No data	
TY-2  CAS# 79651-64-2 CAS or chemical name: 2-Aminopyridine-6-methanol Common name: Unknown/not available Synonyms: (6-Aminopyridin-2-yl)methanol	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		Not detected	Not detected
	Aqueous photolysis	Water	Not detected	Not detected
		pH 9	Not detected	Not detected
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		8.6% (120)	8.6% (120)
	Aerobic aquatic		6.1% (100)	6.1% (100)
	Anaerobic aquatic		**23.4% (100)**	**23.4% (100)**
	Field studies		Not detected	Not detected
	K_{OC}		No data	
MINOR (<10%) TRANSFORMATION PRODUCTS				
TZ-2E	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		9.7% (19.7)	6.7% (27.8)
	Aqueous photolysis	Water	Not detected	Not detected
		pH 9		
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		<14.9%	Not detected

Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
 CAS# Not registered CAS or chemical name: Unknown/not available Common name: Unknown/not available Synonyms: Unknown/not available	*K*OC		No data	
TY-1  CAS# 203321-83-9 CAS or chemical name: Carbamic acid, N-[6-(hydroxymethyl)-2-pyridinyl]-, 1,1-dimethylethyl ester Common name: Unknown/not available Synonyms: tert-butyl [6-(hydroxymethyl)-2-pyridyl]carbamate	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		Not detected	Not detected
	Aqueous photolysis	Water	5.1% (9)	2.4% (30)
		pH 9	2.2% (9)	0.9% (30)
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		0.5% (14)	< LOQ (100)
	Aerobic aquatic		1.9% (63)	< LOQ (100)
	Anaerobic aquatic		7.3% (63)	3.1% (101)
	Field studies			
	Other			
	*K*OC		No data	

Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
TY-10  CAS# 110-15-6 CAS or chemical name: Butanedioic acid Common name: Succinic acid Synonyms: Many synonyms	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		Not detected	Not detected
	Aqueous photolysis	Water	Not detected	Not detected
		pH 9	9.4% (30)	9.4% (30)
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	Other			
	K_{OC}		No data	
TZ-3  CAS# 1083086-53-6 CAS or chemical name: Methanone, (1-methyl-1H-tetrazol-5-yl)phenyl-, oxime, (1Z)- Common name: Unknown/not available Synonyms: Unknown/not available	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected
	Soil photolysis		Not detected	Not detected
	Aqueous photolysis	Water	2.0% (21)	< LOQ (30)
		pH 9	Not detected	Not detected
	Aerobic soil		Not detected	Not detected
	Anaerobic soil		Not detected	Not detected
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	K_{OC}		No data	
TZ-7	Hydrolysis (pH 4, 7 and 9)		Not detected	Not detected

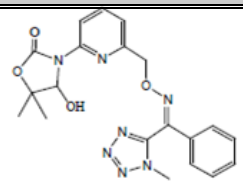
Chemical structure and chemical name	Study type		Maximum %AR (day)	Final %AR by study end (study length in days)
 CAS# Not registered CAS or chemical name: Unknown/not available Common name: Unknown/not available Synonyms: Unknown/not available	Soil photolysis		Not detected	Not detected
	Aqueous photolysis	Water	Not detected	Not detected
		pH 9	Not detected	Not detected
	Aerobic soil		6.7% (62)	6.5% (120)
	Anaerobic soil		6.7% (30)	6.1 (120)
	Aerobic aquatic		Not detected	Not detected
	Anaerobic aquatic		Not detected	Not detected
	Field studies		Not detected	Not detected
	K_{OC}		No data	

Table 11 Summary of fate and behaviour of picarbutrazox in the environment

Study type	Test substance	$DT_{50}/t_{1/2,rep}$ (days)	Transformation products	Comments/ classification	PMRA#
Abiotic transformation					
Hydrolysis	Picarbutrazox	4.8/4.8 (15˚C pH 4) 21.1/21.1 (25˚C pH 7) 24.3/24.3 (25˚C pH 9)	Major: TZ-2 up to 99.8% AR[1] Minor: None	Non-persistent at pH < 4. Slightly persistent at 7 ≤ pH ≤ 9	2809366
Phototransformation on soil	Picarbutrazox	89.0/89.0 (Combined residue of picarbutrazox and TZ-1E)	Major: TZ-1E (e-Isomer of picarbutrazox) up to 33.6% AR TZ-2 up to 15.8% AR Minor: TZ-2E up to 7.9% AR CO_2 up to 0.9% AR	Moderately persistent $t_{1/2,rep}$ includes combined residues of picarbutrazox and TZ-1E	2809368

Phototransformation in water	Combined residues of Picarbutrazox and TZ-1E	3.0/3.0 (distilled water, pH = 6.63-7.75) 3.8/3.8 (natural water, pH = 7.08-7.88)	Major: TZ-1E up to 76.3 % AR TZ-3E up to 14.1% AR TZ-4 up to 34.1% AR TZ-4-1 up to 26.4% AR TY-3 up to 19.5% AR TY-4 up to 12.3% AR TY-5 up to 17.0% AR TY-6 up to 55.0% AR TY-8 up to 23.0% AR TT-1 up to 17.7% AR TT-3 up to 36.6% AR Minor: TZ-2 up to 5.3% AR TZ-3 up to 3.0% AR TY-1 up to 5.1% AR CO_2 up to 3.3% AR	Non-persistent $t_{1/2,rep}$ includes combined residues of picarbutrazox and TZ-1E	2809370, 2809374 & 2809378
Phototransformation in pH 9 buffer (summer light)	Combined residues of Picarbutrazox and TZ-1E	1.7/1.7 (pH 9 buffer)	Major: TZ-1E up to 76.8% AR TZ-4 up to 65.2% AR TY-3 up to 22.1% AR TY-5 up to 18.9% AR TY-6 up to 46.7% AR TY-9 up to 20.0% AR TT-3 up to 34.4% AR TT-1 up to 26.6% AR Minor: TZ-2 up to 1.3% AR TY-1 up to 2.0% AR TY-10 up to 8.7% AR CO2 up to 1.5% AR	Non-persistent $t_{1/2,rep}$ includes combined residues of picarbutrazox and TZ-1E	2809372, 2809376, 2809380
Phototransformation in air	NA	NA	NA	Not expected to be a route of dissipation	NA
Volatilization	NA	NA	NA	Not expected based on vapour pressure and Henry's law constant	NA

