Proposed Registration Decision PRD2021-04

Pyridate and Tough 600 EC Herbicide

(*publié aussi en français*)

6 July 2021

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2021-4E (print version)
H113-9/2021-4E-PDF (PDF version)

Table of Contents

Overview

Proposed registration decision for pyridate

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 Pyridate Technical and Tough 600 EC Herbicide, containing the technical grade active ingredient pyridate, for selective suppression or control of certain emerged broadleaf weeds. Tough 600 EC Herbicide may be applied pre-plant and/or pre-emergence in corn (field and sweet), mint, chickpeas, lentils, field peas and canola, and post-emergence in corn (field and sweet), chickpeas and mint.

Pyridate was previously registered by the PMRA between 1990 and 2002 (Decision Document E91-01, *Pyridate Herbicide*). This represents a new registration for pyridate and its associated end-use product.

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 pyridate and Tough 600 EC Herbicide.

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.

---

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."

For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of the Canada.ca website.

Before making a final registration decision on pyridate and Tough 600 EC Herbicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on pyridate and Tough 600 EC Herbicide, 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 pyridate?

Pyridate is a contact herbicide that inhibits photosynthesis in plants. Pyridate is to be used alone or in combination with other herbicides for selective suppression or control of certain emerged broadleaf weeds either prior to planting or in labelled crops.

Health considerations

Can approved uses of pyridate affect human health?

Tough 600 EC Herbicide, containing pyridate, is unlikely to affect your health when used according to label directions.

Potential exposure to pyridate may occur through the diet (food and drinking water), when handling and applying the end-use product, or when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are 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.

---

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

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

In laboratory animals, the acute toxicity of the technical grade active ingredient pyridate was low by the oral, inhalation and dermal routes. Pyridate was minimally irritating to the eyes. It was mildly irritating to the skin and caused an allergic skin reaction; consequently, the signal word "CAUTION" and the hazard statements "SKIN IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the label.

The acute toxicity of the end-use product, Tough 600 EC Herbicide containing pyridate, was low via the oral, dermal and inhalation routes of exposure. It was moderately irritating to the eyes and skin and caused an allergic skin reaction; consequently, the signal word "WARNING" and the hazard statements "EYE AND SKIN IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of pyridate to cause neurotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on body weight and neurobehavioural changes. There was no evidence to suggest that pyridate damaged genetic material. Pyridate caused benign liver tumours in one mouse study; however, the concern for these tumours and the overall concern for carcinogenicity is low. There was an indication that the young were more sensitive than adult animals in one rabbit study in which non-serious effects were observed in the absence of maternal toxicity. 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.

Aggregate acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups are expected to be less than 21% of the acute reference dose, and are not of health concern.

Aggregate chronic dietary (food plus drinking water) intake estimates for the general population and all population subgroups are expected to be less than 43% of the acceptable daily intake, and are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose a health risk of concern.

MRLs for pyridate determined from the acceptable residue trials conducted throughout Canada, the United States and Austria on field corn, sweet corn, mint, chickpeas, lentils, dry field peas and canola can be found in the Science Evaluation of this document.

Occupational risks from handling Tough 600 EC Herbicide

Occupational risks are not of health concern when Tough 600 EC Herbicide is used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying Tough 600 EC Herbicide, and workers entering recently treated fields can come in direct contact with pyridate residues on the skin and through inhalation. Therefore, the label specifies to wear protective eyewear (goggles or face shield) during all mixing and loading activities. In addition, anyone mixing, loading, applying, or performing clean-up and repair activities with up to 448 L per day of Tough 600 EC Herbicide must wear coveralls over a long-sleeved shirt, long pants, socks, chemical-resistant footwear and chemical-resistant gloves. When mixing, loading, applying, or performing clean-up and repair activities with more than 448 L of product per day, workers must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, socks, chemical-resistant footwear and chemical-resistant gloves. When applying more than 500 L product per day, a closed-cab tractor is required. Gloves are not required when applying within a closed-cab tractor.

The label also requires that workers do not enter or be allowed into treated fields during the preharvest intervals (PHIs) or the restricted-entry intervals (REIs) as specified in Appendix I, Table 9.

Taking into consideration the label statements, the number of applications and the duration of exposure for handlers and postapplication workers, the risks to these individuals are not of health concern.

Health risks in residential and other non-occupational environments

As Tough 600 EC Herbicide is a commercial agricultural end-use product, a residential exposure assessment is not required.

Health risks to bystanders

Bystander risks are not of health concern when Tough 600 EC Herbicide is used according to the proposed label directions and spray drift restrictions are observed.

Environmental considerations

What happens when pyridate is introduced into the environment?

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

When pyridate is used as a ground spray application to control herbicides, it rapidly breaks down in the presence of water and moisture to the major transformation product, pyridafol, and does not remain in the environment. Pyridate and pyridafol will not move from the treatment area to the air, and, therefore, will not be transported to another area through the air or atmosphere. Pyridafol can remain in the environment and move downward in the soil and reach groundwater.

Pyridafol can also move off the treatment area to reach surface waters such as ponds, streams, and rivers. However, there is no known toxicity of pyridafol to terrestrial or aquatic life. Pyridate and its breakdown products are not expected to accumulate in animal tissues.

Pyridate can affect pollinators, non-target terrestrial plants, and small wild mammals following application. Pyridate can also affect some aquatic life if it enters ponds, streams, or rivers after it is sprayed. Precautions and no-spray buffer zones are required to reduce environmental exposures to pyridate. When pyridate is used in accordance with the label and the required precautions, the resulting environmental risk is considered to be acceptable.

Value considerations

Tough 600 EC Herbicide provides suppression or control of certain emerged annual broadleaf weeds in agricultural settings.

What is the value of Tough 600 EC Herbicide?

Tough 600 EC Herbicide provides suppression or control of certain emerged annual broadleaf weeds and has good tank mix flexibility for use in field and sweet corn. It has activity on important weeds present in agricultural systems. Control of broadleaf weeds with Tough 600 EC Herbicide in mint has been identified as a priority by Canadian growers.

The registration of Tough 600 EC Herbicide would provide Canadian growers with access to a product that is currently available in the United States for similar uses. Tough 600 EC Herbicide also has a new mode of action for managing weeds in mint. Tough 600 EC Herbicide may be particularly useful in managing weeds that have developed resistance to other modes of action when used in tank mix with other herbicides.

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 Pyridate Technical and Tough 600 EC Herbicide 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 pyridate on the skin or through inhalation, workers mixing, loading and applying Tough 600 EC Herbicide and performing cleaning and repair activities must wear personal protective equipment as specified below.

Wear protective eyewear (goggles or face shield) during mixing and loading. In addition, wear coveralls over a long-sleeved shirt, long pants, socks, chemical-resistant footwear and chemical-resistant gloves while mixing, loading, applying, or performing clean-up and repair activities with up to 448 L product per day. When mixing, loading, applying or performing clean-up and repair activities with more than 448 L product per day, wear chemical-resistant coveralls over a long-sleeved shirt, long pants, socks, chemical-resistant footwear and chemical-resistant gloves. When applying more than 500 L product per day, a closed-cab tractor is required. Gloves are not required when applying within a closed-cab tractor.

Risks to workers are not of health concern when Tough 600 EC Herbicide is used according to the proposed label directions and when adhering to restricted-entry intervals (REIs) as specified in Appendix I, Table 9.

Furthermore, a standard label statement to protect against drift during application is present on the label.

Environment

- Label statements and no-spray buffer zones to reduce the risk of spray drift to terrestrial and aquatic ecosystems are required.
- Precautionary statements are required on labels to reduce the potential for runoff to adjacent aquatic habitats.
- Label statements to inform users of the potential toxicity to non-target terrestrial plants, mammals, and aquatic organisms are required.

Next steps

Before making a final registration decision on pyridate and Tough 600 EC Herbicide, 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

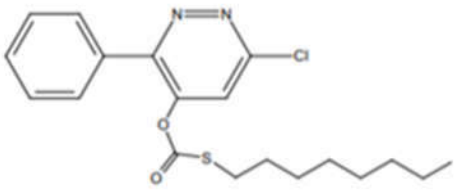
When Health Canada makes its registration decision, it will publish a Registration Decision on pyridate and Tough 600 EC Herbicide (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science evaluation

Pyridate and Tough 600 EC Herbicide

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Pyridate
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*O*-6-chloro-3-phenylpyridazin-4-yl *S*-octyl thiocarbonate
2. Chemical Abstracts Service (CAS)	*O*-(6-chloro-3-phenyl-4-pyridazinyl) S-octyl carbonothioate
CAS number	55512-33-9
Molecular formula	
Molecular weight	378.91
Structural formula	$C_{19}H_{23}ClN_2O_2S$
Purity of the active ingredient	91.22% nominal

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

Technical product—Pyridate Technical

Property	Result
Colour and physical state	Dark brown liquid
Odour	Characteristic odor (mercaptans and sulfur containing compounds)
Melting range	26.5–27.8°C
Boiling point or range	Decomposes without boiling from ~250°C

Property	Result
Density	1.28 g/cm^3
Vapour pressure at 25°C	0.000998 mPa
Ultraviolet (UV)-visible spectrum	pH λ(nm) ε (cm^{-1}mol^{-1}) Log ε neutral 295 2533 3.40 246 14415 4.16 204 22393 4.35 Acidic 295 2790 3.45 247 14275 4.15 204 24257 4.38 Alkaline 307 8809 3.95 295 7491 3.87 260 8581 3.93 227 21374 4.33 204 33893 4.53
Solubility in water at 20°C	0.33 mg/L at pH = 3 1.67 mg/L at pH = 5 0.32 mg/L at pH = 7
Solubility in organic solvents at 20°C	Solvent Solubility (g/L) n-Heptane >250 p-Xylene >250 1,2-Dichloroethane >250 Methanol >250 Acetone >250 Ethyl Acetate >250
n-Octanol-water partition coefficient (K_{ow})	log K_{ow}= 4.01
Dissociation constant (pK_a)	Does not dissociate.
Stability (temperature, metal)	Stable in the presence of metal and metal ions at normal and elevated temperatures, as well as sunlight.

End-use product—Tough 600 EC Herbicide

Property	Result
Colour	Brown
Odour	Mildly unpleasant
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Label concentration	Pyridate 600 g/L nominal
Container material and description	HDPE plastic containers

Property	Result
Density	1.07
pH of 1% dispersion in water	4.8 (1% solution)
Oxidizing or reducing action	The product is a mixture of components that do not represent an oxidising or reducing hazard.
Storage stability	No degradation of active ingredient was observed after accelerated storage stability testing and long term study at ambient temperature.
Corrosion characteristics	Product is corrosive to metal (galvanized metal), slightly corrosive to iron and not corrosive to stainless steel, tin, polyethylene, PE/EV, PET or aluminium bottles.
Explodability	Product is not explosive.

1.3 Directions for use

Tough 600 EC Herbicide is a contact herbicide to be used alone or in combination with other herbicides for selective suppression or control of certain emerged broadleaf weeds. Tough 600 EC Herbicide may be used as a post-emergent contact herbicide in the following crops: corn (field and sweet), chickpeas and mint. Tough 600 EC Herbicide may be used on the following crops prior to emergence as a pre-seed or pre-emergent herbicide, for suppression or control of labelled weeds that are emerged at the time of application in corn (field and sweet), mint, chickpeas, lentils, field peas, and canola.

1.4 Mode of action

Pyridate belongs to the Weed Science Society of America (WSSA) / Herbicide Resistance Action Committee (HRAC) Group 6 mode of action- inhibitors of photosystem II. This mode of action means the herbicide only moves upward in sensitive plants with symptoms such as chlorosis between leaf veins and along leaf margins appearing first in older leaves, followed by necrosis. Pyridate must be applied to young, actively growing weeds as there is no residual activity.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

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

2.2 Method for formulation analysis

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

2.3 Methods for residue analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media.

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method S11-03700 in plant matrices and Method S11-01578 in animal matrices) were relied on for data generation and proposed for enforcement. 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 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 methods were similar to those used in the metabolism and radiolabelled feeding studies; thus, further demonstration of extraction efficiency with radiolabelled food commodities was not required. Methods for residue analysis in plant and animal matrices are summarized in Appendix I, Tables 1a and 1b.

3.0 Impact on human and animal health

3.1 Toxicology summary

A detailed review of the toxicology database for pyridate was conducted. Pyridate is a pyridazine herbicide that acts by inhibiting the photosystem II process, triggering the release of toxic forms of oxygen (single oxygen molecules that act as free radicals) and causing rapid plant cell wall degradation. The mammalian mode of action of pyridate is not known.

The toxicology database for pyridate is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The majority of the studies were conducted in the 1970s and 1980s with a few studies being conducted and discussion papers prepared more recently. The required studies were carried out in accordance with the international testing protocols and Good Laboratory Practice in place at the time the studies were conducted. However, there were a number of studies that were considered supplemental because of limited reporting or they were conducted before international testing protocols or Good Laboratory Practice existed. Several other supplemental and/or non-guideline studies were available, including a metabolism and toxicokinetic study in the dog, a comparative acute oral toxicity study in non-pregnant and pregnant female rats, an electroencephalogram analysis of rats following acute oral dosing, and a comparative pharmacology study in mice, rats and rabbits. Additionally, there were toxicity studies available for two pyridate metabolites, pyridafol and pyridafol-*N*-glucoside. The human health risk assessment also considered any relevant information found in the published scientific literature. Overall, the scientific quality of the toxicology database is acceptable, and the database is considered adequate to characterize the majority of the toxic effects that may result from exposure.

Pyridate is composed of a phenyl-pyridazine moiety linked to an octane-1-thiol side chain via a thiocarbamate group. Metabolism and toxicokinetic studies with pyridate, carbon $(C)^{14}$-radiolabelled on the pyridazine ring, were conducted in the rat via the oral route. Toxicokinetic studies with a radiolabel on the octane-1-thiol side chain portion of the molecule were not available.

The available toxicokinetic studies demonstrated that pyridate was rapidly absorbed and eliminated. Peak plasma concentration data suggested slowing or saturation of absorption as dose levels increased. The clearance of radioactivity was faster in males than in females, resulting in higher plasma concentrations in females. Plasma concentrations were also higher in animals after multiple-dosing compared to single-dosing. Fecal excretion of radioactivity was found to be higher in males than in females and also increased as dose levels increased. Less than 1% of the administered dose was detected in tissues 168 hours post-dosing. The retained radioactivity after a single dose administration was predominantly found in the kidney, bones, liver, gastrointestinal tract and skin in both sexes, the fat of males, and ovaries of females. After multiple doses, radioactivity was also detected in the spleen of both sexes. In general, higher levels of radioactivity were detected in the tissues of females compared to males.

In the urine, eight metabolites were identified, whereas unchanged pyridate was not detected. The primary urinary metabolite identified was pyridafol, which forms from the nearly complete hydrolysis of the thiocarbamate moiety of pyridate. Pyridafol then undergoes oxidation in the para position of the phenyl moiety to form Metabolite A, glucuronidation to form Metabolite B, and sulfation to form Metabolite C. The five minor metabolites (Metabolites D to H) that were identified in urine are formed via sulfation or glucuronidation of Metabolite A or from various transformation reactions of pyridafol (hydrolysis, oxidation, glutathione conjugation, glucuronidation, sulfation, cleavage, methyl transfer, acetylation). The metabolite profile in urine after repeated dosing suggested that higher oxidase and glucuronidase activity occurs when compared to single dose administration. In feces, unchanged pyridate, pyridafol, and Metabolite A were detected. The identification of select metabolites of pyridate (Metabolite A to Metabolite H) is presented in Appendix I, Table 2.

Metabolism and toxicokinetic studies in rats following oral dosing were also available with the metabolite pyridafol, $(C)^{14}$-radiolabelled on the pyridazine ring. The toxicokinetic profile of pyridafol was generally similar to that of pyridate. A metabolism and toxicokinetic study with the metabolite pyridafol-*N*-glucoside (also known as Metabolite A) in rats demonstrated lower absorption when compared to pyridate and pyridafol. In addition to unchanged pyridafol-*N*-glucoside, the urine contained two major metabolites, one identified as pyridafol and an unidentified metabolite similar in structure to pyridafol.

Although toxicokinetic studies that included a radiolabel on the octane-1-thiol side chain were not submitted, it appears as though pyridate is rapidly hydrolyzed to form pyridafol and thiocarbonic acid *S*-octyl ester. The applicant provided a proposed metabolic pathway for thiocarbonic acid *S*-octyl ester based on information from the published scientific literature.

The applicant proposed that thiocarbonic acid *S*-octyl ester will readily undergo decarboxylation due to the position of the carboxyl group in the thioester, resulting in octane-1-thiol, which would then undergo glucuronidation or methylation followed by oxidation of the sulfur to yield octane-1-sulfinic acid.

A supplemental gavage metabolism and toxicokinetic study with pyridate in the dog was also available. Plasma concentration data suggested slower absorption of pyridate in dogs when compared to rats. Similar to rats, female dogs demonstrated a higher degree of absorption when compared to males. In addition, the rate and extent of elimination in the urine and feces of dogs was similar to that of rats. The proportion of urinary metabolites in dogs was slightly different than in rats, with higher relative levels of the Metabolite A compared to pyridafol.

In acute toxicity testing, pyridate technical was of low toxicity by the oral route in mice and rats, by the dermal route in rabbits, and by the inhalation route in rats. Pyridate was mildly irritating to the skin and minimally irritating to the eyes in rabbits. Pyridate was also found to be a dermal sensitizer in guinea pigs by the open-epicutaneous and Buehler tests. The metabolite pyridafol was of slight acute oral toxicity in rats, and the metabolite pyridafol-*N*-glucoside was of low acute oral toxicity in rats.

The end-use product, Tough 600 EC Herbicide, was determined to be of low acute toxicity by the oral, dermal and inhalation routes in the rat. Tough 600 EC Herbicide was moderately irritating to the eyes and skin of rabbits and was positive for dermal sensitization using the maximization assay in guinea pigs.

A 21-day dermal toxicity study in the rat resulted in minimally decreased body weights in male rats, as well as dermal hyperplasia, inflammation, scabbing and ulceration at the application site in both sexes. These effects occurred at the limit dose of testing, which was the only dose tested.

Repeat-dose dietary toxicity studies with pyridate were available in mice, rats, and dogs. Studies in which pyridate was administered via gavage to rats or dogs or via capsule to dogs were also available. In these studies, the dog was the most sensitive species to the effects of pyridate, followed by the rat, and then the mouse. The most sensitive endpoint following dietary administration to rodents was decreased body weight, whereas neurobehavioural effects, such as salivation, hypoactivity, altered gait, and tremors, were the most sensitive endpoints following capsule or gavage administration to rats or dogs. In dogs, these neurobehavioural findings were more severe than in rats and were accompanied by lesions of the sciatic nerve that were initially classified as degenerative myelopathy and subsequently re-classified as myelin digestion chambers.

Renal toxicity, including urinary changes and hydronephrosis, and mineral deposition in the lymph nodes were evident following short-term dosing in rats. Effects in the liver, in the form of increased weight and hepatocellular vacuolation, were also observed in the Swiss mouse after long-term dosing. With long-term dosing of B6C3F1 mice, inflammation and abscesses in the ovaries, resulting in increased deaths due to the abscesses, were observed in females at the highest dose level tested.

These findings were determined to be of uncertain toxicological significance given the lack of other indications in the database that pyridate causes animals to be immunocompromised, and the lack of similar ovarian findings in other studies and species.

Pyridate was negative in a genotoxicity battery that included assessments of reverse mutations in bacteria, chromosomal aberrations in Chinese hamster ovary cells, induction of micronuclei in mice, unscheduled DNA synthesis in rat hepatocytes, cell transformations in Syrian hamster kidney cells, and somatic cell mutations in mice. Negative results in bacterial reverse mutation assays were also obtained for the metabolite pyridafol.

There was no evidence of tumourigenicity in an 18-month dietary oncogenicity study in B6C3F1 mice or in a 28-month dietary chronic toxicity/oncogenicity study in Wistar rats. In a 24-month dietary oncogenicity study in Swiss mice, there was an increase in the incidence of benign liver tumours in males at the high-dose level compared to the concurrent control group. However, the possibility that a higher survival rate, which occurred in the high-dose males in this study, contributed to this increased incidence of liver nodules could not be ruled out. These considerations, combined with the benign nature of the observed tumours, resulted in a low level of concern overall for the potential tumourigenicity of pyridate.

In a 3-generation dietary reproductive toxicity study in rats, there were decreases in body weights in parental animals, as well as in pups from all three generations. Parental animals also exhibited changes in organ weights (decreased absolute and relative thyroid weight, increased absolute and relative liver weight, and increased relative kidney weight). Offspring of the third generation that were maintained on the test diet for four weeks post-weaning also exhibited increased absolute and relative kidney weight and increased relative liver weight. There was no evidence of increased sensitivity of the young noted for the parameters that were assessed in this study. However, there were a number of limitations in the conduct of this study, including the fact that clinical signs of toxicity were not recorded in offspring, and that the litters were culled on post-natal day 1 to ten pups per litter, which could have impacted the assessment of early postnatal survival and other effects. Furthermore, this study was conducted prior to the implementation of internationally recognized test guidelines. Despite the limitations and supplemental nature of the study, the quality of the study was considered to be sufficient for establishing points of departure for the endpoints that were assessed within the study and for consideration for use in the risk assessment.

In a guideline gavage developmental toxicity study in the rat, there was no evidence of sensitivity of the young or treatment-related malformations. Maternal animals exhibited neurobehavioral clinical signs of toxicity and decreased body weights, as well as mortalities at the highest dose level. Fetuses had decreased body weights along with delayed or absent ossification of some bones in the presence of maternal toxicity. In a supplemental gavage developmental toxicity study in the rat, maternal deaths and reduced body weights were observed at the same dose level at which increases in late intrauterine deaths and altered development of the kidney were observed in fetuses. Increased sensitivity of pregnant rats to the acute, high-dose effects of pyridate when compared to non-pregnant rats was demonstrated in a special gavage study.

In Chinchilla rabbits, no treatment-related maternal or developmental effects were noted in the first of two gavage developmental toxicity studies. In the second study conducted at higher dose levels, delayed fetal bone ossification was observed in the absence of maternal toxicity. At the next higher dose level, decreased maternal and fetal body weights were observed, as well as increased early resorptions and post-implantation loss. In a gavage developmental toxicity study in New Zealand White rabbits, there was no evidence of sensitivity of the young. Treatment-related findings included decreased maternal and fetal body weights and an increased incidence of abortions. There were no treatment-related malformations in either strain of rabbit.

In a gavage acute neurotoxicity study in rats, mortality, severe neurotoxic clinical signs and an increased incidence of peripheral nerve degeneration were observed at the highest dose tested. Although there was a lack of neuropathological assessment in the lower dose groups, concern for these missing data was low considering the marginal increase at the high-dose level relative to the control group.

A request to waive the requirement for a short-term neurotoxicity study was submitted by the applicant based on the argument that the toxicology database available for pyridate contains sufficient data to characterize the points of departure for neurotoxic findings in adult dogs and rats. Additionally, the dog was more sensitive than the rat to the neurotoxic effects of pyridate. As such, conducting an additional short-term neurotoxicity study in the rat would be unlikely to provide additional information that is not currently known. Based on these observations, the request to waive the requirement for a short-term neurotoxicity study was granted.

The applicant also requested that the requirement for a development neurotoxicity study be waived using the same rationale as the short-term neurotoxicity waiver request. However, this waiver request was not accepted because the potential sensitivity of the young to the neurotoxic effects of pyridate was not assessed in any of the available studies. Notably, there was no assessment of clinical signs of toxicity in the young in the 3-generation reproductive toxicity study. Therefore, uncertainty remains with regards to potential adverse neurotoxic effects in the young, and as such, a threefold database uncertainty factor will be applied for exposure scenarios relevant to the young.

A supplemental non-guideline study was available investigating the electrical activity in the cortical structures of the brain in rats. The only indications of an effect were a prolonged waking period and corresponding decrease in sleep, suggesting that pyridate activated the cortical regions of the brain of these animals. There was no other evidence of acute or delayed effects on electroencephalogram activity in the central nervous system after dosing with pyridate.

A supplemental non-guideline study examining the effects of pyridate on the central nervous, respiratory, and circulatory systems in mice, rats, and rabbits following acute dosing via the oral (gavage), intravenous, or intraperitoneal routes was available. Clinical signs of toxicity were observed in animals and were similar to those observed throughout the toxicology database. Overall, acute dosing with pyridate had only a slight or no effect on the central nervous, respiratory, and cardiovascular system parameters assessed in this study.

An in vitro study of the estrogenic and antiestrogenic activity of pyridate found in the published scientific literature demonstrated that pyridate had a weak capacity to bind both the antiestrogenic and androgenic receptors.

The identification of select metabolites is presented in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with pyridate (along with studies conducted with metabolites) and its associated end-use products, 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.

Health incident reports

Pyridate is pending registration for use in Canada and as of 18 November 2020, no human or domestic animal incident reports were submitted to the PMRA.

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, there were limitations in the available database. Three guideline gavage developmental toxicity studies conducted in the rabbit, and one in the rat, were available. Additionally, a 3-generation dietary reproductive toxicity study in the rat was available; however, it was considered supplemental due to limitations in the parameters measured, including the lack of assessment of clinical signs in the young. Additionally, the database contained both a dose range-finding and a non-guideline gavage developmental toxicity study in the rat, and a special non-guideline acute oral toxicity study comparing pregnant and non-pregnant rats. A developmental neurotoxicity study conducted with pyridate was not available, and the assessment of potential neurotoxicity in the young in the available studies was limited. Thus, an adequate assessment of neurotoxicity in young animals is currently not available. Given that neurobehavioural clinical signs of toxicity were one of the most sensitive endpoints in the rat and dog, residual uncertainty remains regarding sensitivity of the young to potential neurotoxic effects of pyridate. This residual uncertainty is reflected in the form of a database uncertainty factor of threefold in the risk assessment.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of the offspring compared to parental animals in the parameters measured in the 3-generation dietary reproductive toxicity study in the rat. Observed effects in the offspring (body weight reduction and organ weight changes) only occurred at dose levels at which deceased body weights were observed in parental animals. The prenatal development toxicity studies in rats and New Zealand White rabbits provided no indication of increased sensitivity of the young to in utero exposure. In rats, developmental effects (reduced fetal weight and incomplete bone

ossification) only occurred at a dose level at which mortalities, neurobehavioural clinical signs of toxicity, and decreased body weights were observed in dams. In New Zealand White rabbits, abortions and reduced fetal weight were observed at a dose level causing body weight loss in maternal animals. Concern for the serious effect of abortions noted in New Zealand White rabbits was tempered by the co-occurrence of maternal toxicity.

In the prenatal developmental toxicity studies in the Chinchilla rabbit, there was evidence of increased sensitivity of the young as delayed bone ossification was observed in the absence of maternal toxicity. However, this endpoint is not considered serious in nature. There was a serious effect at a higher dose level in this study in the form of increased early resorptions and post-implantation loss, which occurred in the presence of decreased body weights and food consumption in maternal animals. Concern for this finding was tempered by the co-occurrence of maternal toxicity.

There was evidence of neurotoxicity in adult animals in the available database for pyridate. As described above, an adequate assessment of sensitivity of the young is currently not available and residual uncertainty remains concerning sensitivity of the young to potential neurotoxic effects. As such, a threefold database uncertainty factor was applied for concerns regarding potential sensitivity of the young to neurotoxic effects of pyridate. Since these concerns were addressed with a database uncertainty factor, and the toxicology reference values selected for risk assessment provide an intrinsic margin to the serious endpoints in the rabbit developmental toxicity studies, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold for the current assessment of pyridate.