Biotransformation in soil					
Biotransformation in aerobic soil	Picarbutrazox	48.6/64.0 (DT_{50}: 90% upper bound on the mean: 48.6; n=5) DT_{50} range: 31.3-53 ($t_{1/2,rep}$: 90% upper bound on the mean: 64.0; n=5) $t_{1/2,rep}$ range: 34.6-72.7	Major: TZ-2 up to 45.5% AR TT-3 up to 34.5% AR Minor: TZ-4, TZ-5, TZ-7 up to < 6.4% AR	Moderately persistent	2809382, 2917291
Biotransformation in aerobic soil	TZ-2	131/273.9 (DT_{50}: 90% upper bound on the mean: 102.6; n=4) DT50 range: 29.9-146 ($t_{1/2,rep}$ 90% upper bound on the mean: 244.5; n=4) $t_{1/2,rep}$ range: 191-307	Major: None Minor: Unidentified up to < 8.6% AR	Moderately Persistent	2809384
Biotransformation in anaerobic soil	Picarbutrazox	144.6/144.6 (DT_{50}: 90% upper bound on the mean: 101.5; n=4) $t_{1/2,rep}$ range: 52.7-150 ($t_{1/2,rep}$ 90% upper bound on the mean: 101.5; n=4) $t_{1/2,rep}$ range: 52.7-150	Major: TZ-2 up to 59.4% AR TZ-5 up to 15.0% AR Minor: TZ-4 up to 5.6% AR TZ-7 up to 6.3% AR TY-1 up to 0.3% AR TY-2 up to 7.1% AR	Moderately persistent	2809387
Mobility					
Property	**Test substance**	**Mean K_d/K_{OC} (L/g)**	**Comment**	**Mobility classification**	**PMRA#**
Adsorption in soil	Picarbutrazox	52.58±38.83 (23.39-122.15) / 3741±1550 (1530 - 5849)	Linear adsorption, 6 soils	Immobile to low mobility	2809397
	TZ-2	32.96±35.56 (6.37-90.15)/ 1713.19±2058.77 (426.7 - 5359)	Linear adsorption, 5 soils	Immobile to moderate mobility	2809399

Soil leaching	Picarbutrazox	Non-definitive according to criteria of Cohen et al. Non-leacher according to the GUS index.	NA
	TZ-2	Non-leacher to leacher depending on soil organic carbon content (according to criteria of Cohen et al. and GUS index)	NA

Field dissipation

Test site		Test item and rate	$DT_{50}/t_{1/2,rep}$ (days)	Major transformation products	Classification/comments	PMRA#
Field dissipation	[2]California - Turfgrass	Picarbutrazox applied as formulated product (9.61% w/w picarbutrazox) Four applications of 364 g a.i./ha on a 14 day application interval (Toal 1456 g a.i./ha)	78.9/78.9	TZ-1E (e-isomer of picarbutrazox) up to 29.8% AR TZ-1E was included in $t_{1/2,rep}$ calculations and carry-over percentages) TZ-2 up to 13.3% AR TZ-2E up to 14.9% AR	Moderately persistent, max. depth <15 cm, 1.5% carry-over	2809401, 2835445, 2835446, 2835447
	[2]California – Bareground		92.9/92.9		Moderately persistent, max. depth <30 cm, 1.2% carry-over,	
	[2]Georgia – Turfgrass		122/122		Moderately persistent, max. depth <15 cm, 1.8% carry-over	
	[2]Georgia - Bareground		31.1/112		Slightly persistent, max. depth <45 cm, 2.6% carry-over	
	Iowa – Turfgrass		238/238		Persistent, max. depth <30 cm, 4.2% carry-over	
	Iowa – Bareground		105/105		Moderately persistent, max. depth <30 cm, 3.8% carry-over	
	Idaho – Turfgrass		360/360		Persistent, max. depth <30 cm, 13.8% carry-over	
	Idaho - Bareground		98.6/239		Moderately persistent, max. depth <30 cm, 8.7% carry-over	
	New York – Turfgrass		257/257		Persistent, max. depth <15 cm, 16.8% carry-over	
	New York – Bareground		55.6/357		Moderately persistent, max. depth <15 cm, 14.2% carry-over	

Biotransformation in aquatic environment

Property	Test substance	$DT_{50}/t_{1/2,rep}$ (days)	Major transformation products	Comments/ classification	PMRA#
Biotransformation in aerobic water systems	Picarbutrazox	Water: 10.5-10.9/10.5-10.9 (n=2) Total system:	TZ-2 up to 21.6%AR TZ-5 up to 46.9%AR	Slightly to moderately persistent in whole system	2809389

		33.5-53.2/50.7-85.7 (n=2)			
Biotransformation in aerobic water systems	TZ-2	Water: 3.19-3.58/6.12-13.5 (n=2) Total system: 42.3-53.0/77.3-97.4(n=2)	CO_2 up to 17.3%AR	Slightly to moderately persistent in whole system	2809391
Biotransformation in aerobic water systems	TZ-5	Water: 29-76.2/66.6-842(n=2) Total system: 199-511/199-32400 (n=2)	None	Persistent in whole system	2809393
Biotransformation in anaerobic water systems	Picarbutrazox	Water: 9.33-25.3/9.33-25.3 (n=2) Total system: 20.9-31.7/20.9-31.7 (n=2)	TZ-2 up to 21.6% AR TZ-5 up to 74.9% AR TY-2 up to 22.3% AR	Slightly persistent in whole system	2809395
Partitioning					
Picarbutrazox	Primarily in the sediment layer.				NA
Bioconcentration					
Not expected to bioaccumulate. BCF = 314.					2809514

[1]Percent of applied radioactivity.
[2]Region not considered by the PMRA as they do not represent Canadian field use conditions.