3.2 Acute reference dose (ARfD)

To estimate acute dietary risk, the point of departure from the 90-day oral (capsule) toxicity study in the dog was selected for risk assessment. A NOAEL for acute effects of 80 mg/kg bw/day was selected as the point of departure for neurotoxic clinical signs that were observed after a single dose at the 120 mg/kg bw/day dose level. These effects are relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. Residual uncertainty regarding potential sensitivity of the young to neurotoxic effects was addressed through the application of a threefold database uncertainty factor. As discussed in the *Pest Control Products Act* Hazard Characterization Section, the PCPA factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{80 \text{ mg/kg bw/day}}{300} = 0.3 \text{ mg/kg bw of pyridate}$$

The ARfD provides a margin of 1500 to the NOAEL for increased early resorptions observed in Chinchilla rabbits in the developmental toxicity study. The abortions noted in New Zealand White rabbits were observed late in the study after the administration of several doses and were not considered relevant to an acute scenario.

3.3 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 19 mg/kg bw/day from the 3-generation dietary reproductive toxicity study in the rat was selected. At a dose level of 110 mg/kg bw/day, reductions in body weight in parental animals and offspring were observed. The point of departure selected for risk assessment is similar to the NOAELs of 16 mg/kg bw/day established in the 28-month chronic toxicity/oncogenicity study in the rat and the overall NOAEL of 20 mg/kg bw/day in the 90-day oral (capsule) studies in the dog. These studies were considered along with the 3-generation reproductive toxicity study in selecting the point of departure for repeated dietary exposure as they provided the lowest NOAELs in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. Residual uncertainty regarding potential sensitivity of the young to neurotoxic effects was addressed through the application of a threefold database uncertainty factor. As discussed in the *Pest Control Products Act* Hazard Characterization Section, the PCPA factor was reduced to

1-fold. The CAF is thus 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{19 \text{ mg/kg bw/day}}{300} = 0.06 \text{ mg/kg bw/day of pyridate}$$

The ADI provides margins of 5000 and 7500, respectively, to the NOAELs for abortions observed in New Zealand White rabbits and resorptions observed in Chinchilla rabbits in the developmental toxicity studies.

Cancer assessment

An increased incidence of benign liver tumours was observed in Swiss mice following chronic dosing with pyridate. However, the concern for these tumours was low as the higher survival rate of treated animals likely contributed to this increased tumour development and there was no increase in malignant tumours. There was no evidence of tumourigenicity in rats or in B6C3F1 mice following chronic dosing with pyridate, nor was there any evidence of genotoxicity. Overall, the weight of evidence supported the conclusion that carcinogenicity was not an endpoint of concern for risk assessment.

3.4 Occupational risk assessment

3.4.1 Toxicology reference values

Short- and intermediate-term dermal and inhalation

For short- and intermediate-term occupational dermal and inhalation risk assessments, the NOAEL of 19 mg/kg bw/day from the 3-generation dietary reproductive toxicity study in the rat was selected. At a dose level of 110 mg/kg bw/day, reductions in body weights in parental animals and offspring were observed. The available 21-day dermal toxicity study was not

considered appropriate for use in risk assessment as the study was limited to one dose level and did not assess the most sensitive species (the dog) or other relevant endpoints of concern such as developmental toxicity endpoints observed in various studies with pyridate. Additionally, a short-term inhalation toxicity study was not available. Therefore, an oral study was considered necessary for use in the dermal and inhalation risk assessments, and the NOAEL from the The 3-generation reproductive toxicity study was considered protective of the points of departure established in the dog toxicity studies and the rat and rabbit developmental toxicity studies.

The target margin of exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability, and an additional threefold database uncertainty factor to address residual uncertainty regarding potential sensitivity of the young to neurotoxic effects. 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.

3.4.2 Route and duration of exposure

For mixers, loaders and applicators, occupational exposure to Tough 600 EC Herbicide is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure to Tough 600 EC Herbicide is characterized as short- to intermediate-term in duration and is predominantly by the dermal route.

3.4.3 Dermal absorption

In vivo dermal absorption study in rats and in vitro dermal absorption studies in rat and human skin were reviewed. A dermal absorption value of 33% was selected for the risk assessment of pyridate.

The dermal absorption of pyridate was determined in vivo in male Sprague-Dawley rats after a single dermal application of a concentrate or dilute EC formulation at 0.0225 mg/cm^2 (low dose) or 6 mg/cm^2 (high dose) to three groups of four animals at each dose level. Each dose was washed after 6 hours of exposure and animals were sacrificed 6, 24 or 96 hours post-exposure. The application site was subjected to tape stripping immediately after sacrifice. Mean recovery of the applied dose was acceptable at 100 ± 10 % in both dose groups.

There was an inverse relationship between the applied dose and the absorbed dose (as the sum of amounts in excreta including cage wash, blood, carcass and the remaining surrounding skin). This was reflected in the application site skin radioactivity after tape stripping and in all tape strips, which continued to decrease with increasing sacrifice times to 24 or 96 hours, suggesting that the skin bound residues were bioavailable over time and should be included in the calculation of the absorbed dose.

The majority of the administered dose was recovered either in washing solutions, in the plastic protecting device, or in gauze covers which is considered not available for absorption. Therefore, these very high amounts of pyridate recovered in gauze covers for the high dose groups are not

acceptable. For the low dose groups, the percent available dose for each rat was corrected for the amount recovered in gauze covers at prewash after 6 hours of exposure from the applied dose in each rat. The corrected mean percent absorption in each low dose group were 48% at 6 hours, 36% at 24 hours and 33% at 96 hours.

Dermal absorption was evaluated in vitro after application of pyridate to dermatomed rat or human skin samples mounted on static Franz cells in two separate studies. Identical to the in vivo rat study, nominal applied doses in each study were 0.022 mg/cm^2 and 6 mg/cm^2. In both studies, the test doses remained on the skin for 6 hours before removal by an appropriate washing solution. After the collection of last receptor fluid sample at 24 hours, skin sites were washed again, and the stratum corneum was removed with tape stripping. The majority of the administered dose was unabsorbed and was recovered in the skin washings at 6 hours at both dose levels in rat as well as in human skin. The mean dermal absorption values were 47% at the low dose and 12% at the high dose in the rat in vitro study, and 34% at the low dose and 1% at the high dose in the human in vitro study. This suggests an inverse relationship between the applied dose level and the percent absorbed dose level (as the sum of average residues in the receptor compartment and all skin).

Although there is uncertainty with the selected 33% value from the in vivo rat study due to the high amount in the pre-wash gauze covers, this value is supported by the in vitro dermal absorption values of 34% and 47% at 24 hours from the low dose in vitro dermal absorption studies in human and in rat, respectively.

3.5 Occupational and residential exposure assessment

3.5.1 Acute hazards of Tough 600 EC Herbicide and mitigation measures

3.5.1.1 Tough 600 EC Herbicide

The acute hazard assessment indicated that Tough 600 EC Herbicide is moderately irritating to the eyes and moderately irritating to the skin of rabbits. Based on these acute hazards, coveralls over a long-sleeved shirt, long pants, socks, chemical-resistant footwear and chemical-resistant gloves are required for workers during mixing, loading, application, clean-up and repair. In addition, protective eyewear (goggles or face shield) is required during mixing and loading.

3.5.2 Occupational exposure and risk assessment

3.5.2.1 Mixer, loader and applicator exposure and risk assessment

Individuals have the potential for exposure to Tough 600 EC Herbicide during mixing, loading, application, clean-up and repair activities.

Exposure estimates were derived for workers mixing and loading a liquid with an open-transfer system. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database and/or the Pesticide Handlers Exposure Database (PHED, v1.1) for mixers, loaders and applicators applying Tough 600 EC Herbicide to chickpeas, corn (field and sweet), lentils, field peas, canola and mint using a groundboom sprayer. The unit exposure values in the risk assessment are based on handlers wearing various levels of PPE (Appendix I, Table 6).

Dermal exposure was estimated using the unit exposure values with the amount of product handled per day (derived from the maximum application rate and the default area treated per day for each crop) and the dermal absorption value of 33%. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Dermal and inhalation exposures were combined and normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the selected toxicology reference value to obtain the margin of exposure (MOE); the target MOE is 300. Dermal and inhalation MOEs were combined, since the dermal and inhalation endpoints are based on the same toxicological effects. Calculated MOEs were greater than the target MOE of 300 for farmers wearing a single layer of PPE, but not for custom applicators. As such, various mitigation measures including restricting the amount handled per day, were applied to achieve the target MOE of 300, and are therefore not of health concern (Appendix I, Table 7).

Taking into account both the acute toxicity of the end-use product and the risk assessment of pyridate, workers must wear protective eyewear (goggles or face shield) during all mixing and loading activities. In addition, workers mixing, loading and applying up to 448 L of Tough 600 EC Herbicide per day must wear coveralls over a long-sleeved shirt, long pants, socks, chemical-resistant footwear and chemical-resistant gloves. Workers must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, socks, chemical-resistant footwear and chemical-resistant gloves when mixing, loading and applying more than 448 L product per day. When applying more than 500 L product per day, a closed-cab tractor is required.

3.5.2.2 Exposure and risk assessment for workers entering treated areas

Negligible foliar residues are expected following pre-seed or pre-emergence applications to fields of corn (field and sweet), chickpeas, lentils, field peas, canola and mint. Therefore, the postapplication exposure potential for workers entering treated fields to conduct agronomic activities is low. There is potential for postapplication exposure after early post-emergent applications for workers entering treated fields of corn and chickpeas to conduct scouting, hand line irrigation related activities involving foliar contact and hand weeding. There is also potential for exposure for workers hand harvesting sweet corn and mint.

Given the nature of activities performed, exposure should be primarily via the dermal route based on contact with treated foliage. Inhalation exposure is not expected as pyridate is considered non-volatile with a vapour pressure of 9.98×10^{-10} kPa at 25ºC, which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios and the specified restricted-entry intervals (REIs) will allow residues to dry and suspended particles to settle.

Dermal exposure to workers entering treated areas was estimated using dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients (TCs). Activity specific TCs are based on data from the Agricultural Re-entry Task Force (ARTF). As chemical-specific DFR data were not submitted, a default DFR value of 25% of the application rate coupled with 10% daily dissipation of residues were used in the exposure assessment. Exposure was normalized to mg/kg bw/day by using the default adult body weight of 80 kg and an 8-hour workday.

Exposure estimates were compared to the dermal toxicology reference value to obtain the margin of exposure (MOE); the target MOE is 300. Exposures and MOEs for hand harvesting in sweet corn and mint were calculated on the day of harvest (PHI = 45 days); and were not of health concern. REIs of 7 days are required for hand line irrigation and 3 days for scouting in corn (field and sweet), chickpeas and mint (Appendix I, Table 8). These REIs are feasible based on the frequency of these agronomic activities conducted in these crops in Canada. For all other postapplication activities, the REI of 12 hours is adequate.

All recommended REIs are presented in a combined REI and/or PHI table (Appendix I, Table 9).

3.5.3 Residential exposure and risk assessment

3.5.3.1 Handler exposure and risk assessment

Tough 600 EC Herbicide is a commercial agricultural end-use product. Therefore, a residential handler exposure assessment is not required.

3.5.3.2 Postapplication exposure and risk assessment

As pyridate is a commercial agricultural end-use product, a residential postapplication exposure risk assessment is not required.

3.5.4 Bystander exposure and risk assessment

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

A standard label statement to protect against drift during application is on the label. Therefore, health risks to bystanders are not of concern.

3.6 Aggregate exposure and risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). For pyridate, the aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected. The most relevant toxicology endpoints and assessment factors for the acute and chronic oral aggregate exposure are the same as those selected for the ARfD (see Section 3.2) and ADI (see Section 3.3), respectively.

3.7 Exposure from drinking water

3.7.1 Concentrations in drinking water

Modelling estimates

Environmental concentrations of pyridate 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 scenarios which take into account regional weather and soil characteristics, as well as relevant plant properties.

Environmental water monitoring data can complement modelling estimates, and they are considered together when estimating the potential exposure to humans. Pre-existing monitoring data were not examined for this review, as the registration of the active ingredient pyridate was discontinued in 2002.

Application information and model inputs

Use patterns considered in the modelling included applications below and above crops, which are intended to represent all proposed applications using ground sprayer equipment to soil surface or foliage. The modelling considered one application of 900 g a.i./ha, intended to encompass the highest single and yearly rates for pyridate.

For drinking water, pyridate was modelled as a combined residue with pyridafol. Modelling inputs are listed in Table 3.7.1.

Table 3.7.1 Major fate inputs for the drinking water modelling

Fate Parameter	Value (drinking water)
Residues modelled	Pyridate + Pyridafol
K_{oc}	19.5 L/kg
Water half-life	392 days, at 20°C
Sediment half-life	594 days, at 20°C
Photolysis half-life	stable
Hydrolysis	stable
Soil half-life	93 days, at 20°C

3.7.2 Estimated concentrations in drinking water sources

Estimated environmental concentrations (EECs) in potential drinking water sources are calculated for both groundwater and surface water (Table 3.7.2). Modelling for surface water used the scenario of a small reservoir adjacent to an agricultural field. EECs in groundwater considered the highest EEC from a set of standard scenarios representing different regions of Canada. All scenarios were run for 50 years.

Table 3.7.2 Level 1 Estimated environmental concentrations of the combined residue of pyridate and pyridafol in potential sources of drinking water, reported as parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)		
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Overall[5]
1 × 900 g a.i./ha	326	326	76.6	12.7	7.14

[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

3.8 Dietary exposure and risk assessment

3.8.1 Exposure from residues in food of plant and animal origin

The residue definition for risk assessment and enforcement in plant and animal commodities is pyridate, including the metabolite pyridafol (free and conjugated), expressed as parent equivalents. Submitted metabolism studies in animals were reviewed and found acceptable. Previously reviewed metabolism studies in plants (see Decision Document E91-01, *Pyridate Herbicide*) were reassessed in the context of the current application. The data gathering and enforcement analytical methods are valid for the quantitation of pyridate and pyridafol (free and conjugated) residues in crop and livestock matrices. When stored in a freezer at ≤ -18°C, residues of pyridate and pyridafol are stable in animal-derived commodities for up to 7 months, in crop commodities of high water content for up to 21.2 months, high oil content for up to 9.2 months, high protein content for up to 11.9 months, and high starch content for up to 6.6 months. Residues of pyridafol were not stable in mint, and residues from the mint magnitude of the residues studies were corrected for the in-storage decline. Therefore, pyridate and pyridafol residues are considered stable in all the tested frozen samples, except mint. The canola seeds were not processed since no quantifiable residues were measured in the raw agricultural commodity (RAC) (i.e., canola seeds). The RAC of field corn (in other words, grains) were processed and pyridate residues slightly concentrated in corn oil only (1.1-fold). The RAC of mint (in other words, fresh leaves) were processed and pyridate residues did not concentrate in mint oil (0.12-fold). Adequate feeding studies were carried out to assess the transfer of residues

to livestock matrices resulting from the current uses. Crop field trials conducted throughout Canada and the United States, as well as Austria, using end-use products containing pyridate at the approved or slightly exaggerated rates on sweet corn, mint, chickpeas, lentils, dry field peas and canola are sufficient to support the proposed maximum residue limits. Previously reviewed crop field trials, conducted on field corn, and previously reviewed confined rotational crop studies, conducted on rape (leaves), turnip (leaves and beets), ryegrass (leaves), carrot (foliage and roots), lettuce (leaves, head and roots), and barley (grains and straw), were all reassessed in the context of the current application (see Decision Document E91-01, *Pyridate Herbicide*). Field rotational crop studies were not conducted since no quantifiable residues were observed at the 14-day plant-back interval in the confined rotational crop studies. The data are adequate to demonstrate that no interval is required for non-labelled crops.

3.8.2 Dietary risk assessment

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

3.8.2.1 Acute dietary exposure results and characterization

The following assumptions were applied in the basic acute analysis for pyridate: 100% crop treated, default processing factors, residues in/on crops and animal commodities at the Canadian recommended MRL levels, and American tolerances when higher than the Canadian MRLs or for imported commodities. The following refinements to the residue inputs were applied to the basic acute exposure assessment: Canadian highest average field trial (HAFT) residues from field trials and experimental processing factors (where available).

The intermediate acute dietary exposure (food alone) for all supported pyridate food commodities proposed for registration and/or imported is estimated to be less than 1% (0.0017 mg/kg bw/day) of the ARfD for the general population (95^{th} percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: 6.0% of the ARfD for the general population and 20.1% of the ARfD for all infants, the highest exposed population subgroup.

3.8.2.2 Chronic dietary exposure results and characterization

The same criteria as reported for the basic acute analysis were applied to the basic chronic analysis for pyridate. The following refinements to the residue inputs were applied to the basic chronic exposure assessment: Canadian supervised trial median residues (STMdR) from field trials and experimental processing factors (where available).

The intermediate chronic dietary exposure (food alone) from all supported pyridate food commodities proposed for registration and/or imported for the total population, including infants and children, and all representative population subgroups is less than 5% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The

PMRA estimates that chronic dietary exposure to pyridate from food and drinking water is 11.9% (0.0071 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at 42.5% (0.025 mg/kg bw/day) of the ADI.

3.9 Maximum residue limits

The PMRA recommends that the following MRLs be specified for residues of pyridate.

Table 3.9.1 Recommended maximum residue limits

MRL (ppm[1])	Food Commodity
0.4	Dry lentils, peppermint tops, spearmint tops
0.2	Meat byproducts of cattle, goats, horses and sheep
0.05	Crop subgroup 20A (rapeseeds); dry chickpeas; dry field peas; dry pigeon peas; eggs; fat of cattle, goats, hogs, horses, poultry and sheep; field corn; meat byproducts of hogs and poultry; meat of cattle, goats, hogs, horses, poultry and sheep; milk; sweet corn kernels plus cobs with husks removed

[1] ppm = parts per million

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides section of Canada.ca.

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

The nature of the residues, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1b, 10 and 11.

3.10 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 pyridate. Pyridate belongs to the pyridazine class of herbicides. Exposure to other pesticides in this class is not expected to occur in Canada. Additionally, there was no mammalian mode of action data available to associate pyridate with other classes of pesticides. Overall, for the current evaluation, the PMRA did not identify information indicating that pyridate shares a common mechanism of toxicity with other pesticides to which exposure is expected to occur in Canada. Therefore, no cumulative health risk assessment is required at this time.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Environmental fate properties of pyridate and its transformation products are summarized in Appendix I, Tables 12, 13 and 14.

Pyridate undergoes rapid hydrolysis to the major transformation product, pyridafol, at environmentally relevant pH values and temperatures. Photolysis of pyridate is likely not relevant in the environment because hydrolysis is expected to be the dominant process.

Pyridafol forms from hydrolysis of pyridate in all environmental compartments when water is present. Pyridafol is stable to hydrolysis, but can undergo photolysis in soil and water forming several unidentified major transformation products, including HHAC 062 and HHAC 060 in water only. Observations of photolysis in soil and water studies starting with pyridate are likely attributed to photolytic degradation of pyridafol.

Laboratory and field studies indicate that pyridate is non-persistent in the environment. Pyridafol can be moderately persistent in aerobic soil depending on soil type and is persistent in aquatic systems, where it remains largely in the water phase. Pyridafol has a low potential for residue carry over under field conditions.

Pyridate is not expected to leach to groundwater. However, the major transformation product pyridafol may leach to groundwater based on its solubility in water, very high potential for mobility in most soils, and considering that the criteria of Cohen et al. (1984) and Groundwater Ubiquity Score (GUS) values indicate pyridafol has the potential to leach.

Based on log K_{ow} values and fish bioaccumulation studies, the potential for bioaccumulation of pyridate and its transformation products in fish is low.

Long range atmospheric transport of pyridate and pyridafol is unlikely considering that they are both expected to have low volatility under field conditions based on their vapour pressures, and to be non-volatile from water and moist soil based on the Henry's law constants. The estimated half-lives for pyridate and pyridafol in the atmosphere are less than one day.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil, and air. The EECs are estimated using standard models that 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).

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

Because pyridate is expected to rapidly hydrolyse to pyridafol in all environmental compartments, ecological toxicity studies were available for both pyridate and pyridafol. The screening level risk assessment considered separate exposure scenarios for pyridate and pyridafol for terrestrial and aquatic organisms. EECs for pyridate were based on direct application of pyridate at the highest single rate of 900 g a.i./ha. EECs for pyridafol assumed complete conversion of pyridate to pyridafol in the environment and, therefore, were also based on the highest single rate of 900 g pyridate/ha (= 491 g pyridafol/ha).

4.2.1 Risks to terrestrial organisms

Separate risk assessments for pyridate and pyridafol were conducted for terrestrial organisms. A summary of terrestrial toxicity data is presented in Appendix I, Table 15.

For acute toxicity studies, uncertainty factors of 1/2 and 1/10 of the EC_{50} (LC_{50}) are typically used in modifying the toxicity values for terrestrial invertebrates, birds, and mammals when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints. For organisms where the level of concern (LOC) is exceeded (thus, if RQ≥1), a refined Tier 1 assessment is conducted to determine risk resulting from spray drift. The screening level risk assessment and further characterization of risk for pyridate and pyridafol is presented in Appendix I, Tables 16, 17 and 18.

When used according to approved label directions, no risks are expected for beneficial insects (predators and parasites), birds, or earthworms.

Potential risk to adult bees was identified at the screening level from chronic oral exposure to pyridate, and also to bee larvae from acute and chronic exposures. However, pyridate is not expected to pose actual risk to adult bees and bee larvae considering that pyridate rapidly hydrolyzes to pyridafol, and that pyridafol is water soluble, thus any dried residues on plant surfaces are expected to wash off in dew and rain. As well, dried pyridafol residues are unlikely to adhere to the surface of a bee and thereafter undergo transfer to the hive by honeybees. In addition, exposure through foraging on residues found on pollen or nectar should not occur because application to target crops will take place prior to bloom or pollen shed.

The screening level risk assessment exceeded the level of concern for non-target terrestrial plants following direct (on-field) application of end-use products containing pyridate; however, the level of concern for non-target terrestrial plants was not exceeded in the refined risk assessment that examined off-field exposure due to spray drift. A one metre no-spray buffer zone is required for terrestrial habitats to mitigate potential risk to non-target terrestrial plants. In addition, a label statement to inform users of the potential toxicity to non-target terrestrial plants is required.

No acute risk to small wild mammals was identified for pyridate or pyridafol, and there was no chronic risk from off-field spray drift of pyridate. Although the level of concern was exceeded for chronic exposures to pyridate on-field, the overall risk profile for this group of organisms is low. A label statement to inform users of the potential toxicity to small wild mammals is required.

4.2.2 Risks to aquatic organisms

Separate risk assessments for pyridate and pyridafol were conducted for freshwater and marine aquatic organisms. A summary of aquatic toxicity data is presented in Appendix I, Table 19.

For acute toxicity studies, an uncertainty factor of 1/2 of the EC_{50} is used for aquatic plants and invertebrates, and of 1/10 of the LC_{50} for fish species, when calculating risk quotients (RQs). No uncertainty factors are applied to chronic NOEC endpoints. For groups where the level of concern (LOC) is exceeded (thus, if $RQ \geq 1$), a refined Tier 1 assessment is conducted to determine risk resulting from spray drift and runoff separately.

The screening level risk quotients are summarized in Tables 20 (pyridate) and 21 (pyridafol) in Appendix I. The risk quotients for the Tier 1 assessment of pyridate are presented in Appendix I, Table 22 (spray drift only) and Table 23 (runoff only).

When used according to approved label directions, no risks from pyridate are expected for freshwater aquatic vascular plants or cyanobacteria. As well, from the available studies for pyridafol, no risks were identified for aquatic invertebrates, fish, amphibians, algae, or aquatic vascular plants. The studies available for HHAC 062 indicate lower risk than for pyridafol to aquatic invertebrates and algae.

The screening level risk assessment for pyridate determined that the level of concern was exceeded for several aquatic organisms from acute (amphibians, freshwater green algae, freshwater diatoms, marine diatoms, and freshwater and marine fish) and chronic (freshwater invertebrates) exposures. These risks were further characterized by estimating EECs from spray drift and runoff from treated areas into a receiving water body.

Tier 1: Refined aquatic risk assessment

Assessment of potential risk from spray drift

Risks due to spray drift did not exceed the level of concern. A one metre buffer zone will be required for freshwater and estuarine/marine habitats to mitigate potential risks. With the addition of preventative measures to reduce drift, the environmental risks to amphibians, diatoms, fish, and freshwater invertebrates and green algae are acceptable from application of pyridate when label directions are followed.

Assessment of potential risk from runoff

Environmental concentrations in runoff water were estimated using numerical models for pyridate only as no risk was identified from exposures to pyridafol. Ecological modelling inputs are listed in Table 4.2.1.

Table 4.2.1 Major fate inputs for the ecological modelling

Fate Parameter	Value
Residues modelled	Pyridate
K_{oc}	2.24e+05 L/kg
Water half-life	0.57 days, at 20°C
Sediment half-life	0.49 days, at 20°C
Photolysis half-life	stable
Hydrolysis half-life	2.4 days, at pH 7
Soil half-life	4 days, at 20°C

For the ecological risk assessment, EECs in water are calculated by modelling a ten hectare field adjacent to a one hectare water body of two different depths, 80 cm and 15 cm. The model calculates the amount of pesticide entering the water body by runoff and the subsequent degradation of the pesticide in the water and sediment. Deposition of pesticide on the water body due to spray drift is not included. The model is run for 50 years.

Based on the toxicity endpoints and EECs representing the 90th percentile of concentrations for a timeframe reflecting the exposure duration of the toxicity tests, the level of concern is not exceeded for any of the aquatic organisms identified as being at potential risk at the screening level.

Standard precautionary label statements alerting users of the potential for runoff will be included on the product label for pyridate. As well, a label statement to inform users of the potential toxicity to aquatic organisms is required.

4.2.3 Environmental incident reports

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the United States Environmental Protection Agency (USEPA) Ecological Incident Information System. Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act* can be found at the Report a Pesticide Incident section of Canada.ca.

No incident reports involving pyridate were reported to the PMRA as of 18 November 2020. The EPA Ecological Incident Information System (EIIS), which was last updated 5 October 2015, was searched and six environment incident reports related to pyridate were found. In all six incidents, plant damage was reported and was determined to be possibly related to the pesticide after corn plants were directly treated with pyridate. No further details are available.

5.0 Value

The value information submitted for review included use history information and data from small-scale field trials conducted in the United States and Canada. The information supports the value of Tough 600 EC Herbicide; the supported pest and host crop claims are summarized in the following tables.

Pest claims supported for Tough 600 EC Herbicide.

Rate (L/ha)	Weed	Claim
0.75	Black nightshade	Control
1.5	Common lamb's quarters	Suppression
	Common waterhemp	
	Kochia	
	Wild mustard	
	Redroot pigweed	Control

Host crop claims supported for Tough 600 EC Herbicide.

Application timing	Crop
Pre-plant or Pre-emergence 0.75–1.5 L/ha (up to 2 applications, 1.5 L/ha maximum per year)	Corn (field and sweet) Chickpea Mint Lentil Field pea Canola
Post-emergence 0.75–1.5 L/ha (up to 2 applications, 1.5 L/ha maximum per year)	Corn (field and sweet) Chickpea Mint

Pyridate exhibits efficacy on certain broadleaf weeds and may be tank mixed with a number of other herbicides in field and sweet corn. Group 6 herbicides are not a commonly used mode of action in the Prairie Provinces so the pre-emergence uses in chickpeas, lentils, field peas and canola can provide growers with a different mode of action, where these crops are primarily grown. In addition, for the first time, pyridate will give mint growers a post-emergence broadleaf herbicide option for use in-crop, which has been identified in the past as a priority by Canadian growers.