Table 12 Summary of toxicity effects of picarbutrazox, TZ-1E, TZ-2 and TZ-5 on terrestrial organisms

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA#
Invertebrates					
Eisenia fetida (Earthworm)	Picarbutrazox (technical grade active ingredient)	28 days, mortality	LC_{50} >1000 mg a.i./kg dry soil NOEC = 1000 mg a.i./kg dry soil No statistically significant effects on mortality were observed up to the highest concentration tested.	NA	2809408
		56 days, reproduction	NOEC = 96 mg a.i./kg dry soil	NA	

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA#
	TZ-1E	28 days, mortality	LC_{50} >1100 mg/kg dry soil NOEC = 1100 mg/kg dry soil No statistically significant effects on mortality were observed up to the highest concentration tested.	NA	2809410
		56 day, reproduction	NOEC = 1100 mg/kg dry soil	NA	
	TZ-2	28 day, mortality	LC_{50} >1000 mg/kg dry soil NOEC = 1000 mg/kg dry soil No statistically significant effects on mortality were observed up to the highest concentration tested.	NA	2809412
		56 day, reproduction	56-d NOEC = 560 mg/kg dry soil	NA	
	TZ-5	28 day, mortality	LC_{50} >1000 mg/kg dry soil NOEC = 1000 mg/kg dry soil No statistically significant effects on mortality were observed up to the highest concentration tested.	NA	2809414
		56 day, reproduction	NOEC = 64 mg/kg dry soil	NA	
Apis mellifera (Honey bee)	Picarbutrazox (technical grade active ingredient)	48-hour acute oral adult	LD_{50} > 96.8 µg a.i./bee 6.7 % mortality was observed at the highest test concentration	Practically nontoxic	2809420
		48-hour acute contact adult	LD_{50} > 96.8 µg a.i./bee 1.7% mortality was observed at the highest test concentration	Practically nontoxic	2809418
		10-day chronic diet adult	LD_{50} >37 µg a.i./bee/day NOAEL = 37 µg a.i./bee/day 0% mortality was observed at the highest test concentration	NA	2809416

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA#
		72-hour acute larvae	LD_{50}: >100 µg a.i./larva 14% mortality was observed at the highest test concentration	Practically nontoxic	2809422
		22-day chronic larvae	15-day LD_{50}: > 12.2 µg a.i./larva/day 22-day NOAEL $_{emergence}$ = 5.6 µg a.i./larva/day 28% mortality was observed at the highest test concentration	NA	2809424
Typhlodromus pyri (Predatory mite)	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	14-d contact glass plate Protonymphs	14-d LR_{50}: >1500 g a.i./ha 14-d $ER_{50\ reproduction}$: >1500 g a.i./ha 8.8% mortality was observed at the highest test concentraiton and reproductive output was reduced by 45.5% observed at the highest test rate	NA	2809426
Aphidius rhopalosiphi (parasitoid wasp)	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	48-h contact glass plate	14-d LR50: >1500 g a.i./ha 14-d ER50: >1500 g a.i./ha 10% mortality was observed at the highest test rate and reproductive output was reduced by 8.9% at the highest test rate	NA	2809436
Hypoaspis geolaelaps aculeifer (Predatory mite)	Picarbutrazox formulated product (36.3% w/w picarbutrazox)	14-d Reproduction test in soil	14-d LC_{50}: > 363 mg a.i./kg dry soil 14-d $EC_{50\ reproduction}$: >363 mg a.i./kg dry soil 13% adult mortality was observed in the highest test concentration and reproductive output was reduced by 40% at the highest test concentration	NA	2809428

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA#
	TZ-1E	14-d Reproduction test in soil	14-d LC_{50}: > 1000 mg a.i. /kg dry soil 14-d $EC_{50\ reproduction}$: > 1000 mg a.i. /kg dry soil 10% adult mortality was observed in the highest test concentration and reproductive output was reduced by 6% in the highest test concentration	NA	2809430
	TZ-2	14-d Reproduction test in soil	14-d LC_{50}:> 1000 mg/kg dry soil 14-d $EC_{50\ reproduction}$:> 1000 mg/kg dry soil 33% adult mortality was observed in the highest test concentration and reproductive output was reduced by 25% in the highest test concentration	NA	2809432
	TZ-5	14-d Reproduction test in soil	14-d LC_{50}: >1000 mg/kg dry soil 14-d $EC_{50\ reproduction}$: >1000 mg/kg dry soil 10% mortality was observed at the highest test rate and reproductive output was reduced by 14% at the highest test rate	NA	2809434
Colinus virginianus (Northern Bobwhite quail)	Picarbutrazox (technical grade active ingredient)	Acute oral	LD_{50} > 2000 mg a.i./kg bw No effects on mortality were observed up to the highest concentration tested.	Practically nontoxic	2809516
		5-day Acute Dietary	LC_{50} > 5688 mg a.i./kg diet LD_{50} > 1347 mg a.i./kg bw/d No effects on mortality were observed up to the highest concentration tested.	Practically nontoxic	2809523

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA#
		27 week Reproduction	NOAEC $_{reproduction}$: 515 mg a.i./kg (44.2 mg a.i./kg bw/d)	NA	2809533, 2809535 & 2835461
Anas platyrhynchos (Mallard)	Picarbutrazox (technical grade active ingredient)	Acute oral	LD_{50} > 2000 mg a.i./kg bw No effects on mortality were observed up to the highest concentration tested.	Practically nontoxic	2809519
		5-day Acute Dietary	LC_{50} > 5819 mg a.i./kg diet LD_{50} > 2834 mg a.i./kg bw/d	Practically nontoxic	2809525
		27 week Reproduction	NOAEC $_{reproduction}$: 343 mg a.i./kg (41.8 mg a.i./kg bw/d)	NA	2809536, 2835462
Serinus canaria (Canary)	Picarbutrazox (technical grade active ingredient)	Acute oral	LD_{50} > 2000 mg a.i./kg bw No effects on mortality were observed up to the highest concentration tested.	Practically nontoxic	2809521
Sprague Dawley rats	Picarbutrazox (technical grade active ingredient)	Single dose Acute oral (gavage)	LD_{50}: > 2000 mg a.i./kg bw No effects on mortality were observed up to the highest concentration tested.	Practically nontoxic	2809142
		1 generation reproduction	NOAEL $_{reproductive}$: 45.1 mg a.i./kg bw/day Based on decrease in number of F1 pups.	NA	2809235
		2 generation reproduction	NOAEL $_{reproductive}$: 62.6 mg a.i./kg bw/day Based on decrease in body weight of F2 pups.	NA	2809237
	TZ-1E	Single dose Acute oral (gavage)	LD_{50}: > 2000 mg a.i./kg bw No effects on mortality were observed up to the highest concentration tested.	Practically nontoxic	2809144

[1]Degree of toxicity classification based on criteria developed by Atkins et al. for bees and USEPA for others, where applicable.