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, that is, 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, pyridate 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 pyridate and its transformation products do not meet all of the TSMP Track 1 criteria.

Please refer to Table 24 for further information on the TSMP assessment.

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

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 Science Policy Note SPN2020-01[7] and is based on existing policies and regulations, including the Toxic Substances Management Policy[8] and Formulants Policy,[9] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act*, 1999, (substances designated under the Montreal Protocol).

The PMRA has reached the conclusion that pyridate and its end-use product do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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

7.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Pyridate Technical and Tough 600 EC Herbicide, containing the technical grade active ingredient pyridate, for selective suppression or control of certain emerged broadleaf weeds. Tough 600 EC Herbicide may be applied pre-plant and/or pre-emergence in corn (field and sweet), mint, chickpeas, lentils, field peas and canola and post-emergence in corn (field and sweet), chickpeas and mint.

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.

---

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

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

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

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

List of abbreviations

↑	increased
↓	decreased
♂	male
♀	female
°C	degree Celsius
µg	micrograms
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ALT	alanine aminotransferase
AOPWIN™	EPI Suite™ model
AR	androgen receptor
%AR	percent applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ASAE	American Society of Agricultural Engineers
ATPD	Area Treated Per Day
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
BCF_{ss}	steady-state bioconcentration factor
BCF_k	kinetic bioconcentration factor
BUN	blood urea nitrogen
BW or bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CHO	Chinese hamster ovary
cm	centimetres
Cmax	maximum plasma concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	chemical-resistant
CVS	cardiovascular system
d	day(s)
D8	day 8
DEEM	Dietary Exposure Evaluation Model
DFOP	double first-order in parallel
DFR	dislodgeable foliar residue
DIR	directive
DNA	deoxyribonucleic acid
dpm	disintegration per minute

DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EC	emulsifiable concentrate
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
ERα	estrogen receptor alpha
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ELS	early life stage
F1	first filial generation
F2	second filial generation
F3	third filial generation
fc	food consumption
FDA	Food and Drugs Act
fe	food efficiency
FIR	food ingestion rate
g	gram(s)
GD	gestation day
GLP	Good Laboratory Practice
GUS	Groundwater Ubiquity Score
ha	hectare(s)
HAFT	highest average field trial
HDPE	high density polyethylene
HGB	hemoglobin
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HPLC-UV	high performance liquid chromatography with ultraviolet detection
hr or hrs	hour or hours
HRAC	Herbicide Resistance Action Committee
ILV	independent laboratory validation
IORE	indeterminate order rate equation
i.p.	intraperitoneal
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intravenous
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	kiloPascal
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LAFT	lowest average field trial
LOAEL	lowest observed adverse effect level
LOC	level of concern

LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score
MIS	maximum irritation score
mCi	millicurie
M/L/A	Mixer/Loader/Applicator
MOE	margin of exposure
Mol	mole
mPa	millipascal
MRL	maximum residue limit
MS	mass spectrometry
MWCF	molecular weight conversion factor
N/A	not applicable
NAFTA	North American Free Trade Agreement
NHANES/WWEIA	National Health and Nutrition Examination Survey/What We Eat
Nm	nanometre
NOAEL	no observed adverse effect level
NMR	nuclear magnetic resonance
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NZW	New Zealand white
P	parental generation
PChE	plasma cholinesterase
PCPA	*Pest Control Products Act*
PE/EV	polyethylene/ethylene-vinylalcohol copolymer
PET	polyethylene terephthalate
PHED	Pesticide Handler Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PWC	Pesticides in Water Calculator
RAC	raw agricultural commodity
RBC	red blood cells
REI	Restricted-entry interval
rel.	relative
RQ	risk quotient
SDEV	standard deviation
SFO	single first-order
STMdR	supervised trial median residue
TC	Transfer Coefficient
t_R	representative half-life

TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
Tmax	time to maximum plasma concentration
UK	United Kingdom
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
VOC	volatile organic components
WBC	white blood cells
wk	week(s)
WSSA	Weed Science Society of America
wt	weight

Appendix I Tables and figures

Table 1a Residue analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	GS-18-47-1	Pyridate	HPLC-MS/MS	0.01 mg/kg	PMRA# 2909875
		CL-9673			
Water	Surface and ground	Pyridate	HPLC-MS/MS	0.005 mg/L	PMRA# 3038561, 2909878
		CL-9673			
	Tap	CL-9673	HPLC-MS/MS	0.05 µg/kg	

Table 1b Residue analysis in plant and animal matrices

Analytical Methods	Matrix	Analytes	Method ID/Type	LOQ[1]	Reference
Livestock Commodities					
Enforcement Method	Meat, fat, liver, kidney, milk, eggs	Sum of pyridate + pyridafol + pyridafol hydrolysable conjugates, quantified as pyridafol residues	Method S11-01578/ HPLC-MS/MS	0.03 ppm for pyridafol and 0.05 ppm for pyridate	PMRA# 2910072
Data-Gathering Method			Method R94-95/ HPLC-UV	0.03 ppm for pyridafol and 0.05 ppm for pyridate	PMRA# 3105157
ILV of Enforcement Method			Method S11-01578/ HPLC-MS/MS	0.05 ppm for pyridate and pyridafol	PMRA# 2910073
Radiovalidation	As the extraction solvents and procedures are very similar to those used in the lactating cow metabolism study and in the hen and cow radiolabelled feeding studies, additional extraction efficiency data are not required.				
Plant Commodities					
Enforcement and Data Gathering Method	Sweet corn grain; leek stalk; cauliflower and broccoli inflorescence; oilseed rape seed	Sum of pyridate + pyridafol + pyridafol-*O*-glucoside, expressed as pyridafol and converted to/ reported as pyridate using a	Method S11-03700/ HPLC-MS/MS	0.05 ppm for pyridate	PMRA# 2910071

Analytical Methods	Matrix	Analytes	Method ID/Type	LOQ[1]	Reference
		MWCF[2] of 1.83			
Data-Gathering Method	Maize (whole plant, stem and grain); rape (whole plant, pod, stem & seed); field peas (stem, pod and seed); brassicas (edible parts); leeks (whole plant); onions (whole plant and bulb); grapes (fruit); peppermint (dried tea)	Sum of pyridate + pyridafol + pyridafol hydrolysable conjugates, expressed as pyridafol and converted to/ reported as pyridate using a MWCF[2] of 1.83	Method 758e/ HPLC-UV	0.03 ppm for pyridafol in all matrices, except peppermint tea 0.05 ppm for pyridafol in peppermint tea samples	PMRA# 2910069
ILV of Enforcement Method	Oilseed rape; sweet corn grain; and broccoli	Sum of pyridate + pyridafol + pyridafol-*O*-glucoside determined as pyridafol and converted to and reported as pyridate using a MWCF[2] of 1.83	Method S11-03700/ HPLC-MS/MS	0.05 ppm for pyridate	PMRA# 2910075
Radiovalidation	As the extraction solvents and procedures are very similar to those used in the previously reviewed peanut, corn, spring barley and broccoli metabolism studies, additional extraction efficiency data are not required.				

[1] LOQ: limit of quantitation
[2] MWCF: Molecular weight conversion factor

Table 2 Identification of select metabolites of pyridate

Code	Chemical Name
Metabolite A	6-chloro-3-(4-hydroxyphenyl)-4-pyridazinol; pyridafol-*N*-glucoside/pyridafol-*O*-glucoside
Metabolite B	6-[6-chloro-3-phenyl-4-pyridazinyloxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid
Metabolite C	Sulfuric acid mono-(6-chloro-3-phenyl-pyridazin-4-yl) ester
Metabolite D	6-chloro-3-(4-hydroxy-3-methylsulfanylphenyl)-4-pyridazinol

Code	Chemical Name
Metabolite E	Sulfuric acid mono-(6-chloro-3-(4-hydroxyphenyl)-pyridazin-4-yl) ester
Metabolite F	Sulfuric acid mono-[4-(6-chloro-4-hydroxy-pyridazin-3-yl)-phenyl] ester
Metabolite G	6-[4-(6-chloro-4-hydroxypyridazin-3-yl)phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid and/or 6-[6-chloro-3-(4-hydroxyphenyl)-4-pyridazinyloxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid
Metabolite H	2-acetylamino-3-(6-chloro-3-phenyl-pyridazin-4-ylsulfanyl)-propionic acid

Table 3 Toxicity profile of technical pyridate

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, metabolism, and excretion (single and repeated oral gavage dose) Rat (Sprague Dawley) PMRA# 2909855	^{14}C-pyridate, radiolabelled on the pyridazine ring, was administered via gavage as single oral doses of 20, 200, or 600 mg/kg bw. Multiple oral doses of 20 mg/kg bw/day of non-radiolabelled pyridate were administered for 14 days, followed by a single dose of 20 mg/kg bw of ^{14}C-pyridate, radiolabelled on the pyridazine ring, on day 15. Absorption: Pyridate was rapidly and moderately to well absorbed (>70% of the AD). Peak radioactivity in the plasma was detected at the 1-hour and 2-hour time points for ♂ and ♀, respectively, following a single oral dose of 20 mg/kg bw. Following a single oral dose of 200 mg/kg bw, plasma levels where highest at 1 hour and were reduced by almost twofold by the 6-hour time point. At 600 mg/kg bw, plasma radioactivity was higher at 6 hours when compared to 1 hour, suggesting saturation of absorption and/or a slower rate of absorption at the 600 mg/kg bw dose level. Excretion: Most of the administered radioactivity was eliminated within 24 hours post-dosing. At 96 hours post-dosing, 69–84% of the AD was detected in urine and 11–19% in feces after a single dose of 20 or 200 mg/kg bw, or after multiple doses of 20 mg/kg bw/day. In bile duct-cannulated rats, 6–8% of the AD was detected in bile, 13–30% in urine, and 7–11% in feces within 24 hours of a single oral dose of 20 mg/kg bw. Negligible amounts of radioactivity (<0.15% of the AD) were eliminated in expired air. In ♂ administered a single oral dose of 200 or 600 mg/kg bw, 62–67% of the AD was recovered in urine and 25–34% in feces at 96 hours post-dosing.

Study Type/Animal/ PMRA#	Study Results
	Distribution: Low levels of radioactivity were detected in tissues at sacrifice. Following a single dose of 20 or 200 mg/kg bw or multiple doses of 20 mg/kg bw/day, highest levels of radioactivity were detected in kidney, bone, and liver in both sexes, fat in ♂, and ovaries in ♀. Levels of radioactivity were higher in some tissues after multiple doses compared to a single dose (twofold higher in bone and ovaries; 10-fold higher in fat of ♀ only). Following a single dose of 600 mg/kg bw, the radioactivity in the tissues was disproportionately high at 24 hours post-dosing compared to lower dose levels, suggesting altered kinetics at this dose level. Metabolism: Three highly polar metabolites and unchanged pyridate were identified in various matrices. In single dose studies, fecal samples contained unchanged pyridate (up to 35% of fecal radioactivity), pyridafol (up to 57%), and hydroxylated pyridafol (up to 32%). In urine, pyridafol (up to 30%), pyridafol-*O*-glucuronide (up to 50%), and hydroxylated pyridafol (up to 37%) were detected. In plasma, unchanged pyridate and pyridafol were detected (quantitative data not available). As the dose levels increased, a higher percentage of pyridafol-*O*-glucuronide and lower percentage of hydroxylated pyridafol were detected in urine, and a higher percentage of pyridafol and lower amounts of unchanged pyridate and hydroxylated pyridafol were detected in feces. When multiple doses were administered, unchanged pyridate was no longer detected in feces and a higher proportion of hydroxylated pyridafol was detected.
Absorption, distribution, excretion (single low i.v. dose) Pyridate and Pyridafol Rat (Sprague Dawley) PMRA# 2909851	Single doses of 2.5 mg/kg bw of ^{14}C-pyridate or 5.0 mg/kg bw of ^{14}C-pyridafol, both radiolabelled on the pyridazine ring, were administered via i.v. injection. Absorption: Whole blood and plasma Cmax and AUC values were generally 1.3- to 2-fold higher in ♀ than in ♂ for both test compounds. Tmax values were similar for both compounds and for both sexes, and ranged from 0.5 to 1.0 hour. Elimination: Half-lives of elimination from whole blood and plasma were similar between the sexes, and ranged from 7 to 13 hours for pyridate and 5 to 7 hours for pyridafol. Blood and plasma clearance rate constants were 1.4- to twofold higher for ♂ than for ♀ for both test materials. Both test materials were rapidly excreted in the urine, with >73% of the AD detected in the 0–24 hour urine samples for all groups. The majority of the fecal excretion occurred between 12 and 48 hours post-dosing. At 168 hours post-dosing, 5.2–11% of the AD was recovered in feces and 79–91% in urine plus cage wash. There were no substantial differences in excretion

Study Type/Animal/ PMRA#	Study Results
	profiles for the two test materials. Fecal excretion of radioactivity following dosing with pyridate was twofold higher in ♂ than in ♀. Distribution: Volume of distribution values in whole blood and plasma were 1.3- to 2.5-fold higher for ♂ than for ♀ for both test materials. At 168 hours post-dosing, less than 0.2% of the AD was detected in tissues. Higher levels of radioactivity (1.5- to 1.8-fold) were detected in tissues from ♀ when compared to ♂.
Absorption, distribution, metabolism and excretion (single low and high dose oral gavage; repeated low dose oral gavage) Pyridate and Pyridafol Rat (Sprague Dawley) PMRA# 2909852, 2909856, 2909857, 2909858	Single oral doses of ^{14}C-pyridate (20 or 200 mg/kg bw) or ^{14}C-pyridafol (11, 20, 110, or 200 mg/kg bw), both radiolabelled on the pyridazine ring, were administered. Multiple oral doses of non-radiolabelled pyridate (20 mg/kg bw/day) or pyridafol (11 mg/kg bw/day) were administered for 14 days, followed by a single dose of ^{14}C-pyridate (20 mg/kg bw) or ^{14}C-pyridafol (11 mg/kg bw), both radiolabelled on the pyridazine ring, on day 15. Absorption: Both compounds were rapidly absorbed following a single oral dose, with Tmax values of 0.5–2.8 hours at the low dose and 1–11 hours at the high dose. The AUC was higher in ♀ compared to ♂ in blood and plasma following a single oral dose, for all dose levels and for both compounds. Higher Cmax values were observed following multiple doses when compared to a single dose. Elimination: The half-life of elimination from blood and plasma ranged from 3 to 19 hours for both compounds. The distribution of excreted radioactivity between the urine and feces was very similar for all groups, with >67% of the AD excreted in the urine (>82% of the AD if cage wash is included), and 5–14% of the AD excreted in the feces. The majority of urinary radioactivity was detected within 48 hours after a single dose and within 12 hours after the final multiple dose for both compounds. Distribution: The distribution of radioactivity was generally similar between sexes, dose levels, and compounds. At 168 hours post-dosing, total tissues contained less than 1% of the AD. At the 1-, 6-, and 24-hour time points, the greatest concentrations of radioactivity were detected in the gastrointestinal tract in all groups with the exception of ♀ administered multiple doses of pyridafol (heart at 6 hours, skin at 24 hours). At the 96-hour time point, the greatest amounts of radioactivity were detected in the skin, liver and kidney in all dose group, and also in the spleen following multiple doses of pyridate and the fat and ovaries following dosing with pyridafol.

Study Type/Animal/ PMRA#	Study Results
	Metabolism following dosing with pyridate: Unchanged pyridate was not detected in urine. Eight urinary metabolites were identified. Three predominant pathways result in the formation of the major Metabolites A, B and C. The thiocarbamate moiety of pyridate is almost completely hydrolysed to form pyridafol (14–32% of the AD). Pyridafol then undergoes (1) oxidation in the para position of the phenyl moiety to form Metabolite A (22–39% of the AD), (2) glucuronidation to form Metabolite B (4–16% of the AD), (3) sulfation to form Metabolite C (4–9% of the AD). Five minor metabolites (Metabolites D to H) were identified in urine (each representing ≤3% of the AD). These metabolites are formed via sulfation or glucuronidation of Metabolite A or from various transformation of pyridafol (hydrolysis, oxidation, glutathione conjugation, glucuronidation, sulfation, cleavage, methyl transfer, and acetylation). The higher proportion of Metabolites A, B and G and lower proportion of pyridafol in the urine after repeated dosing suggest that higher oxidase and glucuronidase activity may occur after repeated dosing compared to a single dose administration. In feces, unchanged pyridate (0.5-4% of the AD), pyridafol (0.8–4% of the AD), and Metabolite A (3–4% of the AD) were detected. A lower percentage of pyridafol and higher percentages of Metabolites A, B and G in urine of ♀ versus ♂ may suggest higher oxidase and glucuronidase activity occurring in ♀. A lower percentage of Metabolites C, E and F observed in urine of ♀ compared to ♂ may suggest lower sulfatase activity in ♀. Differences in the relative percentages of metabolites as a function of dose level were not observed. A similar pattern of metabolism was observed following dosing with pyridafol.
Metabolism – proposed metabolic pathway of thiocarbonate acid *S*-octyl ester in mammals PMRA# 2909850	Supplemental Pyridate is composed of a phenyl-pyridazine moiety linked to an octane-1-thiol side chain via a thiocarbamate group, and is rapidly hydrolyzed to form pyridafol and thiocarbonic acid *S*-octyl ester. Since the toxicokinetics of radiolabelled thiocarbonic acid was not investigated in mammals, a metabolic pathway was proposed based on information from the published scientific literature. It was proposed that the thiocarbonic acid *S*-octyl ester will readily undergo decarboxylation due to the position of the carboxyl group in the thioester, resulting in octane-1-thiol. Thiols are commonly metabolized before being excreted. It is proposed that methylation of the thiol and subsequent oxidation of the sulfur is the predominant pathway.

Study Type/Animal/ PMRA#	Study Results
	Minor metabolic pathways are glucuronidation of the thiol and oxidation of the sulfur to yield octane-1-sulfinic acid.
Absorption, distribution, metabolism (single oral gavage dose) Rat (Sprague Dawley) PMRA# 2909853	Supplemental – limited reporting Single doses of ^{14}C-pyridate (position of radiolabel not specified; assumed to be on the pyridazine ring) were administered at 20 mg/kg bw (for assessment of metabolism) or 200 mg/kg bw (for assessment of absorption and distribution). Plasma analysis: Peak radioactivity in the plasma after dosing with 200 mg/kg bw was detected at the 1- and 6-hour time points for ♂ and ♀, respectively. Distribution: Other than the GI tract, the highest mean concentrations of radioactivity after dosing with 200 mg/kg bw were detected in the liver, kidneys and plasma/blood. By the 24-hour time point, < 3% of the total radioactivity was detected in each tissue. No evidence of tissue retention was observed. Metabolism: Pyridafol, and an unknown metabolite (most likely hydroxylated pyridafol), were detected in urine and feces after dosing with 20 mg/kg bw. Pyridafol-*O*-glucuronide was detected in urine only. Unchanged pyridate was not detected in urine or feces.
Absorption, elimination, metabolism (single oral gavage dose) Dog (Beagle) PMRA# 2909854	Supplemental – pilot study Dogs (1/sex) were sequentially dosed with 32, 80, and 200 mg/kg bw of ^{14}C-pyridate, radiolabelled on the pyridazine ring, with at least 10 days between each dose administration. Absorption: Peak plasma radioactivity was detected within 12 hours post-dosing. The ♀ had a higher AUC value (approximately twofold) than ♂ at all dose levels. Elimination: Reduction of plasma radioactivity levels to <10% of peak was observed within 48 hours post-dosing. Vomiting was observed after dosing with 80 (up to 0.7% of the AD) and 200 mg/kg bw (34% of the AD). Higher amounts of radioactivity were detected in urine and lower amounts in feces of ♀ (74–76% of the AD in urine, 19–20% in feces) compared to ♂ (40–46% of the AD in urine, 36–50% in feces) at 32 and 80 mg/kg bw. At 200 mg/kg bw, comparable amounts of radioactivity were detected in urine (♂/♀: 19/24% of the AD in urine; 27/32 % in feces).

Study Type/Animal/ PMRA#	Study Results
	Metabolism: The metabolites pyridafol-*N*-glucuronide / pyridafol-*O*-glucuronide (68–74% of the total radioactivity detected) and pyridafol (18-23% of the total radioactivity detected) were detected in urine. Two other unidentified radioactive components represented ≤8% of the total radioactivity detected.
Acute toxicity studies	
Acute oral (gavage) Mouse (NMRI) PMRA# 2909799	Low acute oral toxicity LD_{50} >10 000 mg/kg bw Clinical signs of toxicity included sedation, dyspnea, central body position, and hunched posture.
Acute oral (gavage) Rat (Wistar) PMRA# 2909793	Low acute oral toxicity LD_{50} (♂) > 2800 mg/kg bw LD_{50} (♀) = 2371 mg/kg bw Clinical signs of toxicity included lethargy, uncoordinated movement, hunched posture, piloerection, red staining (snout, back, and head), ventro-lateral recumbency, slow breathing, and labored respiration.
Acute oral (gavage) Rat (Wistar) PMRA# 3038533	Low acute oral toxicity LD_{50} (♂/♀) = 4690 mg/kg bw LD_{50} (♂) = 5993 mg/kg bw LD_{50} (♀) = 3544 mg/kg bw Clinical signs of toxicity included dyspnea, sedation, ataxia, lateral-abdominal position, curved body position, ruffled fur, and ventral body position.
Acute oral (gavage) Rat (Wistar) PMRA# 2909794	Low acute oral toxicity LD_{50} (♂/♀) > 2000 mg/kg bw Clinical signs of toxicity included lethargy, uncoordinated movements, and hunched posture.
Acute oral (gavage) Rat (Wistar) PMRA# 2909800	Low acute oral toxicity LD_{50} (♂/♀) = 3588 mg/kg bw LD_{50} (♂) = 4174 mg/kg bw LD_{50} (♀) = 2961 mg/kg bw Clinical signs of toxicity included sedation, hunched posture, ruffled fur, ventral body position, and spasms.

Study Type/Animal/ PMRA#	Study Results
Acute oral (gavage) Rat (Wistar) PMRA# 2909801	Low acute oral toxicity LD_{50} (♂) > 2800 mg/kg bw LD_{50} (♀) = 2092 mg/kg bw Clinical signs of toxicity included hunched posture, lethargy, uncoordinated movements, paddling movements, ventro-lateral recumbency, deep or labored respiration, and piloerection.
Acute dermal Rabbit (NZW) PMRA# 3038534	Low acute dermal toxicity LD_{50} (♂/♀) > 2000 mg/kg bw No clinical signs of toxicity. Slight to moderate erythema observed at the application site throughout the study.
Acute inhalation Rat (Wistar) PMRA# 3038535	Low acute inhalation toxicity LC_{50} (♂/♀) > 4.37 mg/L Clinical signs of toxicity included sedation, dyspnea, curved body position, and ruffled fur.
Eye irritation Rabbit (NZW) PMRA# 2909805	Minimally irritating to the eye MAS = 0.77/110 MIS = 2.3/110 at 24 hours
Dermal irritation Rabbit (NZW) PMRA# 2909807	Mildly irritating to the skin MAS = 2.3/8 MIS = 2.5/8 at 48 hours
Dermal sensitization (Open Epicutaneous Test) Guinea Pigs (Dunkin-Hartley, Albino) PMRA# 2909809	Potential dermal sensitizer Positive
Dermal sensitization (Buehler)	Potential dermal sensitizer Positive

Study Type/Animal/ PMRA#	Study Results
Guinea Pigs (Dunkin-Hartley, Albino) PMRA# 2909810	
Short-Term Toxicity Studies	
28-day oral (dietary) Mouse (Swiss) PMRA# 2909821	Supplemental NOAEL and LOAEL not established. Effects at ≥450 mg/kg bw/day: ↓ bw, ↓ bwg (♂); ↑ spleen wt (♀) Effects at 1500 mg/kg bw/day: ↑ fc, ↓ fe, ↑ liver wt (♂/♀); ↓ bw, ↓ bwg (♀) Limitations: pre-guideline, limited hematology and clinical chemistry analysis, limited histopathological examination of collected tissues, no individual data provided, and no analysis of the test diet.
28-day oral (dietary) Rat (Wistar) PMRA# 2909822 Purpose of the study was to determine effect of amine concentration in the diet on the potency of pyridate since pyridate is known to decompose in the presence of amines.	Supplemental NOAEL and LOAEL not established. **Stock diet (high amine concentration):** Effects at ≥300 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc (♂/♀) Effects at 1000 mg/kg bw/day: ↓ fe, ↑ rel. lung wt (♂/♀); ↑ rel. kidney wt (♂); ↑ WBC, ↑ rel. thymus wt (♀) **Semi-purified diet (low amine concentration):** Effects at ≥300 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc (♂/♀) Effects at 1000 mg/kg bw/day: ↓ fe, ↑ RBC, ↑ rel. lung wt (♂/♀); ↑ rel. kidney wt (♂); ↑ WBC, ↑ rel. thymus wt (♀) There was no apparent influence from the diet formulation on the toxicity of pyridate under the conditions of this study. Limitations: pre-guideline, limited hematology and clinical chemistry analysis, limited histopathological examination of collected tissues, no individual data provided, and no analysis of the test diet.
28-day oral (dietary) Rat (Wistar and Sprague Dawley)	Supplemental NOAEL and LOAEL not established. **Wistar rats:**

Study Type/Animal/ PMRA#	Study Results
PMRA# 2997571	Effects at ≥300 mg/kg bw/day: ↓ bw, ↓ fc (♂/♀); ↓ bwg (♂) Effects at 1000 mg/kg bw/day: emaciated appearance, ↓ fe, ↑ rel. lung wt (♂/♀); ↓ bwg, ↑ rel. spleen wt (♀) **Sprague Dawley rats:** Effects at ≥300 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc (♂/♀); ↑ rel. thymus wt, ↑ rel. liver wt (♀) Effects at 1000 mg/kg bw/day: emaciated appearance, ↓ fe, ↑ rel. spleen wt (♂/♀); ↑ rel. lung wt (♂); ↓ HGB (♀) Limitations: pre-guideline, limited hematology and clinical chemistry analysis, no histopathological examination of collected tissues, no individual data provided, and no analysis of the test diet.
90-day oral (dietary) Rat (Sprague-Dawley) PMRA# 2909813	NOAEL = 86/96 mg/kg bw/day (♂/♀) LOAEL = 340/377 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bw, ↓ bwg, ↓ fc, ↓ fe, ↑ reducing substance in urine, ↓ urine pH (♂/♀)
90-day oral (gavage) Rat (Sprague-Dawley) PMRA# 1200231	Supplemental NOAEL and LOAEL not established. Effects at ≥ 92 mg/kg bw/day: lipid macrophages in lung with ↑ serous exudation, ↑ lung wt (♂/♀) Effects at ≥ 228 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fe (♂) Limitations: pre-guideline, limited reporting, individual data for many parameters not included in the report, and no analysis of the dosing formulation.
90-day oral (gavage) with 28-day recovery Rat (albino; strain not further specified) PMRA# 2997558	NOAEL = 63 mg/kg bw/day (♂/♀) LOAEL = 177 mg/kg bw/day (♂/♀) Effects at the LOAEL: salivation, hypoactivity, dark areas/spots on stomach (♂/♀); one mortality (day 39), ↓ thymus wt (♂); ↓ PChE, ↑ bilirubin, ↑ rel. liver wt, ↑ rel. kidney wt, (♀) Salivation and hypoactivity continued into 28-day recovery period.