Table 13 Summary of toxicity effects of picarbutrazox, TZ-1E, TZ-2, TZ-4, TZ-5 and TY-3 (TPs) and its associated end-use products on aquatic organisms

Test organism	Test substance	Exposure	Endpoint	Endpoint Value	Degree of toxicity[1]	PMRA#
Freshwater Invertebrates						
Daphnia magna (Water flea)	Picarbutrazox (technical grade active ingredient)	48-h Acute (flow through)	48-h EC_{50}	> 0.28 mg a.i./L 10% immobility was observed at the highest test concentration	Highly toxic	2809438
		21-day Life-Cycle (flow through)	21-d $NOAEC_{dry\ weight}$	0.13 mg a.i./L	NA	2809459
	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	48-h Acute (static)	48-h EC_{50}	> 1.89 mg a.i./L No effects on mobility were observed up to the highest test concentration	Moderately toxic	2809452
	Picarbutrazox formulated product (20.26% w/w picarbutrazox)	48-h Acute (static)	48-h EC_{50}	> 3.46 mg a.i./L No effects on mobility were observed up to the highest test concentration	Moderately toxic	2809454
	TZ-1E (e-isomer of picarbutrazox)	48-h Acute (flow through)	48-h EC_{50}	> 0.31 mg a.i./L No effects on mobility were observed up to the highest test concentration	Highly toxic	2809441
	TZ-2	48-h Acute (static)	48-h EC_{50}	5.6 mg/L	Moderately toxic	2809443
	TY-3	48-h Acute (static)	48-h EC_{50}	50 mg/L	Slightly toxic	2809445
	TZ-4	48-h Acute (static)	48-h EC_{50}	> 31 mg/L No effects on mobility were observed up to the highest test concentration	Slightly toxic	2809447
	TZ-5	48-h Acute (static)	48-h EC_{50}	> 88 mg/L 5% immobility was observed at the highest test concentration	Slightly toxic	2809450
Chironomus dilutes (Midge)	Picarbutrazox (technical grade active ingredient)	10-d Acute (spiked sediment)	10-d EC_{50}	Pore water: > 0.333 mg a.i./L No mortality was observed up to the highest test concentration	NA	2809461

Test organism	Test substance	Exposure	Endpoint	Endpoint Value	Degree of toxicity[1]	PMRA#
Hyalella Azteca (Amphipod)	Picarbutrazox (technical grade active ingredient)	10-d acute (spiked sediment)	10-d LC_{50}	Pore water: > 0.333 mg a.i./L 5% mortality was observed at the highest test concentration	NA	2809463
Freshwater Fish						
Oncorhynchus mykiss (Rainbow Trout)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	96-h LC_{50}	> 0.29 mg a.i./L No mortality was observed up to the highest test concentration	Highly toxic	2809482 & 2809504
	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	96-h Static	96-h LC_{50}	> 2.33 mg a.i./L 10% mortality was observed at the highest test concentration	Moderately toxic	2809494 & 2809506
	Picarbutrazox formulated product (20.26% w/w picarbutrazox)	96-h Static	96-h LC_{50}	> 3.74 mg a.i./L 5% mortality was observed at the highest test concentration	Moderately toxic	2809496 & 2809506
	Picarbutrazox FS 400 formulated product (36.3% w/w picarbutrazox)	96-h Static	96-h LC_{50}	> 8.14 mg a.i./L No mortality was observed up to the highest test concentration	Moderately toxic	2809498
	TZ-1E	96-h Flow-through	96-h LC_{50}	> 0.337 mg/L No mortality was observed up to the highest test concentration	Highly toxic	2809484
	TZ-2	96-h Static	96-h LC_{50}	> 13 mg/L No mortality was observed up to the highest test concentration	Slightly toxic	2809486
	TY-3	96-h Daily Static-Renewal	96-h LC_{50}	2.2 mg/L	Moderately toxic	2809488
	TZ-4	96-h Static	96-h LC_{50}	33 mg/L	Slightly toxic	2809490
	TZ-5	96-h Static	96-h LC_{50}	> 87 mg/L No mortality was observed at the highest test concentration	Slightly toxic	2809492

Test organism	Test substance	Exposure	Endpoint	Endpoint Value	Degree of toxicity[1]	PMRA#
Pimephales promelas (Fathead Minnow)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	96-h LC_{50}	> 0.31 mg a.i./L No mortality was observed up to the highest test concentration	Highly toxic	2809500
		33-d Early Life-Stage Flow-through	33-d $NOEC_{larval\ survival}$:	0.019 mg a.i./L	NA	2809510
Vascular plants						
Lemna gibba (Duckweed)	Picarbutrazox (technical grade active ingredient)	7-d Static-renewal	7-d IC_{50}:	> 0.314 mg a.i./L No adverse effects up to the highest test concentration	NA	2809572
Freshwater alga						
Pseudo-kirchneriella subcapitata (Green Alga)	Picarbutrazox (technical grade active ingredient)	96-h Static	96-h IC_{50}:	> 0.338 mg a.i./L 34% inhibition was observed at the highest test concentration	NA	2809538
	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	96-h Static	96-h IC_{50}:	>1.3 mg a.i./L 16% inhibition was observed at the highest test concentration	NA	2809554
	Picarbutrazox formulated product (20.26% w/w picarbutrazox)	96-h Static	96-h IC_{50}:	> 2.5 mg a.i./L 59% inhibition was observed at the highest test concentration of 5.1 mg a.i./L	NA	2809552
	TZ-1E	96-h Static	96-h IC_{50}:	>0.366 mg a.i./L 6% inhibition was observed at the highest test concentration	NA	2809542
	TZ-2	96-h Static	96-h IC_{50}:	6.51 mg/L	NA	2809544
	TZ-4	96-h Static	96-h IC_{50}:	20 mg/L	NA	2809548
	TZ-5	96-h Static	96-h IC_{50}:	> 97 mg/L 12% inhibition was observed at the highest test concentration	NA	2809550
	TY-3	96-h Static	96-h IC_{50}:	4.6 mg/L	NA	2809546
Anabaena flos-aquae (Blue-green alga)	Picarbutrazox (technical grade active ingredient)	96-h Static	96-h IC_{50}:	> 0.27 mg a.i./L 30% inhibition was observed at the highest test concentration	NA	2809556