Study Type/Animal/ PMRA#	Study Results
90-day oral (gavage) Dog (Beagle) PMRA# 3038540	Supplemental NOAEL and LOAEL not established. Effects at ≥ 92 mg/kg bw/day: ↑ incidence and severity of diarrhea, staggering gait, weakness in extremities, vomiting (♂/♀); ↓ bw, ↓ bwg (♂) Effects at 228 mg/kg bw/day: unconsciousness after dosing (up to 1 hour) (♂/♀); moribund (1 ♂, unscheduled sacrifice), multifocal epithelial hyperplasia of lungs, multifocal pneumonitis, small cysts in the pituitary gland (♂); ↓ bw, ↓ bwg, ↑ incidence and severity of superficial corneal infiltration of eyes (equivocal) (♀) Limitations: pre-guideline, limited reporting, individual data for many parameters not included in the report, inconsistencies in reporting, and no analysis of the dosing formulation.
90-day oral (capsule) Dog (Beagle) PMRA# 2997570, 2997564, 2909815, 3038542	NOAEL = 20 mg/kg bw/day (♂/♀) LOAEL = 60 mg/kg bw/day (♂/♀) Effects at the LOAEL: emesis, ataxia, mydriasis, salivation, ↓ bw, ↓ bwg (♂/♀); ↑ PChE, ↑ adrenal wt, ↑ pituitary wt (♂); hypoactivity, head swing, nystagmus, laboured respiration, dehydration, opisthotonus (♀) Effects at 200 mg/kg bw/day: myelin digestion chambers of sciatic nerve (♂/♀) Limitation: Analysis of dosing capsules not conducted.
90-day oral (capsule) Dog (Beagle) PMRA# 2909820	NOAEL = 40 mg/kg/day (♂/♀) LOAEL = 80 mg/kg bw/day (♂/♀) Effects at the LOAEL: ataxia, underactivity, salivation, congested blood vessels in fundus of eyes, ↓ ALT, yellow/brown pigmentation of Kupffer cells in liver, ↑ liver wt, ↑ kidney wt, (♂/♀); prostration, emesis, pallor, dry nose, coolness to touch, hunched posture, bronchopneumonia (♀) Effects at 120 mg/kg bw/day: neurotoxic clinical signs following 1–2 doses, myelin digestion chambers of sciatic nerve (♂/♀)
12-month oral (capsule) Dog (Beagle) PMRA# 2909817	Supplemental Dose levels were increased throughout the study due to the absence of clinical signs. Effects at the low dose (5/10/30 mg/kg bw/day): no treatment-related effects

Study Type/Animal/ PMRA#	Study Results
	Effects at the mid dose (20/60/80/100 mg/kg bw/day): no treatment-related clinical signs for the first 38 weeks of the study (up to 60 mg/kg bw/day) Effects at 80 mg/kg bw/day (weeks 39–42): languid (♀) Effects at 100 mg/kg bw/day (weeks 43–52): inability to stand, mydriasis, ataxia, prostrate, lacrimation (♂/♀); languid, no response to pain, slow awareness, salivation, dyspnea, tremors, pupils unresponsive to light, hunched posture, wheezing, legs locked/no muscle control (♂) Effects at the high dose (60/100 (♂)/120/140/150 mg/kg bw/day): no treatment-related clinical signs for the first 35 weeks of the study (up to 100/60 mg/kg bw/day in ♂/♀) Effects at 120 mg/kg bw/day (week 36–38): salivation, ataxia, mydriasis, prostration (♂) Effects at 140 mg/kg bw/day (weeks 39–42): salivation, ataxia, mydriasis, prostration, languid (♂/♀); dyspnea, lacrimation, absent pain response, absent pupil response, hunched posture, unconscious, appears in pain, walking with stiff legs, clenching teeth, tremors (♂) Effects at 150 mg/kg bw/day (weeks 43–52): salivation, ataxia, mydriasis, languid, dyspnea, lacrimation, (♂/♀); legs locked straight with no muscle control, hunched posture, nystagmus, fixed stare, sensitive to touch (♂); prostration, absent pain response, absent pupil response (♀) Some signs in ♂ no longer observed when dose ↑ to 150 mg/kg bw/day Limitations: incremental and staggered increases in dose level confounded interpretation; dose levels not high enough for majority of the study.
12-month oral (dietary) Dog (Beagle) PMRA# 3038541	NOAEL = 77 mg/kg bw/day (♂/♀) LOAEL could not be established. No adverse treatment-related findings.
21-day dermal Rat (Sprague-Dawley) PMRA# 1176115,	NOAEL = could not be established/1000 mg/kg bw/day (♂/♀) LOAEL = 1000 mg/kg bw/day/could not be established (♂/♀) Dose groups limited to control and 1000 mg/kg bw/day. Effects at the LOAEL: dermal hyperplasia, inflammation, scabbing, ulceration, ↓ bwg, ↑ rel. liver wt (♂/♀); ↓ bw, ↓ prothrombin time, ↓ BUN,

Study Type/Animal/ PMRA#	Study Results
3038543	↓ chloride, ↑ albumin, ↑ ALT (♂); ↓ lymphocytes (♀) (effects considered non-adverse in ♀)
Chronic toxicity/Oncogenicity studies	
18-month oncogenicity (dietary) Mouse (B6C3F1) PMRA# 2909830, 2997559	NOAEL = 48/55 mg/kg bw/day (♂/♀) LOAEL = 97/115 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw (♂/♀) No evidence of tumourigenicity.
24-month oncogenicity (dietary) Mouse (Swiss) PMRA# 3038547, 3038548	NOAEL = 140/120 mg/kg bw/day (♂/♀) LOAEL = 684/624 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg (♂/♀); ↑ liver wt, ↑ hepatocellular vacuolation, ↑ benign liver nodules (14%, 12%, 22%, 28%) (♂). Evidence of tumourigenicity (benign liver nodules in ♂)
28-month chronic toxicity/oncogenicity (dietary) Rat (Wistar) PMRA# 1199493, 3038544, 3038545, 3038546	NOAEL = 16/20 mg/kg bw/day (♂/♀) LOAEL = 100/130 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw (♂/♀); ↓ bwg, ↓ fc (♀). No evidence of tumourigenicity.
Developmental/Reproductive toxicity studies	
3-generation reproductive toxicity (dietary) – 2 litters per generation Rat (Wistar) PMRA# 3038549	Supplemental Parental NOAEL = 19 mg/kg bw/day Parental LOAEL = 110 mg/kg bw/day (♂/♀) Effects at the parental LOAEL: ↓ bw [P, F1], ↓ bwg [P, F1], ↓ fc [F1], ↑ rel. kidney wt [F1] (♂/♀); ↓ fc [P], ↑ rel. kidney wt [F2] (♂); ↑ liver wt [F2] (♀) Offspring NOAEL and LOAEL could not be established due to study limitations. Effects in offspring at 110 mg/kg bw/day: ↓ bw PND 14 and 21 [F1a, F2a, F3a litters], ↑ rel. liver wt [F3b 4 weeks post-weaning] (♂/♀)

Study Type/Animal/ PMRA#	Study Results
	Reproductive NOAEL and LOAEL could not be established due to study limitations. No treatment-related effects on reproductive parameters measured in the study. Limitations: No assessment of estrous cycle, sperm parameters, or sexual maturation. Culling of litters on PND 1 may have impacted ability to assess early post-natal survival. Clinical signs of offspring not recorded. Organ weight measurements and histopathological examination in offspring limited to F3b litters at 4 weeks post-weaning.
Acute oral (gavage) – determination of relative sensitivity of pregnant and non-pregnant rats Rat (Wistar) PMRA# 2909797	Supplemental (non-guideline) Single gavage dose was administered to pregnant rats (on GD 6) and non-pregnant rats. Animals were sacrificed 3 days post-dosing. NOAELs and LOAELs were not established. Effects at 2000 mg/kg bw in pregnant rats: Clinical signs of toxicity included prostration and sedation. No mortalities occurred. Effects at 2240 mg/kg bw in pregnant rats: Clinical signs of toxicity included ruffled fur, apathy, unsteady gait, and prostration. Mortality in 5/10 dams. Effects at 2240 mg/kg bw in non-pregnant rats: Clinical signs of toxicity included ruffled fur and apathy. Mortality in 1/10 rats. Conclusion: Pregnant rats showed lower survival rates (50%) than non-pregnant rats (90%). Pregnant rats are considered to be more sensitive to the oral administration of pyridate than non-pregnant rats.
Developmental toxicity (gavage) Rat (Sprague-Dawley) PMRA# 1199504	Supplemental NOAEL and LOAEL could not be established. Maternal Toxicity Effects at ≥100 mg/kg bw/day: mortality, liver necrosis in decedents Effects at 300 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↓ mean placenta wt Developmental Toxicity Effects at 300 mg/kg bw/day: ↑ dilatation of lateral ventricles and pelvis renalis, ↑ late intrauterine deaths.

Study Type/Animal/ PMRA#	Study Results
	Limitations: pre-GLP and pre-guideline, and limited reporting.
Developmental toxicity (gavage) – dose range-finding Rat (Wistar) PMRA# 1199504	Supplemental (dose range-finding) NOAEL and LOAEL could not be established. Maternal Toxicity Effects at 150 mg/kg bw/day: slight bw loss (GD 6-7), ↓ bwg GD (6-11), ↓ fc Developmental Toxicity Effects at 150 mg/kg bw/day: ↓ fetal wt No malformations observed in fetuses upon external examination.
Developmental toxicity (gavage) Rat (Wistar) PMRA# 1213933, 3038550	Maternal NOAEL = 165 mg/kg bw/day Maternal LOAEL = 400 mg/kg bw/day Effects at the maternal LOAEL: 5 deaths (after first dose), clinical signs starting after second dose (ventral or lateral body position, dyspnea, ruffled fur, no reaction to external irritation, clonic or tonic muscle spasms, lacrimation, rolling movements; intensity of clinical signs diminished over time), ↓ bw, ↓ bwg Developmental NOAEL = 165 mg/kg bw/day Developmental LOAEL = 400 mg/kg bw/day Effects at the developmental LOAEL: ↓ fetal wt, incomplete ossification of cranial bones (parietal, interparietal, occipital), absent ossification of phalangeal nuclei, absent ossification of calcanea, absent ossification of cervical vertebrae. No evidence of sensitivity of the young. No treatment-related malformations.
Developmental toxicity (gavage) Rabbit (Chinchilla) PMRA# 3038551	Maternal NOAEL = 90 mg/kg bw/day Maternal LOAEL could not be established. No treatment-related maternal findings. Developmental NOAEL = 90 mg/kg bw/day Developmental LOAEL could not be established. No treatment-related developmental findings.

Study Type/Animal/ PMRA#	Study Results
	No evidence of sensitivity of the young. No treatment-related malformations.
Developmental toxicity (gavage) Rabbit (Chinchilla) PMRA# 2909835	Maternal NOAEL = 450 mg/kg bw/day Maternal LOAEL = 900 mg/kg bw/day Effects at the maternal LOAEL: ↓ bw, bw loss (as early as GD 6-8), ↓ fc, white foci on kidney, ↑ early resorptions, ↑ total litter resorptions, ↑ post-implantation loss Developmental NOAEL = 90 mg/kg bw/day Developmental LOAEL = 450 mg/kg bw/day Effects at the developmental LOAEL: ↑ incomplete ossification of the 2nd sternebra and several phalanges Evidence of sensitivity of the young. No treatment-related malformations.
Developmental toxicity (gavage) Rabbit (NZW) PMRA# 2909834	Maternal NOAEL = 300 mg/kg bw/day Maternal LOAEL = 600 mg/kg bw/day Effects at the maternal LOAEL: dried feces, absence of feces, abortions, bw loss (starting GD 14), ↓ bw, ↓ fc, ↓ gravid uterine wt, ↓ bw when corrected for gravid uterine weight Developmental NOAEL = 300 mg/kg bw/day Developmental LOAEL = 600 mg/kg bw/day Effects at the Developmental LOAEL: ↓ fetal wt, abortions No evidence of sensitivity of the young. No treatment-related malformations.
Genotoxicity studies	
Bacterial reverse mutation assay *E. coli* WP2uvrA PMRA# 2909839	Negative ± metabolic activation Tested up to a limit concentration.
Bacterial reverse mutation assay *S.* Typhimurium TA98, TA100,	Negative ± metabolic activation Tested up to a limit concentration and precipitating and cytotoxic concentrations.

Study Type/Animal/ PMRA#	Study Results
TA1535, TA1537, TA1538 PMRA# 2909840	
Bacterial reverse mutation assay *S.* Typhimurium TA98, TA100, TA1535, TA1537 PMRA# 3038552	Supplemental No evidence of induced mutant colonies in the presence or absence of metabolic activation when tested up to a limit concentration. Limitation: Limited positive control data.
Bacterial reverse mutation assay S. Typhimurium TA98, TA100, TA102, TA1535, TA1537 PMRA# 2997561	Negative ± metabolic activation Tested up to precipitating and cytotoxic concentrations.
Bacterial recombination assay *B. subtillis* PMRA# 2909841	Supplemental (non-guideline) No evidence of recombinogenic activity in the presence or absence of metabolic activation. Tested up to a limit concentration.
In vitro chromosomal aberration assay CHO cells PMRA# 2909844	Negative ± metabolic activation Tested up to cytotoxic concentrations.

Study Type/Animal/ PMRA#	Study Results
In vivo micronucleus assay (gavage) Mouse (Swiss) PMRA# 2909846	Negative Clinical signs of toxicity were not indicated in the report. Mortality at ≥400 mg/kg bw.
In vivo micronucleus assay (gavage) Mouse (CFLP) PMRA# 3038555	Supplemental No increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow. Clinical signs of toxicity included salivation hypopnoea, and lethargy. Mortality after the second dose at 1000 mg/kg bw. Limitations: Details on slide preparation, timing of harvest, evaluation criteria and statistical analysis were not reported.
In vitro cell transformation test BHK 21 C13/HRC 1 (Syrian Hamster Kidney Cells) PMRA# 3038553	Supplemental (non-guideline) No increase in the cell transformation frequency under the conditions of this study. Tested up to cytotoxic concentrations.
In vitro unscheduled DNA synthesis assay Rat hepatocytes PMRA# 3038554	Negative Tested up to cytotoxic concentrations.
In vivo/in vitro unscheduled DNA synthesis assay – oral (gavage) Rat (Fischer) – hepatocytes PMRA# 2909848	Negative Clinical signs included diarrhea. Mortality at 800 mg/kg bw.

Study Type/Animal/ PMRA#	Study Results
In vivo somatic cell mutation assay (gavage) Mouse (T-strain and C57B1/6J) PMRA# 3038557	Negative 725 mg/kg bw: ↓ pup survival rate
Neurotoxicity	
Acute neurotoxicity (gavage) Rat (Sprague Dawley) PMRA# 2909860	NOAEL = 177 mg/kg bw (♂/♀) LOAEL = 500 mg/kg bw (♂/♀) Effects at the LOAEL: mortality, ↓ motor activity, incoordination, lying on side, thin cover of fur, shallow breathing, flattened body posture, ↑ gait score, gait abnormalities, labored respiration, ↓ rearing, ↓ startle response, ↓ tail pinch response, ↓ righting ability, ↓ body temperature, ↓ fc, neuronal degeneration of peripheral nerves (♂/♀); involuntary motor movements (clonic), ↓ touch response (♂); head waving, ↑ respiratory rate, piloerection, ↓ arousal, absent pupil response, ↑ landing foot splay, retropulsion, shallow respiration (♀)
Subchronic neurotoxicity – Waiver request PMRA# 2909861, 2997562	Applicant's waiver rationale: The neurotoxicity of pyridate is well-characterized, having been investigated in 20 previously conducted mammalian toxicity studies. Transient neurobehavioral signs have been observed following single and repeated dosing in rodents and dogs, with dogs the more sensitive species. Effects in rodents consisted primarily of hypoactivity/sedation and uncoordinated movements at high doses while effects in dogs were more significant, including ataxia, opisthotonus, nystagmus, head swing, muscle fasciculations, and tremors in addition to hypoactivity. Effects generally appeared shortly after dosing and cleared within several hours. These effects appeared to be centrally mediated and associated with peak plasma concentrations of pyridate as these effects occurred only with bolus administration and were not observed in feeding studies. The weight of evidence suggests that the neurological effects of pyridate only occur under dose regimens leading to levels close to maximum attainable plasma concentrations. As assessed in repeated dose studies in rats and dogs, the neurological effects are not associated with inhibition of cholinesterase. Pyridate did not cause structural or permanent changes in the central or peripheral nervous system as demonstrated by the absence of pyridate-related histological lesions in the brain, spinal cord, and peripheral nerves and the absence of irreversible neurological impairment with repeated subchronic and chronic exposure in rats and dogs. Well-defined NOAELs and LOAELs for the neurological effects have been identified. Pyridate does not induce histopathological structural changes in

Study Type/Animal/ PMRA#	Study Results
	the nervous system even at lethal doses. The neurological effects of pyridate are not cumulative or progressive with repeated exposure. Therefore, the conduct of another subchronic rat study with neurotoxicity examinations will not provide any additional information to further characterize the neurological effects already established for pyridate or provide a lower point of departure for risk assessment. PMRA Assessment: Although lesions to the peripheral nervous system noted in dogs and rats were determined to be related to treatment, dogs were more sensitive than rats to the neurobehavioural manifestations of pyridate toxicity; therefore, the conduct of a subchronic neurotoxicity study in adult rats is unlikely to have a significant impact on the hazard characterization and risk assessment of pyridate.
Developmental neurotoxicity – Waiver request PMRA# 2997562, 2997563	Applicant's waiver rationale: The neurotoxicity of pyridate has been well characterized, and well-defined NOAELs and LOAELs for the neurological effects have been identified. The dog has been identified as the most sensitive species. Therefore, conducting further developmental neurotoxicity studies would not produce any additional information that would alter the understanding of the neurotoxicity of pyridate beyond what is currently known. PMRA Assessment: The request to waive a developmental neurotoxicity study was not supported due to indications of neurotoxicity in the database. Furthermore, the limited assessment of the offspring in the available 3-generation reproductive toxicity study add to the residual uncertainty regarding the potential sensitivity of the young to the neurotoxic effects of pyridate.
Special Studies	
Effects on spontaneous electroencephalogram – oral (gavage) Rat (Wistar) PMRA# 2997565	Supplemental (non-guideline) The purpose of the study was to determine the effects on electrical activity of cortical structures following sequential single doses of 250, 500, and 1000 mg/kg bw, with 4–7 days between doses. The only indications of an effect were a prolonged waking period and corresponding decrease in sleep at dose levels of ≥250 mg/kg bw, suggesting that pyridate activated the cortical regions of the brain of these animals. There was no other evidence of acute or delayed effects on electroencephalogram activity in the central nervous system after dosing with pyridate.

Study Type/Animal/ PMRA#	Study Results
Comparative effects on CNS and respiratory/ circulatory systems following single dose – oral (gavage), i.v. injection, or i.p. injection (♂ animals) Mouse (NMRI) Rat (Wistar) Rabbit (NZW) PMRA# 2997566	Supplemental (non-guideline) NOAEL and LOAEL not established. **Mice:** Effects at ≥ 1000 mg/kg bw: ↓ activity, ↓dyspnoea Effects at 3000 mg/kg bw: hunched posture Effects at 8000 mg/kg bw: ↓ locomotor activity No significant difference in sleep time up to an oral dose of 8000 mg/kg bw. No significant difference in time of onset of convulsion induced by pentetrazole or strychnine following oral dosing with 8000 mg/kg bw. Pre-treatment of mice with an oral dose of pyridate at 8000 mg/kg bw did not modify symptoms induced by electroshock. Treatment with pyridate at 8000 mg/kg bw via i.p. injection did not modify the symptoms of the tremorine antagonism test. **Rats:** Effects at 2300 mg/kg bw: mortality No effect on body temperature up to an oral dose of 2300 mg/kg bw. **Rabbits:** No effect on blood pressure or heart rate up to a cumulative i.v. dose of 2700 mg/kg bw. Conclusion: Single doses of pyridate have no or only a slight effect on the CNS and CVS parameters measured.
Estrogenic and antiestrogenic activity in vitro PMRA# 3179297	Supplemental (non-guideline) Pyridate had weak capacity to bind both ERα and AR. Pyridate was much more effective as a competitor of estrogen binding to ERα than androgen binding to AR.

Study Type/Animal/ PMRA#	Study Results
Toxicity Studies – Metabolite Pyridafol	
Acute oral (gavage) Rat (Wistar) PMRA# 2909795	Slight acute oral toxicity LD_{50} (♂) = 1511 mg/kg bw LD_{50} (♀) = 1420 mg/kg bw LD_{50} (♂/♀) = 1431 mg/kg bw Clinical signs of toxicity included sedation, dyspnea, ataxia, latero-abdominal position, ruffled fur, hunched posture, rales, spasms, ventral body position, rolling body position, and coma.
Bacterial reverse mutation assay S. Typhimurium, TA100, TA98, TA1535, TA1538, TA1537 PMRA# 2909842	Negative ± metabolic activation Tested up to cytotoxic concentrations.
Toxicity Studies – Metabolite Pyridafol-*N*-glucoside	
Absorption, distribution, metabolism and excretion (single oral gavage dose) Rat (Wistar) PMRA# 2909859	^{14}C-pyridafol-*N*-glucoside, radiolabelled on the pyridazine ring, was administered at 1 mg/kg bw. Absorption: Based on the amount of radioactivity detected in the urine, intestinal tract, carcass, and organs/tissues, 32/53% of the AD was absorbed in ♂/♀. Excretion: At 96 hours post-dosing, radioactivity was excreted via urine and feces in amounts of 32/53% and 65/45% in ♂/♀, respectively. Distribution: After 96 hours, all levels of radioactivity in tissues were at or below the limit of quantification except blood in ♂ and ovaries in ♀. Highest levels of radioactivity were measured in the adrenal and thyroid gland due to their low weights and higher limits of quantification. Metabolism: In addition to unchanged pyridafol-*N*-glucoside, nine and six metabolites were detected in the urine of ♂ and ♀, respectively. Unchanged pyridafol-*N*-glucoside accounted for 12%/6% of urinary radioactivity in ♂/♀. The major metabolites were pyridafol and an unidentified metabolite similar in structure to pyridafol.

Study Type/Animal/ PMRA#	Study Results
Acute oral (gavage) Rat (Wistar) PMRA# 2909796	Low acute oral toxicity LD_{50} (♂/♀) > 2000 mg/kg bw Clinical signs of toxicity included rales, sedation, hunched posture, and ruffled fur.

Table 4 Toxicity profile of Tough EC 600 Herbicide containing pyridate

Study Type/Animal/PMRA #	Study Results
Acute oral (gavage) Rats (Wistar) PMRA# 2910053	Low acute oral toxicity LD_{50} (♂/♀) > 2000 mg/kg bw Clinical signs of toxicity included lateral recumbency, ruffled fur, sedation, hunched posture, dyspnea, and ataxia.
Acute dermal Rats (Wistar) PMRA# 2910054	Low acute dermal toxicity LD_{50} (♂/♀) > 4000 mg/kg bw No clinical signs of toxicity. Slight erythema noted at application site.
Acute inhalation Rats (Wistar) PMRA# 2910055	Low acute inhalation toxicity LC_{50} (♂) = 5.50 mg/L LC_{50} (♂/♀) = 6.92 mg/L LC_{50} (♂/♀) = 6.37 mg/L Clinical signs of toxicity included hunched posture, stiff gait, labored respiration, ruffled fur, somnolence, sedation, bleeding nose, and tremors.
Eye irritation Rabbits (NZW) PMRA# 2910056	Moderately irritating to the eye MAS = 17.2/110 MIS = 21.7/110 at 24 hours
Skin irritation Rabbits (NZW) PMRA# 2910057	Moderately irritating to the skin MAS = 4.22/8 MIS = 4.67/8 at 72 hours

Study Type/Animal/PMRA #	Study Results
Dermal sensitization (Maximization) Guinea Pigs (Himalayan spotted) PMRA# 2910058	Potential dermal sensitizer Positive

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

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	90-day oral toxicity (capsule) in the dog	NOAEL = 80 mg/kg bw/day Neurotoxic clinical signs following 1-2 doses	300
	ARfD = 0.3 mg/kg bw		
Repeated (chronic) dietary	3-generation dietary reproductive toxicity study in the rat	NOAEL = 19 mg/kg bw/day Decreased body weight in parental animals and offspring	300
	ADI = 0.06 mg/kg bw/day		
Short- to intermediate-term dermal[2] and inhalation[3]	3-generation dietary reproductive toxicity study in the rat	NOAEL = 19 mg/kg bw/day Decreased body weight in parental animals and offspring	300
Aggregate	Due to the absence of residential uses, potential aggregation involves food and drinking water exposure only. Use of the ARfD and ADI in this scenario is appropriate.		
Cancer	Overall, the weight of evidence supported the conclusion that carcinogenicity was not an endpoint of concern for risk assessment.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor of 33% was used in route-to-route extrapolation.
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 Agricultural Handler Exposure Task Force / Pesticide Handler Exposure Database (AHETF/PHED) unit exposure values for mixers/loaders and applicators (MLA) handling Tough 600 EC Herbicide using groundboom application (µg/kg a.i. handled)

Dermal				Inhalation[2]			
PHED Mix /Load	**AHETF/ PHED Applicator**	**M/L/A**	**Dermal Absorbed[1]M/L/A**	**PHED Mix/Load**	**AHETF/ PHED Applicator**	**M/L/A**	**Total Unit Exposure[3]**
Liquid open pour mix, load (PHED Scenario 3a) with long-sleeved shirt, long pants and chemical-resistant (CR) gloves + AHETF groundboom open-cab application with single layer of clothing with no gloves.							
51.14	25.4	76.54	25.26	1.6	1.68	3.28	28.54
Liquid open pour mix, load (PHED Scenario 3a) wearing coveralls over long-sleeved shirt, long pants and CR gloves + AHETF groundboom open-cab application with coveralls and gloves.							
32.77	14.19	46.96	15.50	1.6	1.68	3.28	18.78
Liquid open pour mix, load (PHED Scenario 3a) with CR coveralls over long-sleeved shirt, long pants and CR gloves + AHETF groundboom open-cab application with CR coveralls over single layer and CR gloves.							
29.09	11.77	40.86	13.48	1.6	1.68	3.28	16.76
Liquid open pour mix, load (PHED Scenario 3a) with CR coveralls over long-sleeved shirt, long pants and CR gloves + PHED groundboom closed-cab application with single layer and no gloves.							
29.09	11.05	40.14	13.25	1.6	0.06	1.66	14.91

[1] Adjusted with dermal absorption factor of 33%
[2] Light inhalation rate
[3] Total unit exposure = Dermal exposure + inhalation exposure

Table 7 Mixer/loader/applicator (MLA) exposure and risk assessment for Tough 600 EC Herbicide

Worker Exposure Scenario	**Total Unit Exposure (µg/kg a.i.)[1]**	**Rate (kg a.i./ha)**	**ATPD (ha/day)[2]**	**Amount handled per day (kg a.i./day)[3]**		**Exposure (mg/kg bw/day)[4]**	**MOE[5]**
				kg a.i./ha	**L of product applied/day**		
Liquid open pour mix, load (PHED Scenario 3a) with long-sleeved shirt, long pants and chemical-resistant (CR) gloves + AHETF groundboom open-cab application with single layer of clothing with no gloves.							
Farmer	28.54	0.9	107	96.3	160.5	0.0344	553
Custom	28.54	0.9	360	324	540	0.1156	164
Custom	28.54	N/A	N/A	**175 restriction**	**292 L/day restriction**	0.0624	304

Worker Exposure Scenario	Total Unit Exposure (µg/kg a.i.)[1]	Rate (kg a.i./ha)	ATPD (ha/day)[2]	Amount handled per day (kg a.i./day)[3]		Exposure (mg/kg bw/day)[4]	MOE[5]
				kg a.i./ha	L of product applied/day		
Liquid open pour mix, load (PHED Scenario 3a) wearing coveralls over long-sleeved shirt, long pants and CR gloves + AHETF groundboom open-cab application with coveralls and gloves							
Farmer	18.78	0.9	107	96.3	160.5	0.0226	841
Custom	18.78	0.9	360	324	540	0.0760	250
Custom	18.78	N/A	N/A	**269 restriction**	**448 L/day restriction**	0.0631	301
Liquid open pour mix, load (PHED Scenario 3a) with CR coveralls over long-sleeved shirt, long pants + AHETF groundboom open-cab application with CR coveralls and CR gloves							
Farmer	16.76	0.9	107	96.3	160.5	0.0202	942
Custom	16.76	0.9	360	324	540	0.0679	280
Custom	16.76	N/A	N/A	**300 restriction**	**500 L/day restriction**	0.0629	302
Liquid open pour mix, load (PHED Scenario 3a) with CR coveralls over long-sleeved shirt, long pants + PHED groundboom closed-cab application with single layer and no gloves.							
Farmer	14.91	0.9	107	96.3	160.5	0.0179	1059
Custom	14.91	0.9	360	324	540	0.0604	315

Shaded MOEs indicate MOEs below the target.
Bolded values represent restrictions of active ingredient and product handled per day required to reach the target MOE of 300.
[1] Unit exposure based on AHETF/PHED, from Table 6.
[2] Default Area Treated per Day table (updated on 20 September 2020)
[3] Amount handled per day (kg a.i./day) = Rate × ATPD
[4] Daily exposure = (Unit exposure × Amount handled per day [kg a.i./day]) / (80 kg bw× 1000 µg/mg)
[5] Based on NOAEL = 19 mg/kg bw/day, target MOE = 300

Table 8 Postapplication worker exposure and risk for Tough 600 EC Herbicide on day 0 after the last application

Crops with post-emergent applications	# of applica-tions	Maximum rate (g a.i./ha)	Postapplication activity	TC (cm^2/hr)[1]	Days after last applica-tions	Peak DFR[2] (µg/cm^2)	Exposure (mg/kg bw/day)[3]	MOE[4]	REI[5]
Sweet corn	1	900	Hand harvesting (45 days PHI)	17000	45	0.02	0.0110	1728	at PHI
	1	900	Hand set/lineirrigation	1750	0	2.25	0.1300	**146**	N/A

Crops with post-emergent applications	# of applica-tions	Maximum rate (g a.i./ha)	Postapplication activity	TC (cm^2/hr)[1]	Days after last applica-tions	Peak DFR[2] (µg/cm^2)	Exposure (mg/kg bw/day)[3]	MOE[4]	REI[5]
Corn (field and sweet), Chickpeas			related activities involving foliar contact	1750	7	1.08	0.0622	306	7 days
	1	900	Scouting	1100	0	2.25	0.0817	**233**	N/A
				1100	3	1.64	0.0595	319	3 days
	1	900	Hand weeding	70	0	2.25	0.0052	3656	12 hours
Mint	1	900	Hand harvesting (45 days PHI)	1100	45	0.02	0.0007	26705	at PHI
	1	900	Hand set/line irrigation related activities involving foliar contact	1750	0	2.25	0.1300	**146**	N/A
				1750	7	1.08	0.0622	306	7 days
	1	900	Scouting	1100	0	2.25	0.0817	**233**	
				1100	3	1.64	0.0595	319	3 days
	1	900	Hand weeding	70	0	2.25	0.0052	3656	12 hours

Bolded MOEs indicate MOEs below the target.
DFR = Dislodgeable foliar residue; TC = Transfer Coefficient; MOE = Margin of exposure; REI = Restricted-entry interval; DA= dermal absorption
[1] ARTF Transfer coefficients (TC) from PMRA TC Table, Sept 4, 2020
[2] Default DFR of 25% of application rate on the day of application with 10% dissipation per day.
[3] Exposure = (Peak DFR × TC [cm^2/hr] × 33% DA × 8 hrs/day) / (80 kg bw × 1000 µg/mg).
[4] Based on a NOAEL of 19 mg/kg bw/day, Target MOE = 300.
[5] Minimum restricted-entry interval (REI) is 12 hours to allow residues to dry, suspended particles to settle and vapours to dissipate.

Table 9 REI and/or PHI for Tough 600 EC Herbicide

DO NOT enter or allow worker entry into treated areas to perform postapplication activities during the intervals specified in the following table:

Crop	Postapplication Activity	Restricted-entry interval (REI) and/or Preharvest interval (PHI)
Corn (field and sweet)	Harvesting field corn	100 days
	Harvesting sweet corn	45 days

Crop	Postapplication Activity	Restricted-entry interval (REI) and/or Preharvest interval (PHI)
	Hand set/hand line irrigation[1]	7 days
	Scouting	3 days
	All other activities	12 hours
Chickpeas	Harvesting	60 days
	Hand set/hand line irrigation[1]	7 days
	Scouting	3 days
	All other activities	12 hours
Mint	Harvesting	45 days
	Hand set/hand line irrigation[1]	7 days
	Scouting	3 days
	All other activities	12 hours
Dry peas, lentils, canola	Harvesting	At maturity
	All other activities	12 hours

[1] For hand set/hand line irrigation related activities involving foliar contact

Table 10 Integrated food residue chemistry summary

NATURE OF THE RESIDUE IN LAYING HENS		PMRA# 2909865
Species and Numbers	12 laying hens; 3 hens/group; 4 groups	
Radiolabel Position	^{14}C-pyridate (4,5 pyridazine ring) (specific activity at dosing: 20.53 mCi/g)	
Average Dose	3.2 mg a.i/kg feed/day (corresponding to 0.19 mg a.i./kg bw/day)	
Treatment Regimen	Once daily/Oral/Solution administered by intubation into the stomach	
Study Period	5 consecutive days	
Collection Time	**Eggs and excreta**: 1/day (24-hour period) during administration; 4, 8 and 24 hours after the last dose, and then 1/day up to 7 days after last dose	
Tissues Collected	Composite muscle (chest and leg), composite fat (omental and perirenal), liver, kidney, stomach, heart, brain, skin (with adjacent fat), ovaries, spleen, blood (whole and plasma), and eggs (whites and yolks)	
Interval from Last Dose to Sacrifice	Group 1 (control): 168 hours Group 2: 8 hours Group 3: 72 hours Group 4: 168 hours	
Extraction Procedures		
In this study, given that no residual radioactivity in organ, tissue, egg or blood samples was measured above 10% of the TRRs, characterization of residues in various extraction solvents and		

identification of the metabolites were not investigated.						
Distribution of Radioactivity						
Matrices	**Group 2 (8 hours post-dose) Average TRR = 0.89 ppm**		**Group 3 (72 hours post-dose) Average TRR = 0.86 ppm**		**Group 4 (168 hours post-dose) Average TRR = 0.87 ppm**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Excreta	0.829	93.2	0.819	95.2	0.835	96.0
Cage Wash	0.031	3.5	0.027	3.1	0.040	4.6
Eggs	<0.001	<0.1	<0.001	<0.1	<0.001	<0.1
Tissue/organs/blood	0.003	0.3	<0.001	<0.1	<0.001	<0.1

NATURE OF THE RESIDUE IN LAYING HENS & BROILER CHICKENS	**PMRA# 2909864**
Species and Numbers	6 laying hens and 6 broiler chickens
Radiolabel Position	^{14}C-pyridate (4,5 pyridazine ring) (specific activity at dosing: 28.34 μCi/mg)
Average Dose	3.48 mg a.i/kg feed/day (corresponding to 0.2035 mg a.i./kg bw/day)
Treatment Regimen	Once/Oral/Dissolved in corn oil and administered directly into the animal by gavage
Study Period	A single dose
Collection Time	**Eggs**: 2/day (morning and afternoon) for 4 days (96 hours) **Excreta and cage wash**: 1/day for 4 days **Bird wash**: 2/at sacrifice
Tissues Collected	Eggs (whites and yolks) and carcass
Interval from Last Dose to Sacrifice	96 hours
Extraction Procedures	
Matrices	**Extraction solvents**
Excreta (0 – 24 hrs post-dose)	1× distilled water; 1× acetic acid; 1× Sep-Pak column with methanol
PES	Non-extractables determined by combustion; no further analysis.
In this study, extraction prior to characterization and identification was only performed with the pooled excreta samples from the 0–24 hour interval given that these represented 96.0% of the TRRs in laying hens and 93.3% of the TRRs in broiler chickens. No other samples or matrices had TRRs higher than 10%.	

Distribution of Radioactivity				
Matrices	**Laying Hens Average TRR = 0.203 ppm**		**Broiler Chickens Average TRR = 0.204 ppm**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Excreta	0.201	99.07	0.197	96.74

Cage Wash	0.007	3.22	0.012	5.91
Cage Debris	0.005	2.30	0.002	0.82
Bird Wash	0.0003	0.14	0.0002	0.12
Carcass	0.0009	0.43	0.0004	0.20
Egg whites	n.d.[1]	0 to <LOQ[2]	n.d.	n.d.
Egg yolks	n.d.	0 to 0.03	n.d.	n.d.

[1] n.d.: not determined
[2] LOQ: 30 dpm above background

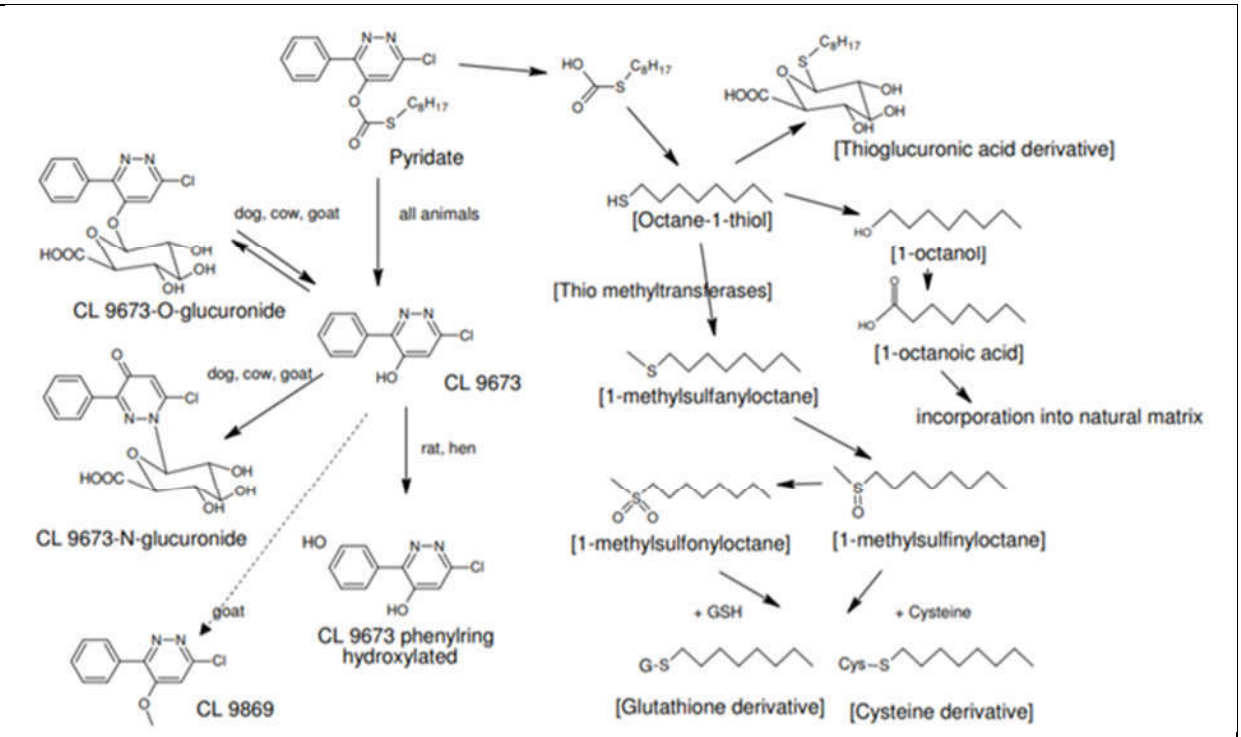
Summary of Metabolites Identified in Laying Hen and Broiler Chicken Matrices		
Radiolabelled Molecule	^{14}C-pyridate in positions 4,5 of the pyridazine ring	
Matrix	Metabolites Identified	
	Major (>10% of the TRR)	Minor (<10% of the TRR)
Excreta (0–24 hour post-dose)	Pyridafol; Hydroxylated pyridafol	-

NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA# 2909866**
Species and Numbers	2 lactating goats (1 control and 1 dosed)
Radiolabel Position	^{14}C-pyridate (4,5 pyridazine ring) (specific activity at dosing: 28.0 mCi/g)
Average Dose	2.93 mg a.i./kg feed/day (corresponding to 0.3775 mg a.i./kg bw/day)
Treatment Regimen	Once daily/Oral/Solution administered by intubation into the stomach
Study Period	10 consecutive days
Collection Time	**Milk**: 1/prior to dosing, 2/day (1- and 8-hour post-dose) during administration, and 1, 8 and 23 hours after last dose **Urine**: 1/prior to dosing, 1/day during administration, and 4, 8 and 24 hours after last dose **Feces**: 1/prior to dosing, 1/day during administration, and 24 hours after last dose. **Cage wash**: once **Blood (whole and plasma)**: 1/prior to dosing, 1/day during administration, and 1, 2, 4, 8 and 24 hours after last dose.
Tissues Collected	Heart, liver, kidney, spleen, mammary, brain, composite muscle, composite fat and bile
Interval from Last Dose to Sacrifice	24 hours
Plateau of Residues in Milk	Very low levels of residues; plateau reached on Day 3 with ~0.003% of the AD
Extraction Procedures	
Matrices	**Extraction solvents**
Urine (8–24 hrs post-dose)	Not extracted prior to TLC analysis
Feces	5 × acetone:water (8:2, v/v), 1 × acetone:water (8:2, v/v) in a

(0–24 hrs post-dose)	Soxhlet apparatus for 16 hours	
Milk (0–1 hr and 1–8 hrs post-dose)	1 × acetone at room temperature overnight, 3 × n-hexane:CH_2Cl_2 (1:1, v/v)	
Blood plasma (1- and 2-hrs post-dose)	1 × acetone	
Liver and kidney	4 × acetone:water (8:2, v/v), 1 × acetone:water (8:2, v/v) in a Soxhlet apparatus overnight, 1 × CH_2Cl_2 for 48 hours	
PES	Non-extractables determined by combustion; no further hydrolysis.	
Distribution of Radioactivity		
Matrices	**Average TRR = 3.775 ppm**	
	TRRs (ppm)[1]	**% of Administered Dose**
Urine	3.594	95.2
Feces	0.244	6.47
Cage Wash	0.048	1.27
Pooled Milk (prior to dosing up to 23 hours post-dose)	0.002	0.04
Tissues, organs and blood	0.002	0.04
Liver	0.00046	0.012
Kidneys	0.00011	0.0029
Muscle	<LOQ	<LOQ
Spleen	<LOQ	<LOQ
Heart	<LOQ	<LOQ
Mammary	<LOD	<LOD
Brain	<LOQ	<LOQ
Fat	<LOD	<LOD
Bile	0.000015	0.00040
[1] The LOD was determined to be the background level for each respective matrix; the LOQ was calculated as two times the background level for each respective matrix.		
Summary of Metabolites Identified in Lactating Goat Matrices		
Radiolabelled Molecule	^{14}C-pyridate (4,5 pyridazine ring)	
Matrices	Metabolites Identified	
	Major (>10% of the TRR)	Minor (<10% of the TRR)
Urine (8–24 hrs post-dose)	None	Pyridafol; Polar conjugate of pyridafol
Feces (0–24 hrs post-dose)	None	Pyridafol
Milk (0–1 hr post-dose)	None	Pyridafol
Milk (1–8 hrs post-dose)	None	Pyridafol
Plasma (1 hour post-dose)	None	Pyridafol
Plasma (2 hours post-dose)	None	Pyridafol
Liver	None	None
Kidney	None	Pyridafol ; 6-chloro-4-methoxy-3-

		phenylpyridazine
NATURE OF THE RESIDUE IN LACTATING COW		**PMRA# 2909867**
Species and Numbers	One lactating cow	
Radiolabel Position	^{14}C-pyridate radiolabelled (4,5 pyridazine ring) (specific activity at dosing: 28.02 µCi/mg)	
Average Dose	**Phase 1**: 35 mg a.i./kg feed/day (corresponding to 0.282 mg a.i./kg bw/day) **Phase 2**: 33 mg a.i./kg feed/day (corresponding to 0.266 mg a.i./kg bw/day)	
Treatment Regimen	**Phase 1**: Once/Intrarumenal/Dissolved in corn oil Recovery period in between where levels of radioactivity returned to normal. **Phase 2**: Once/Intrarumenal/Dissolved in corn oil	
Study Period	**Phase 1**: Days 1–8 (dosing on Day 1) Recovery: Days 9–13 **Phase 2**: Day 14 (dosing on that day) Phase 3: TLC analysis	
Collection Time	**Milk**: 2/day (8 am and 4 pm) for 11 days pre-dose, 13 days of Phase 1 and on Day 14 for Phase 2 **Urine**: During Phase 1, collected for the periods of: 0–6, 6–12, 12–24, 24–48, 48–72, 72–96, 96–120, 120–144 and 144–168 hours post-dose. During Phase 2, bladder urine collected at sacrifice. **Feces**: 1/day during Phase 1 for the periods of: 0–24, 24–48, 48–72, 72–96, 96–120, 120–144 and 144–168 hours post-dose. **Blood (whole and plasma)**: During Phase 1, collected at pre-dose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours post-dose. During Phase 2, collected at sacrifice.	
Tissues Collected	**Phase 1**: No tissues collected. **Phase 2:** Heart, liver, kidney, lung, brain, ovaries, composite skeletal muscle (shoulder and rump), composite fat (subcutaneous and perirenal), skin, section of the sciatic nerve and bile.	
Interval from last dose to sacrifice	6 hours	
Plateau of residues in milk	Rapid increase to 0.10% of the TRRs 7 hours post-dose on Day 1 and decrease to <LOQ by 47 hours post-dose	
Extraction Procedures		
Matrices	**Extraction solvents**	
Urine (Phase 1, 0 – 24 hrs post-dose)	1 × citrate buffer (pH 3) with Sep-Pak C_{18} cartridge, 1 × methanol	
Bladder urine (Phase 2)	Not extracted prior to TLC analysis	
Blood plasma (Phase 2)	2 × methanol	
Bile (Phase 2)	1 × ethanol	
Kidney (Phase 2)	2 × methanol	
Liver (Phase 2)	2 × methanol, 2 × Sep-Pak C_{18} cartridge	

PES	Non-extractables determined by combustion.	
Distribution of Radioactivity in Phase 1 (in-life)		
Matrices	TRR = 0.282 ppm	
	TRRs (ppm)	% of Administered Dose
Urine	0.260	92.1
Feces	0.0242	8.59
Pooled Milk	0.00045	0.16
Distribution of Radioactivity in Phase 2 (post-sacrifice)		
Matrices	TRR = 0.266 ppm	
	TRRs (ppm)	% of Administered Dose
Liver	0.00202	0.759
Kidney	0.00526	1.98
Heart	0.000529	0.199
Lung	0.000706	0.266
Brain	0.0000196	0.0074
Ovaries	0.0000084	0.0032
Bile	0.000167	0.063
Milk just before sacrifice	0.000182	0.0686
Bladder urine	0.00601	2.26
Summary of Metabolites Identified in Lactating Cow Matrices		
Radiolabelled Molecule	^{14}C-pyridate (4,5 pyridazine ring)	
Matrix	Metabolites Identified	
	Major (>10% of the TRR)	Minor (<10% of the TRR)
Phase 1 urine (0–24 hrs post-dose)	Pyridafol; Pyridafol-*O*- or -*N*-glucuronide	None
Phase 2 bladder urine	Pyridafol-*O*- or -*N*-glucuronide	Pyridafol
Phase 2 plasma	Pyridate; Pyridafol	Pyridafol-*O*- or -*N*-glucuronide
Phase 2 bile	None	Pyridafol-*O*- or -*N*-glucuronide
Phase 2 kidney	None	Pyridafol
Phase 2 liver	None	Pyridafol; Pyridafol-*O*- or -*N*-glucuronide
Proposed Metabolic Scheme in Livestock		



FREEZER STORAGE STABILITY IN ANIMAL MATRICES				**PMRA# 2910076**
Tested Matrices	**Analyte**	**Tested Intervals**	**Demonstrated Stability**	**Method ID (Type)**
Beef muscle	Pyridate	3–4 months and 7 months	7 months	Method R94-95 (HPLC-UV)
Beef liver				
Beef fat				
Beef kidney				
Milk				
Eggs	Freezer storage stability data were not required as egg samples in the feeding study were analyzed within 30 days of sampling.			

LIVESTOCK FEEDING – Dairy cattle			**PMRA# 2910107**
Lactating dairy cows were administered ^{14}C-pyridate (4,5 pyridazine ring) at dose levels of 1 ppm, 3.3 ppm and 10 ppm in the feeds for 28 consecutive days. The dose levels represent 14×, 47× and 143×, respectively, of the estimated dietary burden for beef cattle (0.07 ppm) and 2.5×, 8.3× and 25×, respectively, of the estimated dietary burden for dairy cattle (0.40 ppm). Animals were sacrificed approximately 6 hours after the last dose.			
Commodity/ Collection Day	**Actual Feeding Level (ppm)**	**Highest Residues (ppm)[1]**	**Mean Residues ± SDEV (ppm)[1]**
Whole milk/ Day 28 am	1	0.003	0.003 ± 0.001
	3.3	0.015	0.013 ± 0.002
	10	0.027	0.024 ± 0.004

Whole milk/ Day 28 pm	1	0.004	0.003 ± 0.001
	3.3	0.019	0.015 ± 0.004
	10	0.039	0.031± 0.008
Whole milk/ Day 29	1	0.004*	0.003 ± 0.001*
	3.3	0.016*	0.015 ± 0.004*
	10	0.040*	0.030 ± 0.010*
Whole blood/ Day 29	1	0.014	0.012 ± 0.002
	3.3	0.051	0.047 ± 0.004
	10	0.130	0.120 ± 0.020
Plasma/ Day 28, 8 hr	1	0.009	0.008 ± 0.001
	3.3	0.039	0.035 ± 0.006
	10	0.090	0.070 ± 0.015
Plasma/ Day 28, 16 hr	1	0.020	0.017 ± 0.002
	3.3	0.071	0.068 ± 0.005
	10	0.200	0.180 ± 0.026
Plasma/ Day 29	1	0.020*	0.017 ± 0.002*
	3.3	0.063*	0.068 ± 0.005*
	10	0.200*	0.180 ± 0.030*
Liver/ Day 29	1	0.021	0.019 ± 0.002
	3.3	0.226	0.118 ± 0.095
	10	0.220	0.200 ± 0.020
Kidney/ Day 29	1	0.237	0.194 ± 0.053
	3.3	0.673	0.575 ± 0.095
	10	2.28	1.88 ± 0.49
Heart/ Day 29	1	0.011	0.009 ± 0.002
	3.3	0.040	0.033 ± 0.066
	10	0.080	0.080 ± 0.040
Lung/ Day 29	1	0.009	0.009 ± 0.001
	3.3	0.036	0.031 ± 0.005
	10	0.090	0.080 ± 0.020
Brain/ Day 29	1	<0.001	<0.001 ± 0
	3.3	0.007	0.005 ± 0.002
	10	0.020	0.010 ± 0.010
Skeletal muscle (dorsal)/ Day 29	1	0.007	0.004 ± 0.003
	3.3	0.009	0.008 ± 0.001
	10	0.040	0.040 ± 0.010
Skeletal muscle (rump)/ Day 29	1	0.003	0.003 ± 0.001
	3.3	0.010	0.009 ± 0.002
	10	0.030	0.020 ± 0.010
Skeletal muscle (shoulder)/ Day 29	1	0.004	0.003 ± 0.002
	3.3	0.009	0.008 ± 0.002
	10	0.020	0.020 ± 0.010
Fat (subcutaneous)/ Day 29	1	0.004	0.003 ± 0.001
	3.3	0.032	0.017 ± 0.013

	10	0.020	0.020 ± 0.010
Fat (perirenal)/ Day 29	1	0.006	0.007 ± 0.006
	3.3	0.028	0.012 ± 0.013
	10	0.010	0.010 ± 0.01
Bile/ Day 29	1	0.067	0.054 ± 0.016
	3.3	0.236	0.196 ± 0.040
	10	0.780	0.680 ± 0.110
Bladder urine/ Day 29	1	2.036*	1.976 ± 0.070*
	3.3	4.199*	6.034 ± 1.623*
	10	24.91*	20.33 ± 4.55*

[1] Based on total radioactive residues (TRRs; ppm), expressed in equivalents of pyridafol; the asterisks (*) indicate that for those samples, the TRRs were quantified in ppm per mL of sample; SDEV: standard deviation.

Anticipated Residues in Animal Matrices

Matrices	Residue Definition	Dietary Burden (ppm)	Anticipated Residues (equivalents of pyridafol; ppm)	Calculated MRLs (equivalents of pyridafol; ppm)	Converted MRLs (equivalents of pyridate; ppm)[1]
Dairy Cattle					
Whole milk	Pyridate, including the metabolite pyridafol (free and conjugated), expressed in parent equivalents	0.40	0.003	0.01	0.02
Muscle[2]			0.002	0.01	0.02
Liver			0.038	0.04	0.07
Kidney			0.09	0.09	0.16
Fat[3]			0.013	0.015	0.03
Swine					
Muscle[2]	Pyridate, including the metabolite pyridafol (free and conjugated), expressed in parent equivalents	0.06	0	0.01	0.02
Liver			0.006	0.01	0.02
Kidney			0.014	0.015	0.03
Fat[3]			0.005	0.01	0.02

[1] As residues in the cow feeding study were obtained from TRRs (in equivalents of pyridafol), MRLs calculated with the Langmuir Tool were converted to equivalents of pyridate using the molecular weight conversion factor of 1.83.
[2] Highest anticipated residues obtained with dorsal muscles.

[3] Highest anticipated residues obtained with perirenal fat.

LIVESTOCK FEEDING – Laying hens	**PMRA# 2910108**

Laying hens were administered ^{14}C-pyridate (4,5 pyridazine ring) at dose levels of 1.3 ppm, 4 ppm and 13 ppm in the feeds for 28 consecutive days. The dose levels represent 22×, 67× and 217×, respectively, of the estimated dietary burden for poultry (0.06 ppm). Animals were sacrificed approximately 6 hours after the last dose.

Commodity/Collection Day	**Actual Feeding Level (ppm)**	**Highest Residues (ppm)**	**Mean Residues ± SDEV (ppm)[1]**
Egg white/ Pooled Day 28	1.3	0.008	0.004 ± 0.002
	4	0.011	0.008 ± 0.002
	13	0.032	0.025 ± 0.004
Egg yolk/ Pooled Day 28	1.3	0.003	0.003 ± 0
	4	0.008	0.007 ± 0.001
	13	0.023	0.019 ± 0.003
Whole blood/ Day 29	1.3	0.051	0.017 ± 0.013
	4	0.102	0.053 ± 0.027
	13	0.120	0.071 ± 0.035
Plasma/ Day 29	1.3	0.071	0.023 ± 0.020
	4	0.140	0.062 ± 0.038
	13	0.210	0.130 ± 0.044
Heart/ Day 29	1.3	0.032	0.011 ± 0.009
	4	0.056	0.026 ± 0.017
	13	0.078	0.035 ± 0.027
Liver/ Day 29	1.3	0.049	0.023 ± 0.014
	4	0.131	0.062 ± 0.033
	13	0.205	0.090 ± 0.060
Kidney/ Day 29	1.3	0.182	0.050 ± 0.051
	4	0.277	0.136 ± 0.067
	13	0.510	0.228 ± 0.154
Leg Muscle/ Day 29	1.3	0.009	0.004 ± 0.003
	4	0.020	0.008 ± 0.005
	13	0.026	0.014 ± 0.009
Breast Muscle/ Day 29	1.3	0.004	0.003 ± 0.003
	4	0.015	0.007 ± 0.004
	13	0.020	0.009 ± 0.007
Fat Pad/ Day 29	1.3	0.004	0.003 ± 0.003
	4	0.007	0.003 ± 0.003
	13	0.040	0.008 ± 0.012
Skin and Fat/ Day 29	1.3	0.021	0.008 ± 0.006
	4	0.037	0.021 ± 0.010

	13	0.079	0.041 ± 0.019
Excreta/ Day 29 (0–6 hr)	1.3	Data not reported	Data not reported
	4		
	13		

[1] Based on total radioactive residues (TRRs; ppm), expressed in equivalents of pyridafol; SDEV: standard deviation.