Test organism	Test substance	Exposure	Endpoint	Endpoint Value	Degree of toxicity[1]	PMRA#
Navicula pelliculosa (Freshwater diatom alga)	Picarbutrazox (technical grade active ingredient)	96-h Static	96-h IC_{50}:	> 0.326 mg a.i./L 25% inhibition was observed at the highest test concentration	NA	2809540
Marine Invertebrates						
Americamysis bahia (Mysid shrimp)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	96-h LC_{50}	> 0.31 mg a.i./L 5% mortality was observed at the highest test concentration	Highly toxic	2809466
		28-d Flow-through	28-d NOAEC	< 0.0176 mg/L 23% mortality was observed at the lowest test concentration of 0.0176 mg/L	Highly toxic	2809472
Crassostrea virginica (Eastern oyster)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	96-h IC_{50}	> 0.28 mg a.i./L 35% reduction in shell depositon was observed at the highest test concentration	Highly toxic	2809470
Leptocheirus plumulosus (Marine Amphipod)	Picarbutrazox (technical grade active ingredient)	10-d Spiked sediment	10-d LC_{50}	Bulk sediment: > 942 mg a.i./kg Pore water: > 0.333 mg/L No mortality was observed at the highest test concentration	NA	2809468
Marine Fish						
Cyprinodon variegatus (Sheepshead Minnow)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	96-h LC_{50}:	> 0.26 mg a.i./L No mortality was observed up to the highest test concentration	Highly toxic	2809508
		34-d Early Life-Stage Flow-through	34-d NOAEC:	0.077 mg a.i./L	NA	2809512
Marine Alga						
Skeletonema costatum (Marine diatom)	Picarbutrazox (technical grade active ingredient)	96-h Static	96-h IC_{50}:	> 0.236 mg a.i./L 34% inhibition was observed at the highest test concentration	NA	2809562

[1] Degree of toxicity classification based on criteria developed by Atkins et al. for bees and USEPA for others, where applicable.

Table 14 Study endpoints and uncertainty factors used to establish effects metrics for risk assessment

Most sensitive representitive species	Test substance	Exposure/endpoint	Endpoint value	Uncertainty factor applied	Level of concern (LOC)
Invertebrates					
Earthworm (*Eisenia fetida*)	Picarbutrazox a.i.	28d-LC_{50}	> 1000 mg a.i./kg soil dw	2	1
		56-d Reproduction NOAEC	96 mg a.i./kg soil dw	1	1
	TZ-1E	28d-LC_{50}	> 1100 mg a.i./kg soil dw	2	1
		56-d Reproduction NOAEC	1100 mg a.i./kg soil dw	1	1
	TZ-2	28d-LC_{50}	>1000 mg/kg soil dw	2	1
		56-d Reproduction NOAEC	560 mg/kg soil dw	1	1
	TZ-5	28d-LC_{50}	>1000 mg/kg soil dw	2	1
		56-d Reproduction NOAEC	64 mg/kg soil dw	1	1
Birds					
Mallard (*Anas platyrhynchos*)	Picarbutrazox a.i.	Single dose Oral LD_{50}	> 2000 mg a.i./kg bw	10	1
		27 week Reproduction NOAEL	41.8 mg a.i./kg bw/d	1	1
Mammals					
Sprague Dawley rat	Picarbutrazox a.i.	Single dose Oral LD_{50}	> 2000 mg a.i./kg bw	10	1
Sprague Dawley rat	Picarbutrazox a.i.	1 Generation Reproductive NOAEL	45.1 mg/kg bw/day	1	1
Freshwater invertebrates					
Water flea (*Daphnia magna*)	Picarbutrazox a.i.	48-h EC_{50}	> 0.28 mg a.i./L	2	1

Most sensitive representitive species	Test substance	Exposure/endpoint	Endpoint value	Uncertainty factor applied	Level of concern (LOC)
	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	48-h EC_{50}	> 1.89 mg a.i./L	2	1
	Picarbutrazox formulated product (20.26% w/w picarbutrazox)	48-h EC_{50}	> 3.46 mg a.i./L	2	1
	TZ-1E (e-isomer of picarbutrazox)	48-h EC_{50}	> 0.31 mg a.i./L	2	1
	TZ-2	48-h EC_{50}	5.6 mg/L	2	1
	TY-3	48-h EC_{50}	50 mg/L	2	1
	TZ-4	48-h EC_{50}	> 31 mg/L	2	1
	TZ-5	48-h EC_{50}	> 88 mg/L	2	1
	Picarbutrazox a.i.	21 day life-cycle NOAEL	0.13 mg a.i./L	1	1
Midge (*Chironomus dilutes*)	Picarbutrazox a.i.	10-d EC_{50}	Pore water: > 0.333 mg a.i./L	2	1
Freshwater fish					
Rainbow trout (*Oncorhynchus mykiss*)	Picarbutrazox a.i.	96h-LC_{50}	> 0.29 mg a.i./L	10	1
	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	96h-LC_{50}	> 2.33 mg a.i./L	10	1
	Picarbutrazox formulated product (20.26% w/w picarbutrazox)	96h-LC_{50}	> 3.74 mg a.i./L	10	1
	Picarbutrazox FS 400 formulated product (36.3% w/w picarbutrazox)	96h-LC_{50}	> 8.14 mg a.i./L	10	1
	TZ-1E	96h-LC_{50}	> 0.337 mg/L	10	1
	TZ-2	96h-LC_{50}	> 13 mg/L	10	1

Most sensitive representitive species	Test substance	Exposure/endpoint	Endpoint value	Uncertainty factor applied	Level of concern (LOC)
	TY-3	96h-LC_{50}	2.2 mg/L	10	1
	TZ-4	96h-LC_{50}	33 mg/L	10	1
	TZ-5	96h-LC_{50}	>87 mg/L	10	1
Fathead minnow (*Pimephales promelas*)	Picarbutrazox (technical grade active ingredient)	33-d Early Life-Stage NOEC	0.019 mg a.i./L	1	1
Aquatic vascular plants					
Duckweed (*Lemna gibba*)	Picarbutrazox (technical grade active ingredient)	7-d IC_{50}	> 0.314 mg a.i./L	2	1
Freshwater Algae					
Green alga (*Pseudokirchneriella subcapitata*)	Picarbutrazox (technical grade active ingredient)	96-h IC_{50}	> 0.338 mg a.i./L	2	1
	Picarbutrazox formulated product (9.61% w/w picarbutrazox)	96-h IC_{50}	> 1.3 mg a.i./L	2	1
	Picarbutrazox formulated product (20.26% w/w picarbutrazox)	96-h IC_{50}	> 2.5 mg a.i./L	2	1
	TZ-1E	96-h IC_{50}	> 0.3666 mg a.i./L	2	1
	TZ-2	96-h IC_{50}	6.51 mg/L	2	1
	TZ-4	96-h IC_{50}	20 mg/L	2	1
	TZ-5	96-h IC_{50}	> 94 mg/L	2	1
	TY-3	96-h IC_{50}	4.6 mg/L	2	1
Blue-green alga (*Anabaena flos-aquae*)	Picarbutrazox (technical grade active ingredient)	96-h IC_{50}	> 0.27 mg a.i./L	2	1
Saltwater invertebrates					
Mysid shrimp (*Americamysis bahia*)	Picarbutrazox (technical grade active ingredient)	28-d NOEC	< 0.0176 mg a.i./L	1	1
Eastern oyster (*Crassostrea virginica*)	Picarbutrazox (technical grade active ingredient)	96-h IC_{50}	> 0.28 mg a.i./L	2	1