Anticipated Residues in Poultry Matrices

Matrices	Residue Definition	Dietary Burden (ppm)	Anticipated Residues (equivalents of pyridafol; ppm)	Calculated MRLs (equivalents of pyridafol; ppm)	Converted MRLs (equivalents of pyridate; ppm)[1]
Eggs	Pyridate, including the metabolite pyridafol (free and conjugated), expressed in parent equivalents	0.06	0	0.01	0.02
Muscle			0.001	0.01	0.02
Liver			0.003	0.01	0.02
Kidney			0.008	0.01	0.02
Fat[2]			0.001	0.01	0.02

[1] As residues in the hen feeding study were obtained from TRRs (in equivalents of pyridafol), MRLs calculated with the Langmuir Tool were converted to equivalents of pyridate using the molecular weight conversion factor of 1.83.
[2] Highest anticipated residues obtained with skin and fat.

FREEZER STORAGE STABILITY IN PLANT MATRICES			**PMRA#s 2910102, 2910103, 1223052, 1223053**	
Tested Matrices	**Analyte(s)**	**Tested Intervals (months)**	**Demonstrated Stability (months)**	**Category**
Mint forage	Pyridate and pyridafol	9.2 months; Pyridate residues were stable, but pyridafol residues showed a 47% decline between the 0-day and 281-day interval, thus correction due to in-storage dissipation was applied to residue values.	None	High-water
Succulent peas	Pyridate and pyridafol	Various intervals	21.2	High-water
Succulent pea vines				

Alfalfa green plants				
Cabbage green plants				
Corn green plants				
Rape green plants				
Peanut foliage	Pyridate			
Peanut vines				
Broccoli green plants				
Mint oil	Pyridate and pyridafol			
Peanut nutmeat	Pyridate		9.2	High-oil
Succulent peas	Pyridate and pyridafol		11.9	High-protein
Peanut nutmeat	Pyridate			
Wheat grain	Pyridate		6.6	High-starch

CROP FIELD TRIALS AND RESIDUE DECLINE ON SWEET CORN **PMRA# 3105159**

14 crop field trials were conducted in 1997 in growing regions 1 (3 trials), 2 (1 trial), 3 (1 trial), 5/5A/5B (6 trials), 10 (1 trial), 11 (1 trial) and 12 (1 trial). SAN-319H EC 361 LZ was applied in five different treatments as a foliar broadcast spray. There was either one mid-postemergence application over the top at the rate of 1.05 kg a.i./ha with or without an adjuvant; one mid-postemergence application over the top at the rate of 0.53 or 1.05 kg a.i./ha followed by one late postemergence soil application (in other words, below the crop foliage) at the rate of 1.05 or 0.53 kg a.i/ha; or one late postemergence soil application (in other words, below the crop foliage) at the rate of 1.58 kg a.i./ha. Residue decline testing in forage and grains showed that residue levels decreased with increasing PHIs.

Analyte	Total Application Rate (kg a.i./ha)	Matrix	PHI (days)	Residue Levels (expressed as parent equivalents, ppm)					
				n	LAFT[1]	HAFT[1]	Median[1]	Mean[1]	SDEV[1]
Sum of pyridate, pyridafol and hydrolysable pyridafol conjugates	1.05	Forage	6–21	3	0.097	4.67	0.375	1.72	2.57
			22–71	16	<0.05	<0.05	<0.05	<0.05	<0.05
	1.58		28–61	14	<0.05	0.337	<0.05	0.071	0.077
	1.05	K+CWHR[2]	43–72	23	<0.05	<0.05	<0.05	<0.05	<0.05
	1.08		28–61	14	<0.05	<0.05	<0.05	<0.05	<0.05

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

[1] Values based on per-trial averages; for computation of the LAFT, HAFT, median, mean, and SDEV, values <LOQ are assumed to be at the LOQ for pyridate (0.05 ppm).

[2] K+CWHR = Kernels plus cobs with husks removed

CROP FIELD TRIALS ON MINT | **PMRA# 2910102**

5 crop field trials were conducted in 1994 in growing regions 5/5A/5B (3 trials) and 11 (2 trials). Tough 3.75 EC was applied as two postemergence foliar broadcast sprays at the rate of 1.01 to 2.02 kg a.i./ha/application for a total seasonal application rate of 2.02 to 4.04 kg a.i./ha. No residue decline testing was included. As residues of the metabolite pyridafol showed a dissipation of 47% over the 9.2-month storage period in mint plant samples, total residues of pyridafol (including pyridate and pyridafol conjugates hydrolyzed to pyridafol, as determined by the method) were corrected by multiplying by a factor of 100/47.

Analyte	Total Application Rate (kg a.i./ha)	Matrix	PHI (days)	Residue Levels (expressed as parent equivalents, ppm)[1]					
				n	LAFT[1]	HAFT[1]	Median[1]	Mean[1]	SDEV[1]
Sum of pyridate, pyridafol and hydrolysable pyridafol conjugates	2.02	Mint plant	39–48	5	<0.05	0.489	<0.05	<0.138	0.196
	4.04				<0.05	1.936	<0.05	<0.427	0.844

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

[1] Corrected by a factor of 100/47 for dissipation observed during freezer storage testing.

[2] Values based on per-trial averages; for computation of the LAFT, HAFT, median, mean, and SDEV, values <LOQ are assumed to be at the LOQ for pyridate (0.05 ppm).

CROP FIELD TRIALS AND RESIDUE DECLINE ON CHICKPEAS | **PMRA# 2910086 and 2910088**

9 crop field trials were conducted in 1993 and 2016 in growing regions 7 (4 trials), 7A (1 trial), 10 (1 trial) and 11 (3 trials). Tough 3.75 EC or Pyridate EC were applied as one or two postemergence foliar broadcast sprays at the rate of 0.89–0.92, 0.99–1.01 or 1.94–2.01 kg a.i./ha/application for a total seasonal application rate of 0.89–0.92, 1.99–2.01 or 3.94–4.03 kg a.i./ha. Residue decline testing in seeds showed that residue levels decreased with increasing PHIs.

Analyte	Total Application Rate (kg a.i./ha)	Matrix	PHI (days)	Residue Levels (expressed as parent equivalents, ppm)					
				n	LAFT[1]	HAFT[1]	Median[1]	Mean[1]	SDEV[1]
Sum of pyridate, pyridafol and hydrolysable pyridafol conjugates	0.89–0.92	Hay	16 – 32	5	0.208	2.440	0.438	0.844	0.915
		Vines			<0.050	0.706	0.130	0.252	0.272
		Dried seeds	109 – 116		<0.050	<0.050	<0.050	<0.050	0
	1.99–2.01		60 - 64	3[2]	<0.05	0.080	<0.05	<0.060	0.017
	3.94–4.03			4	<0.05	<0.05	<0.05	<0.05	0

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

[1] Values based on per-trial averages; for computation of the LAFT, HAFT, median, mean, and SDEV, values < LOQ are assumed to be at the LOQ for pyridate (0.05 ppm).

[2] Due to the lateness of planting and cold weather, samples from one trial conducted at ~2 kg a.i./ha

were too small to be considered adequate for analysis. As such, n = 3 rather than n = 4.

CROP FIELD TRIALS AND RESIDUE DECLINE ON LENTILS **PMRA# 2910093**

8 crop field trials were conducted in 2016-17 in growing regions 7 (7 trials) and 14 (1 trial). Pyridate 600 EC was applied as a single postemergence foliar broadcast spray treatment at the rate of 0.87–0.95 kg a.i./ha. Residue decline testing in seeds showed that residue levels decreased with increasing PHIs.

Analyte	Total Application Rate (kg a.i./ha)	Matrix	PHI (days)	Residue Levels (expressed in parent equivalents, ppm)					
				n	LAFT[1]	HAFT[1]	Median[1]	Mean[1]	SDEV[1]
Sum of pyridate, pyridafol and pyridafol-*O*-glucoside	0.87–0.95	Dried seeds	53–89	8	<0.050	0.255	<0.088	<0.088	0.070

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

[1] Values based on per-trial averages; for computation of the LAFT, HAFT, median, mean, and SDEV, values < LOQ are assumed to be at the LOQ for pyridate (0.05 ppm).

CROP FIELD TRIALS AND RESIDUE DECLINE ON DRY FIELD PEAS **PMRA#s 2910090 & 2910092**

7 crop field trials were conducted in 1989 (3 trials) and 1992 (4 trials) in Austria. Lentagran WP was applied as a single postemergence foliar broadcast spray treatment at the rate of 0.9 kg a.i./ha. Residue decline testing in seeds showed that residue levels decreased with increasing PHIs.

Analyte	Total App. Rate (kg a.i./ha)	Matrix	PHI (days)	Residue Levels (expressed in parent equivalents, ppm)					
				n	LAFT[1]	HAFT[1]	Median[1]	Mean[1]	SDEV[1]
Sum of pyridate, pyridafol andhydrolysable pyridafol conjugates	0.9	Whole plant	0	4	20.0	25.6	23.61	23.20	2.53
			14–21		<0.05	0.67	<0.23	<0.30	0.27
		Leaf + stem	33–41		<0.05	<0.08	<0.05	<0.06	0.01
		Pod (with seed)			<0.05	<0.05	<0.05	<0.05	0
		Straw	58–68		0.06	0.32	0.19	0.19	0.14
		Pod (without seed)	58–85	7	<0.05	<0.05	<0.05	<0.05	0
		Seed			<0.05	<0.05	<0.05	<0.05	0

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

[1] Values based on per-trial averages; for computation of the LAFT, HAFT, median, mean, and SDEV, values < LOQ are assumed to be at the LOQ for pyridate (0.05 ppm).

CROP FIELD TRIALS AND RESIDUE DECLINE ON CANOLA **PMRA# 2910081**

12 crop field trials were conducted in 2016-17 in growing regions 5/5A/5B (1 trial), 7/7A (2 trials) and 14 (9 trial). Pyridate EC was applied as a single postemergence foliar broadcast spray treatment at the rate of 0.45–0.49 kg a.i./ha. Residue decline testing in seeds showed that residue levels decreased with increasing PHIs.

Analyte	Total Application Rate (kg a.i./ha)	Matrix	PHI (days)	Residue Levels (expressed in parent equivalents, ppm)					
				n	LAFT[1]	HAFT[1]	Median[1]	Mean[1]	SDEV[1]
Sum of pyridate, pyridafol and hydrolysable pyridafol conjugates	0.44–0.49	Dried seeds	50 – 80	12	<0.050	<0.050	<0.050	<0.050	0

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

[1] Values based on per-trial averages; for computation of the LAFT, HAFT, median, mean, and SDEV, values < LOQ are assumed to be at the LOQ for pyridate (0.05 ppm).

PROCESSED FOOD AND FEED – FIELD CORN **PMRA# 2910106**

A processing study for field corn was conducted with 2 trials (growing region 1 or 8). A pyridate end-use product was applied at onefold and fivefold the maximum labelled rate for field corn.

RAC	Processed Fractions	HAFT[field corn grain][1] (ppm)	Median Processing Factor	Anticipated Residues[1] (ppm)
Field corn grain	Starch, grits, meal, flour, crude oil (from dry and wet mill), refined oil (from, dry and wet mill), reclaimed hexane (from dry and wet mill)	Residues[1] were all <LOQ (<0.05 ppm) in field corn grains and all processed commodities. As such, processing factors could not be calculated for pyridate in corn processed fractions.		

[1] Expressed in parent equivalents.

PROCESSED FOOD AND FEED – FIELD CORN **PMRA# 2910105**

A processing study for field corn was conducted in one trial in Austria. Samples with incurred radioactive residues were taken from metabolism studies in which field corn was grown on a soil treated with a ^{14}C-pyridate end-use product formulated as a 45% a.i. wettable powder (WP). The application rate was 1.8 kg a.i./ha.

RAC	Processed Fractions	HAFT[field corn grain][1] (ppm)	Median Processing Factor	Anticipated Residues[1,2] (ppm)
Field corn grain	Corn oil	0.05	1.1	0.055

[1] Expressed in parent equivalents.

[2] Anticipated residues in corn oil are slightly higher than the recommended MRL of 0.05 ppm in/on RAC, in other words, field corn grains. However, given that residues in field corn grain were all non-quantifiable and that corn oil is a highly blended commodity, there is no expectation that residues in corn oil will exceed the recommended MRL of 0.05 ppm for field corn grain. Therefore, a separate MRL is not required for corn oil.

PROCESSED FOOD AND FEED – MINT				PMRA# 2910102
A processing study for mint was conducted with four trials in growing regions 5/5A and 11. The product Tough 3.75 EC was applied at a rate 2.2-fold and 4.5-fold the proposed maximum rate of 0.9 kg a.i./ha. Adequate storage stability data are available for mint oil; however, residues in mint plants were corrected by a factor of 100/47 due to dissipation observed in the freezer storage testing.				
RAC	**Processed Fractions**	**HAFT$_{[mint\ plant]}$[1,2] (ppm)**	**Median Processing Factor**	**Anticipated Residues[1,3] (ppm)**
Mint plant	Mint oil	0.222	0.12	0.027
[1] Expressed in parent equivalents. [2] The HAFT was corrected by a factor of 100/47 due to freezer storage dissipation; and was adjusted based on the proportionality principle. [3] Anticipated residues in mint oil are not higher than the recommended MRL of 0.4 ppm in/on RAC, in other words, mint tops. Therefore, a separate MRL is not required for mint oil.				
PROCESSED FOOD AND FEED – CANOLA				**PMRA# 2910081**
A processing study for canola was conducted with one trial in growing region 14. The product Pyridate 600 EC was applied at the proposed maximum rate of 0.9 kg a.i./ha in/on canola.				
RAC	**Processed Fractions**	**HAFT$_{[canola\ dried\ seeds]}$[1] (ppm)**	**Median Processing Factor**	**Anticipated Residues[1] (ppm)**
Canola dried seeds	Residues[1] were all <LOQ (<0.05 ppm) in dried canola seeds. As such, seeds were not processed and processing factors could not be calculated.[2]			
[1] Expressed in parent equivalents. [2] Therefore, a separate MRL is not required for canola processed commodities.				

Table 11 Food residue chemistry overview of metabolism studies and risk assessment

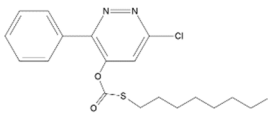
PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops** **Rotational crops**	Pyridate, including the metabolite pyridafol (free and conjugated) (expressed as parent equivalents)
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**	
METABOLIC PROFILE IN DIVERSE CROPS (field corn, peanut, rice, broccoli and spring barley)	The profile is similar in all crops investigated.

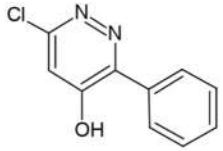
ANIMAL STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Ruminant and poultry matrices**		Pyridate, including the metabolite pyridafol (free and conjugated) (expressed as parent equivalents)	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Ruminant and poultry matrices**			
METABOLIC PROFILE IN ANIMALS (hen, chicken, goat, cow and rat)		The profile is similar in all animals investigated.	
FAT SOLUBLE RESIDUE		Yes	
DIETARY RISK FROM FOOD AND DRINKING WATER			
	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Drinking Water**
Intermediate acute dietary exposure analysis, 95th percentile **ARfD = 0.3 mg/kg bw** **Estimated acute drinking water concentration = 0.326 ppm**	All infants <1 year	1.1	20.1
	Children 1–2 years	1.8	9.2
	Children 3–5 years	1.1	7.1
	Children 6–12 years	0.7	5.5
	Youth 13–19 years	0.4	5.0
	Adults 20–49 years	0.3	5.8
	Adults 50+ years	0.2	5.1
	Females 13–49 years	0.3	5.8
	Total population	0.6	6.0
Intermediate chronic dietary exposure analysis **ADI = 0.06 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.326 ppm**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Drinking Water**
	All infants <1 year	1.5	42.5
	Children 1–2 years	4.4	19.5
	Children 3–5 years	2.7	15.0

	Children 6–12 years	1.6	10.7
	Youth 13–19 years	0.8	8.6
	Adults 20–49 years	0.6	11.5
	Adults 50+ years	0.5	11.1
	Females 13–49 years	0.6	11.3
	Total population	0.9	11.9

Fate and behaviour in the environment

Table 12 Pyridate and its environmental transformation products identified in laboratory and field dissipation studies

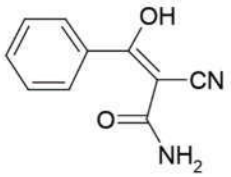
Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
Pyridate  IUPAC: 6-chloro-3-phenylpyridazin-4-yl S-octylsulfanylformate CAS#: 55512-33-9	**Hydrolysis** (PMRA# 2909881)	**pH 4** 98.1 (0) **pH 5** 96.8 (0) **pH 7** 99.6 (0) **pH 9** 98.2 (0)	**pH 4** 22.0 (11) **pH 5** 14.2 (10) **pH 7** 30.0 (4.2) **pH 9** 26.0 (0.5)
	Soil Phototransformation (PMRA# 2909882)	**Irradiated** 81.2 (0) **Dark** 81.2 (0)	**Irradiated** 1.8 (31) **Dark** 25.6 (31)
	Aqueous Phototransformation (PMRA# 2909886)	**Irradiated** **pH 5** 91.4 (0.04) **pH 7** 91.0 (0) **pH 9** 53.7 (0) **Dark** **pH 5** 95.1 (0.04) **pH 7** 84.6 (0) **pH 9** 42.1 (0)	**Irradiated** **pH 5** 0 (16) **pH 7** 0 (16) **pH 9** n.d (30) **Dark** **pH 5** 9.5 (16) **pH 7** 9.1 (16) **pH 9** 1.6 (30)

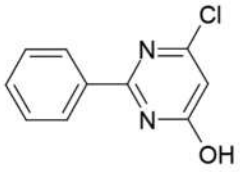
Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
	Aerobic soil (PMRA# 2909892)	**California** (loam) 97.6 (0)	**California** (loam) 1.03 (120)
	Aerobic soil (PMRA# 2909895)	**Collombey** (sand/loamy sand) 91.6 (0) **Speyer 2.2** (sand) 104.2 (0) **Auboden** (silt loam) 91.7 (0) **Les Evouettes** (silt loam/ loam) 94.1 (0)	**Collombey** (sand/loamy sand) 0.5 (98) **Speyer 2.2** (sand) 1.3 (350) **Auboden** (silt loam) 0.3 (98) **Les Evouettes** (silt loam/ loam) 0 (98)
	Aerobic aquatic (PMRA# 2909902)	**Swiss Lake** (sand) 76.2 (0) **Calwich Abbey** (silt loam) 69.3 (0)	**Swiss Lake** (sand) 0 (0) **Calwich Abbey** (silt loam) 0 (0)
	Anaerobic aquatic (PMRA # 2909903)	**Pasture Pond** (clay loam) 63.5 (0) **Golden Lake** (sand) 76.7 (0)	**Pasture Pond** (clay loam) 0 (100) **Golden Lake** (silt loam) 0 (100)
	Field studies **Iowa** (Site 1; PMRA# 2910111) **Illinois** (Site 2; PMRA# 2910111) **Northern France** (PMRA# 2910120) **England** (PMRA# 2910121) **Germany** (PMRA# 2910125)	 69.0 (0) 55.7 (0) 27.7 (0) 20.8 (0) 50.0 (0)	 0 (479) 0 (491) 0 (242) 0 (112) 0 (178)
	K_{oc}	223 807 L/kg	
MAJOR TRANSFORMATION PRODUCTS (≥10%)			
Pyridafol (NOA 402989, CL 9673, SAN 1367H) 	**Hydrolysis** (PMRA# 2909881)	**pH 4** 78.0 (11) **pH 5** 85.7 (10) **pH 7** 70.0 (4.2) **pH 9** 73.8 (0.5)	**pH 4** 78.0 (11) **pH 5** 85.7 (10) **pH 7** 70.0 (4.2) **pH 9** 73.8 (0.5)

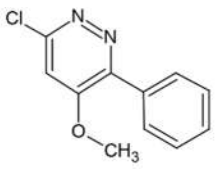
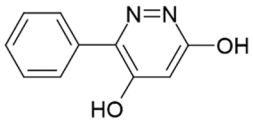
Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
	Soil Phototransformation (PMRA# 2909882)	**Irradiated** 51.4 (4) **Dark** 57.1 (31)	**Irradiated** 24.7 (31) **Dark** 57.1 (31)
	Aqueous Phototransformation (PMRA# 2909886)	**Irradiated** **pH 5** 12.7 (2) **pH 7** 40.6 (4) **pH 9** 59.7 (2) **Dark** **pH 5** 47.6 (16) **pH 7** 71.1 (16) **pH 9** 92.1 (30)	**Irradiated** **pH 5** 0 (16) **pH 7** 23.2 (16) **pH 9** 7.7 (30) **Dark** **pH 5** 47.6 (16) **pH 7** 71.1 (16) **pH 9** 92.1 (30)
	Aqueous Phototransformation (pyridafol) (PMRA# 3038595)	**Irradiated** **pH 4** 99.3 (0) **pH 7** 99.9 (0) **pH 9** 99.5 (0) **Dark** **pH 4** 99.3 (0) **pH 7** 100 (0) **pH 9** 100 (0)	**Irradiated** **pH 4** 0 (6) **pH 7** 0.41 (8.2) **pH 9** 2.22 (10) **Dark** **pH 4** 96.4 (6) **pH 7** 97.4 (8.2) **pH 9** 99.9 (10)
	Aerobic soil (PMRA# 2909892)	**California** (loam) 83.0 (14)	**California** (loam) 54.5 (120)
	Aerobic soil (PMRA# 2909895)	**Collombey** (sand/loamy sand) 88.1 (1) **Speyer 2.2** (sand) 72.3 (3) **Auboden** (silt loam) 90.7 (2) **Les Evouettes** (silt loam/loam) 89.9 (2)	**Collombey** (sand/loamy sand) 3.6 (64) **Speyer 2.2** (sand) 6.2 (350) **Auboden** (silt loam) 13.4 (98) **Les Evouettes** (silt loam/loam) 7.2 (98)
	Aerobic soil (pyridafol) (PMRA# 2909896)	**Borstel** (sandy loam) 96.4 (0)	**Borstel** (sandy loam) 36.6 (176)

Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
	Aerobic soil (pyridafol-o-methyl) (PMRA# 2909898)	**Gramastetten** (sandy loam) 5.5 (8) **Flaach** (sandy clay loam) 2.7 (8) **Feldkirchen** (sandy loam) 6.3 (8)	**Gramastetten** (sandy loam) 1.5 (120) **Flaach** (sandy clay loam) 0.2 (64) **Feldkirchen** (sandy loam) 0.3 (64)
	Aerobic aquatic (PMRA# 2909902)	**Swiss Lake** (sand) 96.2 (7) **Calwich Abbey** (silt loam) 96.6 (3)	**Swiss Lake** (sand) 81.6 (101) **Calwich Abbey** (silt loam) 83.7 (101)
	Aerobic aquatic (pyridafol) (PMRA# 2909901)	**Irsee** (sandy loam) 97.5 (1) **Rodl** (sand) 98.9 (0)	**Irsee** (sandy loam) 49.8 (120) **Rodl** (sand) 47.0 (175)
	Anaerobic aquatic (PMRA# 2909903)	**Pasture Pond** (clay loam) 104 (4) **Golden Lake** (sand) 99.4 (14)	**Pasture Pond** (clay loam) 82.5 (100) **Golden Lake** (silt loam) 90.4 (100)
	Field studies **Iowa** (Site 1; PMRA # 2910111) **Illinois** (Site 2; PMRA# 2910111) **Northern France** (PMRA# 2910120) **England** (PMRA# 2910121) **Germany** (PMRA# 2910125) **Northern Germany (pyridafol)** (PMRA# 2910124)	 78.9 (14) 58.0 (4) 39.5 (14) 54.1 (7) 65.5 (3) 96.2 (0) 97.5 (14)	 0 (479) 0 (491) 0 (242) 1.94 (112) 0 (178) 6.88 (332)
	K_{oc} South Witham Clay loam: 25 L/kg Lufa 5M Sandy loam: 19 L/kg Hareby Clay: 34 L/kg Icklingham Sand: 18 L/kg Quilen Loam: 140 L/kg		
Unextracted residues	**Soil Phototransformation** (PMRA# 2909882)	**Irradiated** 27.4% (31) **Dark** 3.6% (17)	**Irradiated** 27.4% (31) **Dark** 3.4% (31)
	Aerobic soil (PMRA# 2909892)	**California** (loam) 29.8 (120)	**California** (loam) 29.8 (120)

Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
	Aerobic soil (PMRA# 2909895)	**Collombey** (sand/loamy sand) 51.9 (98) **Speyer 2.2** (sand) 67.0 (350) **Auboden** (silt loam) 55.5 (98) **Les Evouettes** (silt loam/ loam) 59.7 (98)	**Collombey** (sand/loamy sand) 51.9 (98) **Speyer 2.2** (sand) 67.0 (350) **Auboden** (silt loam) 55.5 (98) **Les Evouettes** (silt loam/ loam) 59.7 (98)
	Aerobic soil (pyridafol) (PMRA# 2909896)	**Borstel** (sandy loam) 35.4 (176)	**Borstel** (sandy loam) 35.4 (176)
	Aerobic soil (pyridafol-o-methyl) (PMRA# 2909898)	**Gramastetten** (sandy loam) 36.4 (32) **Flaach** (sandy clay loam) 59.1 (32) **Feldkirchen** (sandy loam) 45.8 (32)	**Gramastetten** (sandy loam) 35.1 (120) **Flaach** (sandy clay loam) 44.5 (64) **Feldkirchen** (sandy loam) 34.9 (64)
	Aerobic aquatic (PMRA# 2909902)	**Swiss Lake** (sand) 9.25 (101) **Calwich Abbey** (silt loam) 7.89 (101)	**Swiss Lake** (sand) 9.25 (101) **Calwich Abbey** (silt loam) 7.89 (101)
	Aerobic aquatic (pyridafol) (PMRA# 2909901)	**Irsee** (sandy loam) 30.2 (120) **Rodl** (sand) 32.3 (175)	**Irsee** (sandy loam) 30.2 (120) **Rodl** (sand) 32.3 (175)
	Anaerobic aquatic (PMRA# 2909903)	**Pasture Pond** (clay loam) 10.1 (100) **Golden Lake** (sand) 7.21 (100)	**Pasture Pond** (clay loam) 10.1 (100) **Golden Lake** (silt loam) 7.21 (100)
M3 Unknown	**Soil Phototransformation** (PMRA# 2909882)	**Irradiated** 0.5% (0) **Dark** 0.5% (0)	**Irradiated** 0 (31) **Dark** 0 (31)
	Aqueous Phototransformation (PMRA# 2909886)	**Irradiated pH 5** 6.9 (0.5) **pH 7** 10.1 (2)	**Irradiated pH 5** 0 (16) **pH 7** 0 (16)
	Aerobic soil (PMRA# 2909896)	**Borstel** (sandy loam) 2.3 (176)	**Borstel** (sandy loam) 2.3 (176)
	Aerobic aquatic (PMRA# 2909901)	**Irsee** (sandy loam) 0.3 (105, 120) **Rodl** (sand) 0.4 (105)	**Irsee** (sandy loam) 0.3 (120) **Rodl** (sand) 0.3 (175)

Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
M9 Unknown	**Soil Phototransformation** (PMRA# 2909882)	**Irradiated** 1.9% (31)	**Irradiated** 1.9% (31)
	Aqueous Phototransformation (PMRA# 2909886)	**Irradiated** **pH 5** 10.2 (0.25) **pH 7** 13.4 (0.25) **Dark** **pH 5** 5.0 (0.25) **pH 7** 12.6 (0.25)	**Irradiated** **pH 5** 0 (16) **pH 7** 0 (16) **Dark** **pH 5** 0 (16) **pH 7** 0 (16)
M8.8 Unknown	**Aqueous Phototransformation** (PMRA# 2909886)	**Irradiated** **pH 5** 32.2 (16) **pH 7** 8.2 (16) **pH 9** 9.5 (8)	**Irradiated** **pH 5** 32.2 (16) **pH 7** 8.2 (16) **pH 9** 4.3 (30)
M8.10 Unknown	**Aqueous Phototransformation** (PMRA# 2909886)	**Irradiated** **pH 5** 7.9 (16) **pH 7** 7.6 (16) **pH 9** 10.1 (8)	**Irradiated** **pH 5** 7.9 (16) **pH 7** 7.6 (16) **pH 9** 4.4. (30)
M8.12 Unknown	**Aqueous Phototransformation** (PMRA# 2909886)	**Irradiated** **pH 5** 11.3 (16) **pH 7** 14.6 (8) **pH 9** 10.6 (30)	**Irradiated** **pH 5** 11.3 (16) **pH 7** 9.0 (16) **pH 9** 10.6 (30)
HHAC 062  	**Aqueous Phototransformation (pyridafol)** (PMRA# 3038595)	**Irradiated** **pH 4** 63.1 (3) **pH 7** 12.1 (6) **pH 9** 4.0 (8)	**Irradiated** **pH 4** 49.6 (6) **pH 7** 0 (8.2) **pH 9** 3.91 (10)

Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
HHAC 060  	**Aqueous Phototransformation (pyridafol)** (PMRA# 3038595)	**Irradiated** **pH 4** 23.6 (0.04) **pH 7** 1.24 (0.33)	**Irradiated** **pH 4** 0 (6) **pH 7** 0 (8.2)
MINOR (<10%) TRANSFORMATION PRODUCTS			
RT 1.30	**Aqueous Phototransformation (pyridafol)** (PMRA# 3038595)	**Irradiated** **pH 7** 9.44 (8.2)	**Irradiated** **pH 7** 9.44 (8.2)
Other unknown TPs (for example, from vessel washes)	**Aerobic soil** (PMRA# 2909892)	**California** (loam) 4.28 (120)	**California** (loam) 4.28 (120)
	Aerobic soil (PMRA# 2909895)	**Collombey** (sand/loamy sand) 4.9 (2) **Speyer 2.2** (sand) 10.7 (28) **Auboden** (silt loam) 6.5 (7) **Les Evouettes** (silt loam/ loam) 7.7 (7)	**Collombey** (sand/loamy sand) 3.1 (98) **Speyer 2.2** (sand) 4.3 (350) **Auboden** (silt loam) 3.0 (98) **Les Evouettes** (silt loam/ loam) 3.9 (98)
	Aerobic soil (pyridafol-o-methyl) (PMRA# 2909898)	**Gramastetten** (sandy loam) 46.8 (64) **Flaach** (sandy clay loam) 14.6 (32) **Feldkirchen** (sandy loam) 12.3 (8)	**Gramastetten** (sandy loam) 44.6 (120) **Flaach** (sandy clay loam) 11.3 (64) **Feldkirchen** (sandy loam) 4.4 (64)
	Aerobic aquatic (PMRA# 2909902)	**Swiss Lake** (sand) 4.38 (101) **Calwich Abbey** (silt loam) 4.39 (60)	**Swiss Lake** (sand) 4.38 (101) **Calwich Abbey** (silt loam) 4.39 (60)
	Aerobic aquatic (pyridafol) (PMRA# 2909901)	**Irsee** (sandy loam) 4.7 (3) **Rodl** (sand) 11.9 (175)	**Irsee** (sandy loam) 3.6 (120) **Rodl** (sand) 11.9 (175)
	Anaerobic aquatic (PMRA# 2909903)	**Pasture Pond** (clay loam) 2.86 (60) **Golden Lake** (sand) 1.13 (100)	**Pasture Pond** (clay loam) 0 (100) **Golden Lake** (silt loam) 1.13 (100)

Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
Pyridafol-o-methyl (CL-9869; NOA 406847) 	**Aerobic soil** (PMRA# 2909892)	**California** (loam) 1.89 (120)	**California** (loam) 1.89 (120)
	Aerobic soil (PMRA# 2909895)	**Collombey** (sand/loamy sand) 0.6 (64, 98) **Speyer 2.2** (sand) 5.7 (7) **Auboden** (silt loam) 3.5 (28) **Les Evouettes** (silt loam/loam) 5.9 (64)	**Collombey** (sand/loamy sand) 0.6 (98) **Speyer 2.2** (sand) 2.7 (350) **Auboden** (silt loam) 2.9 (98) **Les Evouettes** (silt loam/loam) 1.8 (98)
	Aerobic soil (pyridafol) (PMRA# 2909896)	**Borstel** (sandy loam) 7.2 (176)	**Borstel** (sandy loam) 7.2 (176)
	Aerobic soil (pyridafol-o-methyl) (PMRA# 2909898)	**Gramastetten** (sandy loam) 97.4 (0) **Flaach** (sandy clay loam) 89.8 (0) **Feldkirchen** (sandy loam) 93.7 (0)	**Gramastetten** (sandy loam) 7.2 (120) **Flaach** (sandy clay loam) 5.5 (64) **Feldkirchen** (sandy loam) 4.7 (64)
	Aerobic aquatic (pyridafol) (PMRA# 2909901)	**Rodl** (sand) 0.4 (175)	**Rodl** (sand) 0.4 (175)
	Field studies **Iowa** (Site 1; PMRA# 2910111) **Illinois** (Site 2; PMRA# 2910111) **Northern Germany (pyridafol)** (PMRA# 2910124)	 3.67 (60) 8.82 (330) 2.86 (21)	 0 (479) 0 (491) 0 (332)
HHAC 047 	**Aqueous Phototransformation (pyridafol)** (PMRA# 3038595)	**Irradiated** **pH 4** 3.64 (0.17) **pH 7** 6.58 (1) **pH 9** 8.65 (1)	**Irradiated** **pH 4** 1.3 (6) **pH 7** 0.1 (8.2) **pH 9** 0 (10)

Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
M1 Unknown	**Aerobic soil** (PMRA# 2909895)	**Collombey** (sand/loamy sand) 4.7 (3) **Speyer 2.2** (sand) 6.0 (28) **Auboden** (silt loam) 2.1 (28) **Les Evouettes** (silt loam/ loam) 3.6 (28)	**Collombey** (sand/loamy sand) 1.2 (98) **Speyer 2.2** (sand) 2.0 (350) **Auboden** (silt loam) 1.3 (98) **Les Evouettes** (silt loam/ loam) 2.0 (98)
	Aerobic aquatic (PMRA# 2909901)	**Irsee** (sandy loam) 0.3 (105) **Rodl** (sand) 1.1 (65)	**Irsee** (sandy loam) 0.2 (120) **Rodl** (sand) 0.1 (175)
M2 Unknown	**Soil Phototransformation** (PMRA# 2909882)	**Irradiated** 0.6 (0) **Dark** 0.6 (0)	**Irradiated** 0 (31) **Dark** 0 (31)
	Aqueous Phototransformation (PMRA# 2909886)	**Irradiated** **pH 5** 2.9 (0, 0.04, 5) **pH 7** 5.3 (0.04) **pH 9** 2.0 (0) **Dark** **pH 5** 3.0 (0.04) **pH 7** 4.7 (0)	**Irradiated** **pH 5** 0 (16) **pH 7** 0 (16) **pH 9** 0 (30) **Dark** **pH 5** 0 (16) **pH 7** 0 (16)
	Aerobic soil (PMRA# 2909895)	**Collombey** (sand/loamy sand) 1.6 (28) **Speyer 2.2** (sand) 2.1 (28) **Auboden** (silt loam) 2.1 (28) **Les Evouettes** (silt loam/ loam) 2.7 (98)	**Collombey** (sand/loamy sand) 0.3 (98) **Speyer 2.2** (sand) 1.5 (350) **Auboden** (silt loam) 2.0 (98) **Les Evouettes** (silt loam/ loam) 2.7 (98)
	Aerobic soil (PMRA# 2909896)	**Borstel** (sandy loam) 3.6 (176)	**Borstel** (sandy loam) 3.6 (176)
	Aerobic aquatic (PMRA# 2909901)	**Irsee** (sandy loam) 0.1 (105) **Rodl** (sand) 1.4 (65)	**Irsee** (sandy loam) 0 (120) **Rodl** (sand) 0.1 (175)

Code, Chemical Name, and Chemical Structure	Study (PMRA#) (test item is pyridate except where noted)	Mean Max %AR (day)	Mean %AR at Study End (study length, day)
M4 Unknown	**Soil Phototransformation** (PMRA# 2909882)	**Irradiated** 3.7 (17)	**Irradiated** 2.7 (31)
	Aqueous Phototransformation (PMRA# 2909886)	**Irradiated pH 5** 6.1 (2)	**Irradiated pH 5** 0 (16)
	Aerobic soil (PMRA# 2909896)	**Borstel** (sandy loam) 3.2 (176)	**Borstel** (sandy loam) 3.2 (176)
M5 Unknown	**Aqueous Phototransformation** (PMRA# 2909886)	**Irradiated pH 5** 4.5 (0.5)	**Irradiated pH 5** 0 (16)
	Aerobic soil (PMRA# 2909896)	**Borstel** (sandy loam) 1.7 (121)	**Borstel** (sandy loam) 1.7 (121)
M6 Unknown	**Soil Phototransformation** (PMRA# 2909882)	**Irradiated** 8.6 (8) **Dark** 2.4 (0)	**Irradiated** 1.8 (31) **Dark** 0 (31)
	Aqueous Phototransformation (PMRA# 2909886)	**Irradiated pH 5** 3.5 (0.5)	**Irradiated pH 5** 0 (16)
Sum of Unknowns: MO, M7, M8 **(all minor TPs)**	**Soil Phototransformation** (PMRA# 2909882)	**Irradiated** 4.2% (31)	**Irradiated** 4.2% (31)
Sum of Unknowns: **M10, M8.1, M8.2, M8.3, M8.4, M8.6, M8.7, M8.9, M8.11** **(all minor TPs)**	**Aqueous Phototransformation** (PMRA# 2909886)	**Irradiated pH 5** 25.8 (8) **pH 7** 21.2 (8) **pH 9** 21.2 (16)	**Irradiated pH 5** 17.3 (16) **pH 7** 20.5 (16) **pH 9** 12.0 (30)
Sum of Unknowns: **RRT 0.25, RRT 0.31, RRT 0.36, RRT 0.47, RRT 0.73, other minor, HHAC 062 region** **(all minor TPs)**	**Aqueous Phototransformation (pyridafol)** (PMRA# 3038595)	**Irradiated pH 4** 38.6 (6) **pH 7** 48.5 (8.2) **pH 9** 48.19 (10)	**Irradiated pH 4** 38.6 (6) **pH 7** 48.5 (8.2) **pH 9** 48.19 (10)

Table 13 Fate and behaviour in the terrestrial environment

Property	Test substance	Value	Transformation products (maximum %)	Comments	PMRA #
Abiotic transformation					
Hydrolysis	See Table 14: Fate and behaviour of pyridate in the aquatic environment				
Phototransformation on soil	Pyridate parent 1 label: [4,5-14C-pyridazine ring]pyridate	DT_{50} = 1.62 days (SFO; natural sunlight) **Supplemental**	Pyridafol 42.41% Unextracted residues 26.94% CO_2 17.81%	Pyridate may be expected to degrade in the field in natural sunlight; however, it is likely that hydrolysis of pyridate occurs simultaneously with photolysis of pyridafol.	2909883
Phototransformation on soil	Pyridate parent 1 label: [4,5-14C-pyridazine ring]pyridate	Pyridate DT_{50} = 2.09 days (SFO; natural sunlight) Pyridafol DT_{50} = 27.7 days (SFO; natural sunlight) **Reliable with restrictions**	Pyridafol 51.4% Unextracted residues 27.4% CO_2 12.1%	Pyridate may be expected to degrade in the field in natural sunlight; however, it is likely that hydrolysis of pyridate occurs simultaneously with photolysis of pyridafol.	2909882
Phototransformation in air	Pyridate and pyridafol are expected to have a low volatility under field conditions based on vapour pressure and to be non-volatile from water and moist soil based on the Henry's law constants. A phototransformation study in air is not required.				
Biotransformation					
Biotransformation in aerobic soil	Pyridate parent 1 label:	t_R = 5.84 days, DT_{50} = 3.88 days (IORE)	Major: pyridafol (83.0%, 14 days, SFO DT_{50}	Pyridate is classified as non-persistent in soil.	2909892

Property	Test substance	Value	Transformation products (maximum %)	Comments	PMRA #
	[4,5-pyradizine ring-^{14}C] California loam Study duration: 120 days		= 163 days), unextracted residues (32.4%, 120 days) Minor: pyridafol-o-methyl, CO_2	Pyridafol is classified as moderately persistent in soil.	
Biotransformation in aerobic soil	Pyridate parent 1 label: ^{14}C-pyridate 4 soils (2 in Switzerland, 1 in Germany, 1 in Austria) Study duration: 96 days, except Germany (350 days)	DT_{50}/t_R = 0.637-3.37 days (IORE, SFO) **Reliable with restrictions**	Major: pyridafol (DT_{50}/t_R = 16.7-87.1 days), CO_2, unextracted residues (51.9–67.0%, study termination) Minor: pyridafol-o-methyl, M1, M2, VOCs, other unknowns	Pyridate is classified as non-persistent in soil. Pyridafol is classified as slightly to moderately persistent in soil.	2929895
Biotransformation in aerobic soil	Pyridafol 1 label: ^{14}C-pyridafol Germany sandy loam Study duration: 176 days	DT_{50} = 129 days (SFO)	Major: unextracted residues (35.4%, 176 days) Minor: pyridafol-o-methyl, M2, M3, M4, M5, CO_2, VOCs	Pyridafol is classified as moderately persistent in soil.	2909896

Property	Test substance	Value	Transformation products (maximum %)	Comments	PMRA #
Biotransformation in aerobic soil	Pyridafol-o-methyl 1 label : ^{14}C-pyridafol-*o*-methyl 3 European soils Study duration: 64 (2 soils) and 120 days (1 soil)	DT_{50}/t_R = 12.1-12.7 days (IORE, SFO) **Reliable with restrictions**	Major: CO_2, unextracted residues (37.3-61.5%) Minor: pyridafol	Pyridafol-o-methyl is classified as slightly to moderately persistent in soil.	2909898
Biotransformation in anaerobic soil	Pyridate parent 1 label: [4,5-pyradizine ring -^{14}C] Austria silt loam Study duration: 0.21 days (aerobic conditions) + 60 days (anaerobic conditions)	**Supplemental - qualitative**	Major: pyridafol (99.3% at 4 days) Minor: CO_2		2909899
Mobility					
Adsorption/desorption in soil	Pyridate parent HPLC	K_{oc} = 223,807 mL/g	N/A	Pyridate is considered immobile in soil.	2909906

Property	Test substance	Value	Transformation products (maximum %)	Comments	PMRA #
	analysis				
Adsorption/desorption in soil	Pyridafol 1 label: [4,5-pyridazine ring-labelled-^{14}C] 5 European soils	K_{oc} = 18.24-141.59 mL/g **Reliable with restrictions**	N/A	Pyridafol is classified as having a very high to high potential for mobility in soil.	2909908
Soil leaching	No soil leaching study with pyridate was submitted and none is required.				
Volatilization	Pyridate and pyridafol are expected to have a low volatility under field conditions based on vapour pressure and to be non-volatile from water and moist soil based on the Henry's law constants.				
Field studies					
Field dissipation (Iowa and Illinois, United States)	Pyridate parent Corn-cropped (Ecoregion NA0805: Iowa and NA0804: Illinois) 1 application of 1737 g a.i./ha	t_R IORE = 4.02 days (Iowa) and 3.62 days (Illinois)	Pyridafol: 78.9% at 14 days in Iowa and 58.0% at 4 days in Illinois (SFO DT_{50} = 39.83 days and 83.19 days, respectively) Pyridafol-o-methyl	Residues of pyridate, pyridafol, and pyridafol-o-methyl were not measured below the 0–15 cm soil depth.	2910111
Field dissipation (Northern France)	Pyridate parent Bare ground site (Ecoregion PA0445)	DT_{50} = 5.11 days (SFO) **Reliable with restrictions**	Pyridafol (34.7% at 14 days; SFO DT_{50} = 33.56 days)	Residues of pyridate and pyridafol were not measured below the 0–10 cm soil depth.	2910120

Property	Test substance	Value	Transformation products (maximum %)	Comments	PMRA #
	1 application of 900 g a.i./ha				
Field dissipation (England)	Pyridate parent Bare ground site (Ecoregion PA0409) 1 application of 1120 g a.i./ha	DT_{50} = 6.28 days (SFO) **Reliable with restrictions**	Pyridafol (54.1% at 7 days; t_R = 20.43 days (IORE))	Pyridate and pyridafol did not leach below the 15–30 cm depth, with the exception of two single replicate detections of pyridafol in the 30–45 cm depth at 56 and 84 days post-treatment.	2910121
Field dissipation (Germany)	Pyridate parent Bare ground site (Ecoregion PA0412) 1 application of 900 g a.i./ha	DT_{50} < 3 days (observed) **Reliable with restrictions**	Pyridafol (65.5% at 3 days; t_R = 6.09 days (IORE))	Residues of pyridate and pyridafol did not leach below the 0–10 cm soil depth.	2910125
Field dissipation (Northern Germany)	Pyridafol Bare ground and grass-cropped sites (Ecoregion PA0412)	DT_{50} = 24.38 days (SFO; bare ground) t_R = 46.23 days (IORE; grass-cropped) **Reliable with**	Pyridafol-o-methyl (2.86 % at 21 days for bare ground and 4.83% at 61 days for grass-cropped)	Residues of pyridafol were measured down to the 20–30 cm soil depth for Plot A and 30–40 cm depth for Plot B;	2910124

Property	Test substance	Value	Transformation products (maximum %)	Comments	PMRA #
	1 application of 667 g a.i./ha (bare ground) 1 application of 659 g a.i./ha (grass-cropped)	**restrictions**		pyridafol-o-methyl was only observed at the 0–10 cm soil depth.	
Field leaching	No field leaching study with pyridate or pyridafol was submitted and none is required.				

SFO – single first-order; IORE – indeterminate order rate equation

Table 14 Fate and behaviour in the aquatic environment

Study type	Test material	Value	Transformation products	Comments	PMRA#
Abiotic transformation					
Hydrolysis	Pyridate parent 1 label: [4,5-pyridazine ring-14C]pyridate	At 25°C: pH 4 (DT_{50} = 117 hrs) pH 5 (DT_{50} = 88.8 hrs) pH 7 (DT_{50} = 58.5 hrs) pH 9 (DT_{50} = 6.17 hrs)	Pyridafol 69.99% (pH 7) to 85.71% (pH 5) No minor identified.	Pyridate is expected to undergo rapid hydrolysis in all environmental compartments in the presence of water.	2909881
Hydrolysis	Pyridafol 1 label : [4,5-pyridazine ring-14C]SAN	pH 4, 7, and 9: stable to hydrolysis	No transformation products.	Hydrolysis is not expected to be an important route of dissipation for pyridafol in the environment.	2909880

	1367 H				
Phototransformation in water	Pyridate parent 1 label: [4,5-pyradizine ring-14C]	DT_{50} = 0.445 days (pH 5, SFO) DT_{50} = 12.4 days (pH 7, SFO) DT_{50} = 1.65 days (pH 9, SFO) **Reliable with restrictions**	**Supplemental - qualitative**	It is likely that hydrolysis of pyridate occurs simultaneously with photolysis of pyridafol.	2909886
Phototransformation in water	Pyridafol 1 label: [^{14}C]-CL-9673	DT_{50} = 0.148 days (pH 4, SFO) DT_{50} = 3.51 days (pH 7, SFO) DT_{50} = 5.29 days (pH 9, SFO)	Major: HHAC 062 63.1% (pH 4), HHAC 060 23.6% (pH 4), CO_2 44.0% (pH 9), unidentified residues 34.3% Minor: CO_2, HHAC 047, HHAC 060, HHAC 062, multiple unidentified degradates	Pyridafol is expected to undergo photolysis in natural sunlight.	3038595
Biotransformation					
Biotransformation in aerobic water systems	Pyridate parent 1 label: [4,5-pyradizine ring-14C] 2 water-sediment systems from the UK (Swiss Lake and Calwich	**Swiss Lake:** Total system DT_{50} = 0.57 days (SFO) Water DT_{50} = 0.33 d (SFO) **Calwich Abbey:**	Major: Pyridafol (97.26% at 7 days in Swiss Lake with a total system DT_{50} = 416 days; 96.74% at 3 days in Calwich Abbey with a total system DT_{50} = 409 days)	Pyridate is non-persistent and hydrolyzes rapidly to pyridafol in aerobic water systems. Pyridafol is persistent in aerobic water systems.	2909902

	Abbey Lake) Study duration: 101 days	Total system DT_{50} = 0.347 days (SFO) Water DT_{50} = 0.333 days (SFO)	Unextracted residues (10.26% at 101 days in Swiss Lake) Minor: CO_2 (1.08% at 101 days in Swiss Lake and 1.98% at 60 days in Calwich Abbey) Unextracted residues (9.58% at 101 days in Calwich Abbey)		
Biotransformation in aerobic water systems	Pyridafol 1 label: ^{14}C-labelled pyridafol 2 water-sediment systems from Austria (Irrsee Lake, and Rodl River) Study duration: 120 days (Irrsee) and 175 days (Rodl)	**Irrsee:** Total system DT_{50} = 156 days (SFO) Water DT_{50} = 45.4 days (DFOP) **Rodl:** Total system DT_{50} = 194 days (SFO) Water DT_{50} = 82.2 days (DFOP)	Major: Unextracted residues (30.2% at 120 days in Irrsee and 32.3% at 175 days in Rodl) CO_2 (10.7% at 175 days in Rodl) Minor: Pyridafol-o-mehtyl, M1, M2, M3, other unknowns, CO_2, VOCs	Pyridafol is moderately persistent to persistent in aerobic water systems.	2909901
Biotransformation in anaerobic water systems	Pyridate parent 1 label: [4,5-pyradizine ring-^{14}C] 2 water-sediment	**Pasture Pond:** Total system DT_{50} = 0.491 days (SFO) Water DT_{50}	Major: Pyridafol (105% at 4 days in Pasture Pond with DT_{50} of 402 and 235 days in total system, and water,	Pyridate is non-persistent and hydrolyzes rapidly to pyridafol in anaerobic water systems. Pyridafol is	2909903

	systems from the United States: Pasture Pond (Oklahoma, United States) and Golden Lake (North Dakota, United States) Study duration: 100 days	= 0.611 days (DFOP) Sediment DT_{50} = 0.0273 days (IORE) **Golden Lake:** Total system DT_{50} = 0.0356 days (IORE) Water DT_{50} = 0.131 days (SFO) Sediment DT_{50} = 0.00134 days (IORE)	respectively; 99.9% at 14 days in Golden Lake with DT_{50} of 689 and 473 days in total system, and water, respectively) Unextracted residues (10.54% at 100 days in Pasture Pond) Minor: Pyridafol-o-methyl CO_2 (0.6% at 100 days in Pasture Pond and 0.8% at 60 days in Golden Lake) Organic volatiles, nextracted residues	persistent in anaerobic water systems.	
Partitioning					
Adsorption/desorption in sediment	Not required as an acceptable adsorption/desorption studies for soil were submitted.				
Field studies					
Field dissipation	No aquatic field dissipation study with pyridate was submitted and none is required.				
Bioconcentration/bioaccumulation					
Bioconcentration in fish	Pyridate parent ^{14}C-labelled and unlabelled at 0.05 mg a.i./L	BCFss of 29.8, 202, and 129 was calculated by the PMRA for edible, non-edible, and	Pyridafol accounted for 54.0%, 65.9%, 43.8% and 57.5% of radioactivity at Day 2,7, 22 and 28, respectively, in tank exposure	Combined residues (pyridate = transformation products) were depurated with a half-life of 2.3, 1.7 and 1.8 days in edible, non-	3038623

	Bluegill sunfish (*Lepomis macrochirus*) Study duration: 28 days (exposure) + 14 days (depuration)	whole fish BCF_k values of 32, 219, and 138 in edible, non-edible, and whole fish **Reliable with restrictions**	water.	edible and whole fish, respectively. Low bioaccumulation of combined residues of pyridate and its transformation products is expected in fish.	