Most sensitive representitive species	Test substance	Exposure/endpoint	Endpoint value	Uncertainty factor applied	Level of concern (LOC)
Marine amphipod (*Leptocheirus plumulosus*)	Picarbutrazox (technical grade active ingredient)	10-d LC_{50}	Pore water: > 0.333 mg a.i./L	2	1
Saltwater fish					
Sheepshead minnow (*Cyprinodon variegatus*)	Picarbutrazox (technical grade active ingredient)	96-h LC_{50}	> 0.26 mg a.i./L	2	1
		34-d NOEC	0.077 mg a.i./L	1	1
Saltwater algae					
Marine diatom (*Skeletonema costatum*)	Picarbutrazox (technical grade active ingredient)	96-h IC_{50}	> 0.236 mg a.i./L	2	1

Table 15 Seed treatment screening level terrestrial organisms risk assessment: Earthworms, pollinators and arthropods from seed treatment

Most sensitive representative species	Test Substance	Exposure	Effect metric	EEC[1]	RQ[2]	Level of Concern[3]
Invertebrates						
Earthworm (*Eisenia fetida*)	Picarbutrazox (technical grade active ingredient)	28-d Chronic	$LC_{50}/2$[4]: >500 mg a.i./kg soil dw	0.0012 mg a.i./kg soil[5]	<0.000002	Not exceeded
		56-d Chronic	$NOEC_{repro}/1$: 96 mg a.i./kg soil dw	0.0012 mg a.i./kg soil	0.000013	Not exceeded
	TZ-1E	28-d Chronic	$LC_{50}/2$: >550 mg a.i./kg soil dw	0.0012[6] mg a.i./kg soil	<0.000002	Not exceeded
		56-d Chronic	$NOEC_{repro}/1$: 1100 mg a.i./kg soil dw	0.0012 mg a.i./kg soil	0.000001	Not exceeded
	TZ-2	28-d Chronic	$LC_{50}/2$: >500 mg/kg soil dw	0.0009 mg a.i./kg soil	<0.000002	Not exceeded
		56-d Chronic	$NOEC_{repro}/1$: 560 mg/kg soil dw	0.0009 mg a.i./kg soil	0.000002	Not exceeded

Most sensitive representative species	Test Substance	Exposure	Effect metric	EEC[1]	RQ[2]	Level of Concern[3]
	TZ-5	28-d Chronic	LC_{50}/2: >500 mg/kg soil dw	0.0006 mg a.i./kg soil	<0.000001	Not exceeded
		56-d Chronic	$NOEC_{repro}$/1: 64 mg/kg soil dw	0.0006 mg a.i./kg soil	0.00001	Not exceeded
Soil dwelling predatory mite (*Hypoaspis geolaelaps aculeifer*)	Picarbutrazox formulated product (36.3% w/w picarbutrazox)	14-d Reproduction test in soil	LR_{50}/1: > 363 mg a.i./kg dry soil	0.0012 mg a.i./kg soil	< 0.000003	Not exceeded
			ER_{50}/1: > 363 mg a.i./kg dry soil	0.0012 mg a.i./kg soil	< 0.00003	Not exceeded
	TZ-1E	14-d Reproduction test in soil	LR_{50}/1: > 1000 mg a.i./kg dry soil	0.0012 mg a.i./kg soil	< 0.000001	Not exceeded
			ER_{50}/1: >1000 mg a.i./kg dry soil	0.0012 mg a.i./kg soil	< 0.000001	Not exceeded
	TZ-2	14-d Reproduction test in soil	LR_{50}/1: > 1000 mg a.i./kg dry soil	0.0009 mg a.i./kg soil	< 0.000001	Not exceeded
			ER_{50}/1: > 1000 mg a.i./kg dry soil	0.0009 mg a.i./kg soil	< 0.000002	Not exceeded
	TZ-5	14-d Reproduction test in soil	LR_{50}/1: > 1000 mg a.i./kg dry soil	0.0006 mg a.i./kg soil	< 0.000001	Not exceeded
			ER_{50}/1: >1000 mg a.i./kg dry soil	0.0006 mg a.i./kg soil	< 0.000001	Not exceeded

[1] EEC = Estimated Environmental Concentration.
[2] RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the endpoint value (RQ = EEC/endpoint value)
[3]Level of concern. The RQ is compared to the level of concern (LOC = 2 for predators and parasites and 1 for all other species). If the screening level risk quotient is below the level of concern, the risk is considered acceptable and no further risk characterization is necessary. For groups where the level of concern (LOC) is exceeded (RQ ≥ 1), further characterization of the risk is conducted.
[4]For acute toxicity studies, uncertainty factors of 1/2 of the EC_{50} (LC_{50}) are typically used in modifying the toxicity

values for terrestrial invertebrates, and 1/10 of the EC_{50} (LC_{50}) are typically used in modifying the toxicity values for birds and mammals when calculating risk quotients. No uncertainty factors are used to modify bee toxicity values or chronic NOEC endpoints.

[5]The soil EEC of 0.0012 mg a.i./kg soil was calculated based on the proposed seed treatment rate of 2.5 g a.i./100 kg seed for soybean seed, a seeding rate of 109 kg soybean seed/ha and accounting for soil degradation using the 90th upper percentile on the mean of the aerobic soil representative half-lives of 64 days. This concentration was calculated assuming that the product is evenly distributed in the top 0 to 15 cm depth of soil with a bulk density of 1.5 g/cm^3.

[6] EECs for transformation products were calculated conservatively assuming that 100% of the applied picarbutrazox active ingredient was instantly transformed into the transformation product on a molecular weight/weight basis.

Table 16 Consumption of treated seed screening level risk assessment for birds and mammals

	Toxicity (mg a.i./kg bw/d)	EDE[1] (mg a.i./kg bw/day)	RQ[2]	Level of Concern[3]
Small bird (0.02 kg)				
Acute	200.00	12.697	0.1	Not Exceeded
Reproduction	41.80	12.697	0.3	Not Exceeded
Medium bird (0.10 kg)				
Acute	200.00	9.974	0.05	Not Exceeded
Reproduction	41.80	9.974	0.2	Not Exceeded
Large bird (1.00 kg)				
Acute	200.00	2.908	0.01	Not Exceeded
Reproduction	41.80	2.908	0.1	Not Exceeded
Small mammals (0.015 kg)				
Acute	20.00	7.256	0.4	Not Exceeded
Reproduction	45.10	7.256	0.2	Not Exceeded
Medium mammals (0.035 kg)				
Acute	20.00	6.240	0.3	Not Exceeded
Reproduction	45.10	6.240	0.1	Not Exceeded
Large mammals (1.00 kg)				
Acute	20.00	3.436	0.2	Not Exceeded
Reproduction	45.10	3.436	0.1	Not Exceeded

[1]EDE = Estimated dietary exposure. Screening level EDEs were calculated based on the proposed seed treatment rate of 5.0 g a.i./100 kg seed for corn seed and a seeding rate of 3.15 kg corn seed/ha. The EDE is calculated using the following formula: (FIR/BW) × EEC, where: FIR = Food Ingestion Rate and BW = Body weight. 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(BW in g)$^{0.850}$. All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g)$^{0.651}$. For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g)$^{0.822}$

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

[3]Level of concern. The RQ is compared to the level of concern (LOC = 1 for birds and mammals). If the screening level risk quotient is below the level of concern, the risk is considered acceptable and no further risk characterization is necessary. For groups where the level of concern (LOC) is exceeded (RQ ≥ 1), further characterization of the risk is conducted.

Table 17 Screening level risk assessment of picarbutrazox, its end-use product and its transformation products to aquatic organisms from seed treatment

Most sensitive representitive species	Test substance	Exposure	Effects metric[1]	EEC[2]	Risk quotient[3]	Level of concern[4]
Freshwater invertebrates						
Water flea (*Daphnia magna*)	Picarbutrazox (technical grade active ingredient)	48-h Acute	EC_{50}/2: > 0.14 mg a.i./L	0.0003 mg a.i./L	< 0.003	Not Exceeded
		21 day life-cycle	NOAEC/1: 0.13 mg a.i./L	0.0003 mg a.i./L	0.003	Not Exceeded
	TZ-1E (e-isomer of picarbutrazox)	48-h Acute	EC_{50}/2: > 0.155 mg a.i./L	0.0003 mg a.i./L	< 0.003	Not Exceeded
	TZ-2	48-h Acute	EC_{50}/2: 2.8 mg/L	0.0002 mg a.i./L	0.0001	Not Exceeded
	TZ-4	48-h Acute	EC_{50}/2: > 15.5 mg/L	0.0001 mg a.i./L	< 0.00001	Not Exceeded
	TZ-5	48-h Acute	EC_{50}/2: > 44 mg/L	0.0001 mg a.i./L	< 0.000005	Not Exceeded
	TY-3	48-h Acute	EC_{50}/2: 25 mg/L	0.0002 mg a.i./L	0.00001	Not Exceeded
Midge (*Chironomus dilutes*)	Picarbutrazox (technical grade active ingredient)	10-d spiked sediment	EC_{50}/2: > 0.166 mg a.i./L	0.0024 mg a.i./L[5]	< 0.01	Not Exceeded
Freshwater fish						
Rainbow Trout (*Oncorhynchus mykiss)*	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	LC_{50}/10: >0.029 mg a.i./L	0.0003 mg a.i./L	< 0.01	Not Exceeded
	Picarbutrazox FS 400 formulated product (36.3% w/w picarbutrazox)	96-h Static	LC_{50}/10: > 8. 14 mg a.i./L	0.0003 mg a.i./L	< 0.0004	Not Exceeded
	TZ-1E	96-h Flow-through	LC_{50}/10: >0.0377 mg a.i./L	0.0003 mg a.i./L	< 0.01	Not Exceeded
	TZ-2	96-h Static	LC_{50}/10: >1.3 mg/L	0.0002 mg a.i./L	< 0.0002	Not Exceeded
	TZ-4	96-h Static	LC_{50}/10: 3.3 mg/L	0.0001 mg a.i./L	0.00003	Not Exceeded
	TZ-5	96-h Static	LC_{50}/10: >8.7 mg/L	0.0001 mg a.i./L	< 0.00001	Not Exceeded

Most sensitive representitive species	Test substance	Exposure	Effects metric[1]	EEC[2]	Risk quotient[3]	Level of concern[4]
	TY-3	96-h Daily static-renewal	LC_{50}/10: 0.22 mg/L	0.0002 mg a.i./L	0.001	Not Exceeded
Fathead minnow (*Pimephales promelas*)	Picarbutrazox (technical grade active ingredient)	33-d Early life-stage flow-through	NOAEC/1: 0.019 mg a.i./L	0.0003 mg a.i./L	0.01	Not Exceeded
Amphibians (using rainbow trout fish data as a surrogate)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	LC_{50}/10: >0.029 mg a.i./L	0.00182 mg a.i./L	< 0.1	Not Exceeded
	Picarbutrazox FS 400 formulated product (36.3% w/w picarbutrazox)	96-h Static	LC_{50}/10: > 8.08 mg a.i./L	0.00182 mg a.i./L	< 0.002	Not Exceeded
	TZ-1E	96-h Flow-through	LC_{50}/10: >0.0377 mg a.i./L	0.00182 mg a.i./L	< 0.05	Not Exceeded
	TZ-2	96-h Static	LC_{50}/10: >1.3 mg/L	0.001 mg a.i./L	< 0.001	Not Exceeded
	TZ-4	96-h Static	LC_{50}/10: 3.3 mg/L	0.001 mg a.i./L	0.0003	Not Exceeded
	TZ-5	96-h Static	LC_{50}/10: >8.7 mg/L	0.001 mg a.i./L	< 0.0001	Not Exceeded
	TY-3	96-h Daily static-renewal	LC_{50}/10: 0.22 mg/L	0.001 mg a.i./L	0.005	Not Exceeded
Freshwater vascular plants						
Duck weed (*Lemna gibba*)	Picarbutrazox (technical grade active ingredient)	7-d static renewal	IC_{50}/2: > 0.157 mg a.i./L	0.0003 mg a.i./L	< 0.002	Not Exceeded
Freshwater algae						
Green alga (*Pseudokirchneriella subcapitata*)	Picarbutrazox (technical grade active ingredient)	96-h Static	IC_{50}/2: > 0.169 mg a.i./L	0.0003 mg a.i./L	< 0.002	Not Exceeded
	TZ-1E	96-h Static	IC_{50}/2: > 0.183 mg a.i./L	0.0003 mg a.i./L	< 0.002	Not Exceeded
	TZ-2	96-h Static	IC_{50}/2: 3.255 mg/L	0.0002 mg a.i./L	0.0001	Not Exceeded
	TZ-4	96-h Static	IC_{50}/2: 10 mg/L	0.0001 mg a.i./L	0.00001	Not Exceeded

Most sensitive representitive species	Test substance	Exposure	Effects metric[1]	EEC[2]	Risk quotient[3]	Level of concern[4]
	TZ-5	96-h Static	IC_{50}/2: > 47 mg/L	0.0001 mg a.i./L	< 0.000002	Not Exceeded
	TY-3	96-h Static	IC_{50}/2: 2.3 mg/L	0.0002 mg a.i./L	0.0001	Not Exceeded
Blue-green alga (*Anabaena flow-aquae*)	Picarbutrazox (technical grade active ingredient)	96-h Static	IC_{50}/2: > 0.135 mg a.i./L	0.0003 mg a.i./L	< 0.002	Not Exceeded
Marine invertebrates						
Mysid shrimp (*Americamysis bahia*)	Picarbutrazox (technical grade active ingredient)	28-d Flow-through	NOAEC/1: < 0.0176 mg a.i./L	0.0003 mg a.i./L	> 0.02	Unlikely to be Exceeded
Eastern oyster (*Crassostrea virginica*)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	LC_{50}/2: > 0.14 mg a.i./L	0.0003 mg a.i./L	< 0.002	Not Exceeded
Marine Amphipod (*Leptocheirus plumulosus*)	Picarbutrazox (technical grade active ingredient)	10-d spiked sediment	EC_{50}/2: 0.166 mg a.i./L	0.0024 mg a.i./L[5]	< 0.01	Not Exceeded
Marine fish						
Sheepshead minnow (*Cyprinodon variegatus*)	Picarbutrazox (technical grade active ingredient)	96-h Flow-through	LC_{50}/10: > 0.026 mg a.i./L	0.0003 mg a.i./L	< 0.02	Not Exceeded
		34-d Early Life Stage, Flow-through	NOAEC/1: 0.077 mg a.i./L	0.0003 mg a.i./L	0.004	Not Exceeded
Marine alga						
Marine diatom (*Skeletonema costatum*)	Picarbutrazox (technical grade active ingredient)	96-h static	IC_{50}/2: > 0.118 mg a.i./L	0.0003 mg a.i./L	< 0.003	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, 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]Estimated environmental concentrations (EECs) at the screening level in water bodies 80 cm and 15 cm deep were determined using maximum exposure scenarios for picarbutrazox to achieve the proposed yearly cumulative rate of 2.725 g a.i./ha.

[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.

[5]The seed treatment peak pore water EEC of 0.0024 mg a.i./L was conservatively used for the screening level risk assessment of picarbutrazox used as a seed treatment (Table 19).

Table 18 Major fate input parameters for the ecological water modelling

Fate parameter	Ecological water
Residues modelled	Picarbutrazox and TZ-1E
Adsorption K_d (mL/g)	24.3 (20^{th} percentile of 6 K_d values for picarbutrazox)
Hydrolysis half-life at pH 7 and 20°C (days)	21.1
Photolysis half-life in water at 35°N latitude (days)	3.0
Aerobic soil biotransformation half-life at 20°C (days)	64 (90% confidence bound on the mean of 5 half-lives)
Aerobic aquatic biotransformation half-life at 20°C (days)	85.7 (the longer of two half-lives)
Anaerobic aquatic biotransformation half-life at 20°C (days)	31.7 (the longer of two half-lives)

Table 19 Estimated environmental concentrations of combined residues of picarbutrazox and TZ-1E in aquatic environments from run-off

Use	Water depth	Pore water Peak
Seed treatments, modelled as 1 application of 2.725 g a.i./ha per year	80 cm	0.0024[1,2]

[1]Most conservative value chosen for use in the risk assessment for sediment dwelling aquatic organisms
[2]Based on modelling input parameters presented in Table 18

Table 20 Toxic substances management policy considerations-comparison to TSMP Track 1 Criteria

TSMP track 1 criteria	TSMP track 1 criterion value		Endpoints	
			Picarbutrazox	Transformation products
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]			Laboratory studies	
	Soil	Half-life ≥ 182 days	No: Half-lives of 34.6 to 150 days	Yes: Half-lives of 191 to 307 days
	Water	Half-life ≥ 182 days	No: Total system half-lives of 20.9 to 85.7 days	Yes: Total system half-lives of 77.3 to 32400 days
	Sediment	Half-life ≥ 365 days	No: Total system half-lives of 20.9 to 85.7 days	Yes: Total system half-lives of 77.3 to 32400 days

TSMP track 1 criteria	TSMP track 1 criterion value		Endpoints	
			Picarbutrazox	Transformation products
	Air	Half-life ≥ 2 days, or evidence atmospheric transport to remote regions such as the Arctic.	Unlikely to enter the atmosphere based on the vapour pressure (<1.2 x 10^{-7} Pa at 50°C) and Henry's law constant (<1.5 x 10^{-9} atm m^3/mole); therefore, long-range atmospheric transport not expected to be important route of dissipation.	Not applicable
Bioaccumulation[4]	Log K_{OW} ≥ 5		No: 3.77±0.01	No: ≤ 3.77 based on episuit prediction
	BCF ≥ 5000		No: 342 (Corrected for fish growth and normalised to 5% lipid content)	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}).

Table 21 List of supported use claims for VAYANTIS Seed Treatment

Supported Uses
Corn (field, pop, sweet, seed): Control of seed decay/pre-emergence damping-off and post-emergence damping-off caused by *Pythium* spp. at 2.5 –12.5 mL/100 kg seed: - 2.5 mL/100 kg seed for fields with a known low level of pre-emergence damping-off; ~6.25 mL/100 kg seed for fields with a known higher level of pre-emergence damping-off; and, - up to 12.5 mL/100 kg seed for fields with a known history of post-emergence damping-off.
Soybean: Control of seed decay/pre-emergence damping-off and post-emergence damping-off caused by *Pythium* spp. at 2.5–6.25 mL/100 kg seed: - 2.5 mL/100 kg seed for fields with a known low level of damping-off; and, - up to 6.25 mL/100 kg seed for fields with a known higher level of pre-emergence damping-off.

Appendix II Supplemental maximum residue limit information – International situation and trade implications

Picarbutrazox is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for picarbutrazox in Canada are the same as corresponding tolerances to be promulgated in the United States, except for certain livestock commodities, in accordance with Table 1.

Once established, the American tolerances for picarbutrazox will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[9] listed for picarbutrazox in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1 Comparison of Canadian MRLs and American Tolerances (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)
Eggs; fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; milk	0.01	Not established

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.

References

PMRA Document Number | References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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