SFO – single first-order; DFOP – double first-order in parallel; IORE – indeterminate order rate equation

Effects on non-target organisms

Non-target terrestrial organisms

Table 15 Effects on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Earthworm (*Eisenia fetida*)	8-wk Chronic	Pyridafol	Reproduction and survival: NOEC ≥ 3.16 mg/kg dw soil	N/A	2909987
			Reproduction and survival: NOEC = 13.99 mg/kg dw soil	N/A	2909988
Pollinator (honey bee; *Apis mellifera*)	48-hr Acute oral 48-hr Acute contact	Pyridate Technical	Survival: Oral LD_{50} > 100.4 µg a.i./bee Survival: Contact LD_{50} > 91.4 µg a.i./bee No mortalities observed.	Relatively nontoxic	2909922/ 2909923
	10-d Chronic oral		Mortality: LD_{50} > 45.8 µg a.i./bee NOED = 22.3 µg a.i./bee	N/A	3038606

			LC_{50} > 2500 mg a.i./kg diet NOEC = 1250 mg a.i./kg diet **Reliable with restrictions**		
	22-d larval toxicity		Adult emergence: NOED = 0.53 µg a.i./larva/day Day 8 larval mortality: LD_{50}: > 5.8 µg a.i./larva/day	N/A	3038605
	4-d Semi-field	Lentagran 600 EC (a.i.: pyridate)	Mortality, Hive Movement, Crop Foraging and Food Reserves: NOAEL = 1200 g a.i./ha LOAEL = 1200 g a.i./ha (based on no effects) Crop Foraging Activity and % Comb Area Containing Brood: NOAEL < 1200 g a.i./ha LOAEL = 1200 g a.i./ha (based on increased crop foraging activity and bee movement into the hives, and decrease in % comb area containing brood) Study is **not reliable for effects on brood**, but is **reliable with restrictions for**	Relatively non toxic	2909925

			acute effects on adult bees.		
Predatory arthropod (Green lacewing; *Chrysoperla carnea*)	6-wk Chronic (extended lab, freshly dried residue)	SAN 319 EC (a.i.: pyridate)	Survival: LR_{50} > 911 g a.i./ha Reproduction: NOEL ≥ 911 g a.i./ha	N/A	2909926
Predatory arthropod (*Typhlodromus pyri*)	2-wk Contact (lab)	Lentagran 600 EC (a.i.: pyridate)	Survival: LR_{50} < 879 g a.i./ha Reproduction: NOEL < 879 g a.i./ha **Reliable with restrictions**	N/A	2909929
	2-wk Contact (extended lab, freshly dried residue)		Survival: LR_{50} > 911 g a.i./ha Reproduction: NOEL < 911 g a.i./ha	N/A	2909930
Predatory arthropod (*Coccinella septempunctata*)	4-d Semi-field (maize crop)		Survival: LR_{50} > 1173 g a.i./ha	N/A	2909932
Parasitic arthropod (*Aphidius rhopalosiphi*)	11-d Contact (extended lab, freshly dried residue)		Survival: LR_{50} > 906 g a.i./ha	N/A	2909933
Birds					
Bobwhite quail (*Colinus virginianus)*	Acute oral	Pyridate Technical	LD_{50} = 1269 mg a.i./kg bw/d **Reliable with restrictions**	Slightly toxic	2909958
	20-wk Reproduction		NOED = 53 mg a.i./kg bw/d Most sensitive endpoints: egg viability, egg hatchability, and 14-d chick body weight	N/A	2909963

Zebra finch (*Taeniopygia guttata)*	Acute oral		LD_{50} > 440 mg a.i./kg bw	Practically non-toxic to moderately toxic	2909966
Mallard duck (*Anas platyrhynchos)*	18-wk Reproduction		NOED = 93.3 mg a.i./kg bw/d Most sensitive endpoints: hatchlings per eggs set, egg hatchability, and hatchling survival	N/A	2909965
Mammals					
Rat (Wistar)	Acute oral (gavage)	Pyridate	LD_{50} (♀) = 2092 mg/kg bw	N/A	2909801
Rat (Wistar)	3-generation reproductive toxicity (dietary) – 2 litters per generation	Pyridate	**Parental** NOAEL = 19 mg/kg bw/day **Offspring** NOAEL = 19 mg/kg bw/day	N/A	3038549
Rat (Wistar)	Acute oral (gavage)	Pyridafol	LD_{50} (♀) = 1420 mg/kg bw	N/A	2909795
Vascular plants					
Vascular plant	21-d Seedling emergence	A 9921 A (a.i.: pyridate)	Most sensitive monocot: Could not be determined due to lack of toxicity EC_{25}: Not calculable NOEC = 0.896 kg a.i./ha Most sensitive dicot: carrot (based on dry weight) EC_{25} = 0.353 kg a.i./ha NOEC = 0.437 kg a.i./ha	N/A	2909982
	21-d Seedling emergence	A 8985 A (a.i.: pyridate)	Most sensitive monocot: Could not be determined due to	N/A	3038641

			lack of toxicity EC_{25}: Not calculable NOEC = 0.963 kg a.i./ha Most sensitive dicot: sugar beet (based on survival) EC_{25} = 0.118 kg a.i./ha NOEC = 0.437 kg a.i./ha		
	14-d Seedling emergence	Pyridate 600 EC	Most sensitive monocot: Could not be determined due to lack of toxicity EC_{25}: Not calculable NOEC = 1.23 kg a.i./ha Most sensitive dicot: bean (based on height) EC_{25} = 6.95 kg a.i./ha* NOEC = 0.605 kg a.i./ha *outside the range of concentrations; not useable	N/A	2909980
Vascular plant	21-d Vegetative vigour	SAN 319 EC 600 (a.i.: pyridate)	Most sensitive monocot: Could not be determined due to lack of toxicity EC_{25}: Not calculable NOEC = 0.896 kg a.i./ha Most sensitive dicot: carrot (based on dry weight)	N/A	2909983

			EC_{25} = 0.0446 kg a.i./ha NOEC = 0.0105 kg a.i./ha		
	21-d Vegetative vigour	A 8985 A (a.i.: pyridate)	Most sensitive monocot: onion (based on dry weight) EC_{25} = 0.78 kg a.i./ha NOEC = 0.24 kg a.i./ha Most sensitive dicot: sugar beat (based on dry weight) EC_{25} = 0.0245 kg a.i./ha NOEC = 0.0064 kg a.i./ha	N/A	3038642
	21-d Vegetative vigour	Pyridate 600 EC	Most sensitive monocot: onion (based on dry weight) EC_{25} = 0.42 kg a.i./ha NOEC = 0.28 kg a.i./ha Most sensitive dicot: bean (based on dry weight) EC_{25} = 0.23 kg a.i./ha NOEC = 0.16 kg a.i./ha	N/A	2909981

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

Risk assessment on non-target terrestrial organisms

Table 16 Screening level risk assessment of pyridate and pyridafol for non-target terrestrial species other than birds and mammals

Organism	Exposure	Endpoint value	EEC	RQ	Level of Concern[1]
Invertebrates: Pyridafol					
Earthworm (*Eisenia fetida*)	Reproduction and survival	8-wk NOEC: 13.99 mg/kg dw soil	0.2181 mg a.i./kg	0.02	Not exceeded
Invertebrates: Pyridate					
Pollinator (honey bee; *Apis mellifera*)	Acute oral	48-hr LD_{50}: > 100.4 µg a.i./bee	25.75 µg a.i./bee	0.26	Not exceeded
	Acute contact	48-hr LD_{50}: > 91.4 µg a.i./bee	2.16 µg a.i./bee	0.02	Not exceeded
	22-d larval toxicity	Adult emergence: NOED: 0.53 µg a.i./larva/day	10.94 µg a.i./bee	**21**	**Exceeded**
	22-d larval toxicity	D8 larval mortality: LD_{50}: > 5.8 µg a.i./larva/day	10.94 µg a.i./bee	**1.9**	**Exceeded**
	Dietary	Mortality: 10-d NOED: 22.3 µg a.i./bee	25.75 µg a.i./bee	**1.2**	**Exceeded**
Predatory mite (*Typhlodromus pyri*)	Contact, extended lab, freshly dried residue	2-wk LR_{50}: > 911 g a.i./ha (survival)	In-field[2]: 900 g a.i./ha	0.99	Not exceeded
Parasitoid wasp (*Aphidius rhopalosiphi*)	Contact, extended lab, freshly dried residue	11-d LR_{50}: > 906 g a.i./ha (survival)	In-field[2]: 900 g a.i./ha	0.99	Not exceeded
Predatory arthropod (Green lacewing; *Chrysoperla carnea*)	Contact, extended lab, freshly dried residue	6-wk LR_{50}: > 911 g a.i./ha (survival)	In-field[2]: 900 g a.i./ha	0.99	Not exceeded

Predatory arthropod (Seven-spotted ladybug, *Coccinella septempunctata*)	Semi-field, maize crop	4-d LR_{50}: > 1173 g a.i./ha (survival)	In-field[2]: 900 g a.i./ha	0.77	Not exceeded
Vascular plants: Pyridate					
Vascular plant	Seedling emergence, sugar beet, *Beta vulgaris*	21-d EC_{25}: 118 g a.i./ha	In-field: 900 g a.i./ha	**7.6**	**Exceeded**
			Off-field[3]: 54 g a.i./ha	0.46	Not exceeded
	Vegetative vigour	HC_5: 90.1 g a.i./ha	In-field[2]: 900 g a.i./ha	**10**	**Exceeded**
			Off-field[3]: 54 g a.i./ha	0.60	Not exceeded

[1] Level of concern = 1 for most species; 0.4 for acute risk to pollinators; 1 for chronic risk to pollinators; and 2 for glass plate studies using the standard beneficial arthropod test species, *Typhlodromus pyri* and *Aphidius rhopalosiphi*. A level of concern = 1 is used for higher tier tests of the standard arthropod test species and for other arthropod test species.
Note: Contact exposure= application rate (kg a.i./ha) × (2.4 µg a.i./bee); adult oral exposure= application rate (kg a.i./ha) × (98 µg a.i./g) × (0.292 g/day); brood exposure= application rate (kg a.i./ha) × (98 µg a.i./g) × (0.124 g/day).
Note: acute LOC for bees is set at 0.4; chronic LOC for bees is set at 1.0.
[2] In-field EEC based on single maximum application rate of 900 g a.i./ha
[3] Off-field EEC based on single maximum application rate of 900 g a.i./ha and 6% drift from ground application, medium spray quality (ASAE)

Table 17 Screening level risk assessment for birds and mammals

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	Level of Concern[2]
Pyridate					
Small Bird (0.02 kg)					
Acute	126.9	Insectivore	73.26	0.58	Not exceeded
Reproduction	93.3	Insectivore	73.26	0.79	Not exceeded
Medium Sized Bird (0.1 kg)					
Acute	126.9	Insectivore	57.17	0.45	Not exceeded
Reproduction	93.3	Insectivore	57.17	0.61	Not exceeded
Large Sized Bird (1 kg)					
Acute	126.9	Herbivore (short grass)	36.93	0.29	Not exceeded
Reproduction	93.3	Herbivore (short grass)	36.93	0.40	Not exceeded
Small Mammal (0.015 kg)					
Acute	209.2	Insectivore	42.13	0.20	Not exceeded
Reproduction	19	Insectivore	42.13	**2.22**	**Exceeded**
Medium Sized Mammal (0.035 kg)					
Acute	209.2	Herbivore (short grass)	81.72	0.39	Not exceeded

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	Level of Concern[2]
Reproduction	19	Herbivore (short grass)	81.72	**4.30**	**Exceeded**
Large Sized Mammal (1 kg)					
Acute	209.2	Herbivore (short grass)	43.67	0.21	Not exceeded
Reproduction	19	Herbivore (short grass)	43.67	**2.30**	**Exceeded**
Pyridafol					
Small Mammal (0.015 kg)					
Acute	142	Insectivore	22.99	0.16	Not exceeded
Medium Sized Mammal (0.035 kg)					
Acute	142	Herbivore (short grass)	44.58	0.31	Not exceeded
Large Sized Mammal (1 kg)					
Acute	142	Herbivore (short grass)	23.82	0.17	Not exceeded

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

Table 18 Refined risk assessment of pyridate for mammals

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./ kg bw)[1]	RQ	EDE (mg a.i./ kg bw)[1]	RQ	EDE (mg a.i./ kg bw)[1]	RQ
Small Mammal (0.015 kg)										
Acute	209.2	Insectivore	42.13	0.2014	2.53	0.0121	29.09	0.1391	1.75	0.0083
	209.2	Granivore (grain and seeds)	6.52	0.0312	0.39	0.0019	3.11	0.0149	0.19	0.0009
	209.2	Frugivore (fruit)	13.04	0.0623	0.78	0.0037	6.22	0.0297	0.37	0.0018
Reproduction	19	Insectivore	42.13	**2.2176**	2.53	0.1331	29.09	**1.5312**	1.75	0.0919
	19	Granivore (grain and seeds)	6.52	0.3432	0.39	0.0206	3.11	0.1637	0.19	0.0098
	19	Frugivore (fruit)	13.04	0.6864	0.78	0.0412	6.22	0.3274	0.37	0.0196
Medium Sized Mammal (0.035 kg)										
Acute	209.2	Insectivore	36.94	0.1766	2.22	0.0106	25.50	0.1219	1.53	0.0073
	209.2	Granivore (grain and seeds)	5.72	0.0273	0.34	0.0016	2.73	0.0130	0.16	0.0008
	209.2	Frugivore (fruit)	11.43	0.0546	0.69	0.0033	5.45	0.0261	0.33	0.0016
	209.2	Herbivore (short grass)	81.72	0.3906	4.90	0.0234	29.02	0.1387	1.74	0.0083
	209.2	Herbivore (long grass)	49.90	0.2385	2.99	0.0143	16.29	0.0779	0.98	0.0047
	209.2	Herbivore (forage crops)	75.61	0.3614	4.54	0.0217	24.99	0.1195	1.50	0.0072

Reproduction	19	Insectivore	36.94	**1.9440**	2.22	0.1166	25.50	**1.3423**	1.53	0.0805
	19	Granivore (grain and seeds)	5.72	0.3009	0.34	0.0181	2.73	0.1435	0.16	0.0086
	19	Frugivore (fruit)	11.43	0.6017	0.69	0.0361	5.45	0.2870	0.33	0.0172
	19	Herbivore (short grass)	81.72	**4.3010**	4.90	0.2581	29.02	**1.5275**	1.74	0.0916
	19	Herbivore (long grass)	49.90	**2.6261**	2.99	0.1576	16.29	0.8575	0.98	0.0515
	19	Herbivore (Broadleaf plants)	75.61	**3.9794**	4.54	0.2388	24.99	**1.3155**	1.50	0.0789
Large Sized Mammal (1 kg)										
Acute	209.2	Insectivore	19.74	0.0943	1.18	0.0057	13.63	0.0651	0.82	0.0039
	209.2	Granivore (grain and seeds)	3.05	0.0146	0.18	0.0009	1.46	0.0070	0.09	0.0004
	209.2	Frugivore (fruit)	6.11	0.0292	0.37	0.0018	2.91	0.0139	0.17	0.0008
	209.2	Herbivore (short grass)	43.67	0.2087	2.62	0.0125	15.51	0.0741	0.93	0.0044
	209.2	Herbivore (long grass)	26.66	0.1274	1.60	0.0076	8.71	0.0416	0.52	0.0025
	209.2	Herbivore (Broadleaf plants)	40.40	0.1931	2.42	0.0116	13.36	0.0638	0.80	0.0038
Reproduction	19	Insectivore	19.74	**1.0387**	1.18	0.0623	13.63	0.7172	0.82	0.0430
	19	Granivore (grain and seeds)	3.05	0.1608	0.18	0.0096	1.46	0.0767	0.09	0.0046
	19	Frugivore (fruit)	6.11	0.3215	0.37	0.0193	2.91	0.1533	0.17	0.0092
	19	Herbivor	43.67	**2.29**	2.62	0.13	15.5	0.81	0.93	0.0490

		e (short grass)		**82**		79	1	62		
	19	Herbivore (long grass)	26.66	**1.4032**	1.60	0.0842	8.71	0.4582	0.52	0.0275
	19	Herbivore (Broadleaf plants)	40.40	**2.1263**	2.42	0.1276	13.36	0.7029	0.80	0.0422

[1] EDE = Estimated daily exposure calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). Off-field EEC values account for 6% spray drift.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g)$^{0.822}$

BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994).

Non-target aquatic organisms

Table 19 Effects on aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA #
Freshwater invertebrates					
Daphnia magna	48-hr Acute	Pyridate Technical	EC_{50} = 0.49 mg a.i./L	Highly toxic	2909937
	48-hr Acute	Pyridafol (as CL-9673)	EC_{50} = 33 mg/L	Slightly toxic	2909939
	48-hr Acute	Pyridafol-o-methyl (as NOA 406847)	EC_{50} = 67.2 mg/L	Slightly toxic	2909935
	48-hr Acute	HHAC 062	EC_{50} > 100 mg/L	Practically nontoxic	3038664
	21-d Semi-static	Pyridate Technical	NOEC = 0.028 mg a.i./L, survival and reproduction **Reliable with restrictions**	NA	2909940
	21-d Semi-static	Pyridafol	NOEC = 4.39 mg/L, survival, growth and reproduction	NA	2909941

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA #
Freshwater fish					
Rainbow trout (*Onhorynchus mykiss*)	96-hr Acute	Pyridate Technical	LC_{50} > 0.38 mg a.i./L	Highly toxic	3038618
		Lentagran 600 EC (a.i.: pyridate)	LC_{50} = 0.78 mg a.i./L	Highly toxic	3038617
		Pyridafol (as CL-9673)	LC_{50} > 16 mg/L	Slightly toxic	2909948
		Pyridafol-o-methyl (as NOA 406847)	LC_{50} = 52.7 mg/L	Slightly toxic	2909947
	69-d Early life cycle	Pyridafol (as CL-9673)	NOEC = 1.01 mg/L, hatching success	NA	2909954
Bluegill (*Lepomis macrochirus*)	96-hr Acute	Pyridafol (as CL-9673)	LC_{50} = 138 mg/L	Practically nontoxic	2909949
Freshwater algae					
Green algae (*Raphidocelis subcapitata*)	72-hr Static	Pyridate (as BCP 209H)	Yield: EC_{50} = 0.045 mg a.i./L	Very highly toxic	3038662
			Yield: EC_{50} = 0.040 mg a.i./L		3038634
		Pyridate (as BCP 258H)	Yield: EC_{50} = 0.052 mg a.i./L		3038635
			Yield: EC_{50} = 0.042 mg a.i./L		3038636
		Pyridafol-o-methyl (as NOA 406847)	Yield: EC_{50} = 2.46 mg/L	Moderately toxic	2909969
	96-hr Static	Pyridafol (as CL 9673)	Yield: EC_{50} = 3.97 mg/L		2909970
Cyanobacteria (*Anabaena flos-aquae*)	72-hr Static	Pyridate Technical	Yield/growth rate: EC_{50} > 1.98 mg a.i./L	Moderately toxic	3038629
		Pyridate (as BCP 258H)	Yield: EC_{50} = 4.84 mg a.i./L		3038632

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA #
		Pyridafol (as CL 9673)	Yield: EC_{50} = 9.76 mg//L		2909971
		HHAC 062	Yield: EC_{50} = 9.57 mg/L		3038655
Freshwater diatom (*Navicula pelliculosa*)	96-hr Static	Pyridate Technical	Yield: EC_{50} = 0.025 mg a.i./L	Very highly toxic	2909974
Freshwater vascular plants					
Duckweed (*Lemna gibba* G3)	7-d Semi-static	Pyridate EC (57.28%, as BCP258H)	Yield/growth rate (frond number, biomass): EC_{50} > 17.8 mg a.i./L (initial measured concentrations) EC_{50} > 15.6 mg a.i./L (mean measured concentrations) **Reliable with restrictions**	Slightly toxic	3038646
	7-d Semi-static	Pyridate EC (43.4%, as BCP 209H)	Yield (frond number): EC_{50} = 1.24 mg a.i./L (mean measured concentrations)	Moderately toxic	3038648
	7-d Static	Pyridafol (95.4%, as SAN 1367 H)	Area under the growth curve (biomass): EC_{50} = 8.8 mg a.i./L (nominal concentrations)	Slightly toxic	2909986
	7-d Semi-static	Pyridafol-o-methyl (98.16%, as CL Sl9869)	Yield (biomass): EC_{50} = 2.95 mg a.i./L (nominal concentrations)	Moderately toxic	3038656
Marine invertebrates					
Eastern oysters (*Crassostrea virginica*)	96-hr Acute	Pyridate Technical	LC_{50} = 0.66 mg a.i./L	Highly toxic	3038615

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA #
Mysids (*Mysidopsis bahia*)	96-hr Acute	Pyridafol (as CL-9673)	LC_{50} = 72 mg/L	Slightly toxic	2909943
Amphipods (*Leptocheirus plumulosus*)	10-d Flow-through	Pyridate Technical	LC_{50} > 28.7 mg a.i./kg	NA	3153901
Marine algae					
Marine diatom (*Skeletonema costatum*)	96-hr Static	Pyridate Technical	Area under the growth curve: EC_{50} = 0.034 mg a.i./L	Very highly toxic	2909979

[a] USEPA classification, where applicable

Risk assessment on non-target aquatic organisms

Table 20 Screening level risk assessment of pyridate for aquatic organisms

Organism	Exposure	Endpoint value (mg a.i./L)	Converted value[1] (mg a.i./L)	EEC (mg a.i./L)		RQ		LOC[2] = 1 exceeded
				15 cm	80 cm	15 cm	80 cm	
Freshwater								
Invertebrate (*Daphnia magna)*	Acute	48-hr EC_{50}: 0.49	0.245		0.11		0.46	No
	Chronic	21-d NOEC: 0.028	0.028		0.11		**4.02**	**Yes**
Rainbow trout (*Oncorhynchus mykiss)*	Acute	96-hr LC_{50}: 0.78	0.078		0.11		**1.44**	**Yes**
Freshwater alga (green; *Raphidocelis subcapitata*)	Acute	72-hr EC_{50}: 0.04	0.020		0.11		**5.63**	**Yes**
Cyanobacteria (*Anabeana flos-aquae*)	Acute	72-hr EC_{50}: 4.84	2.42		0.11		0.05	No
Freshwater diatom (*Navicula pelliculosa*)	Acute	96-hr EC_{50}: 0.025	0.0125		0.11		**9.00**	**Yes**
Vascular plant (duckweed; *Lemna gibba G3*)	Acute	7-d EC_{50}: 1.24	0.62		0.11		0.18	No

Amphibians (rainbow trout surrogate)	Acute	96-hr LC_{50}: 0.78	0.078	0.60	--	**7.69**		**Yes**
Marine								
Eastern oysters, (*Crassostrea virginica*)	Acute	96-hr LC_{50}: 0.66	0.33		0.11		0.34	No
Marine fish (rainbow trout surrogate)	Acute	96-hr LC_{50}: 0.78	0.078		0.11		**1.44**	**Yes**
Diatom (*Skeletonema costatum*)	Acute	96-hr EC_{50}: 0.034	0.017		0.11		**6.62**	**Yes**

[1] Conversions for acute (LC_{50}/EC_{50}) values: 1/10 for fish and amphibians; 1/2 for algae, macrophytes, pelagic, and benthic invertebrates. No conversion required for chronic (NOEC) values.
[2] Level of concern (LOC) = 1

Table 21 Screening level risk assessment of pyridafol (and hhac 062*) for aquatic organisms

Organism	Exposure	Endpoint value (mg a.i./L)	Converted value[1] (mg a.i./L)	EEC (mg a.i./L)		RQ		LOC[2] = 1 exceeded
				15 cm	80 cm	15 cm	80 cm	
Freshwater								
Invertebrate (*Daphnia magna*)	Acute	48-hr EC_{50}: 33	16.5		0.061		0.0037	No
	Chronic	21-d NOEC: 4.39	4.39		0.061		0.0140	No
	Acute*	48-hr EC_{50}: > 100	> 50		0.056		0.0011	No
Rainbow trout (*Oncorhynchus mykiss*)	ELS	69-d NOEC: 1.01	1.01		0.061		0.0607	No
Bluegill sunfish *Lepomis macrochirus*	Acute	96-hr EC_{50}: 138	13.8		0.061		0.0044	No
Freshwater alga (green;*Raphidocelis subcapitata*)	Acute	96-hr EC_{50}: 3.97	1.99		0.061		0.0309	No
Cyanobacteria (*Anabeana flos-aquae*)	Acute	72-hr EC_{50}: 9.76	4.88		0.061		0.0126	No
	Acute*	72-hr EC_{50}: 9.57	4.79		0.056		0.0117	No

Vascular plant (duckweed;*Lemna gibba G3)*	Acute	7-d EC_{50}: 8.8	4.4		0.061		0.0139	No
Amphibians (bluegill sunfish surrogate)	Acute	96-hr EC_{50}: 138	13.8	0.33		0.0237		No
	ELS	69-d NOEC: 1.01	1.01	0.33		0.3240		No
Marine								
Mysid (*Mysidopsis bahia*)	Acute	96-hr LC_{50}: 72	36		0.061		0.0017	No
Marine fish (bluegill sunfish surrogate)	Acute	96-hr LC_{50}: 138	13.8		0.061		0.0044	No

[1] Conversions for acute (LC_{50}/EC_{50}) values: 1/10 for fish and amphibians; 1/2 for algae, macrophytes, pelagic, and benthic invertebrates. No conversion required for chronic (NOEC) values.
[2] Level of concern (LOC) = 1
* Study examined HHAC 062

Table 22 Refined risk assessment for non-target aquatic organisms exposed to drift of pyridate

Organism	Exposure	Endpoint value (mg a.i./L)	Converted value[1] (mg a.i./L)	EEC (mg a.i./L)		RQ		LOC[2] = 1 exceeded
				15 cm	80 cm	15 cm	80 cm	
Freshwater								
Invertebrate (*Daphnia magna*)	Chronic	21-d NOEC: 0.028	0.028		0.00675		0.24	No
Rainbow trout (*Oncorhynchus mykiss*)	Acute	96-hr LC_{50}: 0.78	0.078		0.00675		0.087	No
Freshwater alga (green; *Raphidocelis subcapitata*)	Acute	72-hr EC_{50}: 0.04	0.020		0.00675		0.34	No
Freshwater diatom (*Navicula pelliculosa*)	Acute	96-hr EC_{50}: 0.025	0.0125		0.00675		0.54	No
Amphibians (rainbow trout surrogate)	Acute	96-hr LC_{50}: 0.78	0.078	0.036		1.00		No
Marine								
Marine fish (rainbow trout	Acute	96-hr LC_{50}: 0.78	0.078		0.00675		0.087	No

surrogate)								
Diatom (*Skeletonema costatum*)	Acute	96-hr EC_{50}: 0.034	0.017		0.00675		0.40	No

[1] Conversions for acute (LC_{50}/EC_{50}) values: 1/10 for fish and amphibians; 1/2 for algae, macrophytes, pelagic, and benthic invertebrates. No conversion required for chronic (NOEC) values.
[2] Level of concern (LOC) = 1

Table 23 Refined risk assessment for non-target aquatic organisms exposed to run-off of pyridate

Organism	Exposure	Endpoint value (mg a.i./L)	Converted value[1] (mg a.i./L)	EEC (µg a.i./L)		RQ		LOC[2] = 1 exceeded
				15 cm	80 cm	15 cm	80 cm	
Freshwater								
Invertebrate (*Daphnia magna*)	Chronic	21-d NOEC: 0.028	0.028		0.0406		0.0015	No
Rainbow trout (*Oncorhynchus mykiss*)	Acute	96-hr LC_{50}: 0.78	0.078		0.151		0.0019	No
Freshwater alga (green; *Raphidocelis subcapitata*)	Acute	72-hr EC_{50}: 0.04	0.020		0.151		0.0076	No
Freshwater diatom (*Navicula pelliculosa*)	Acute	96-hr EC_{50}: 0.025	0.0125		0.151		0.012	No
Amphibians (rainbow trout surrogate)	Acute	96-hr LC_{50}: 0.78	0.078	0.160		0.0021		No
Marine								
Marine fish (rainbow trout surrogate)	Acute	96-hr LC_{50}: 0.78	0.078		0.151		0.0019	No
Diatom (*Skeletonema costatum*)	Acute	96-hr EC_{50}: 0.034	0.017		0.151		0.0089	No

[1] Conversions for acute (LC_{50}/EC_{50}) values: 1/10 for fish and amphibians; 1/2 for algae, macrophytes, pelagic, and benthic invertebrates. No conversion required for chronic (NOEC) values.
[2] Level of concern (LOC) = 1

Table 24 Toxic substances management policy considerations: comparison to TSMP track 1 criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Pyridate endpoints	Pyridafol endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	No: DT_{50} = 0.0601–3.88 days (aerobic)	No: DT_{50} = 16.7–163 days (aerobic)
	Water	Half-life ≥ 182 days	No: Whole system DT_{50} = 0.0356–0.57 days (aerobic and anaerobic water sediment systems)	Yes: Whole system DT_{50} = 156–689 days (aerobic and anaerobic water sediment systems)
	Sediment	Half-life ≥ 365 days		
	Air	Half-life ≥ 2 days, or shown to be subject to atmospheric transport to remote regions such as the Arctic.	No: AOPWIN™ (v1.92) predicted half-life < 1 day in the atmosphere based on the hydroxyl radical reaction during 12 hours of daylight. Long range atmospheric transport unlikely based on properties of parent. Pyridate is not expected to enter the atmosphere based on its chemical properties. Pyridate rapidly hydrolyzes to pyridafol in all environmental compartments in the presence of water; pyridate that does not transform to pyridafol is expected to have a low volatility under field conditions based on vapour pressure and to be non-volatile from water and moist soil based on the Henry's law constants.	No: AOPWIN™ (v1.92) predicted half-life < 1 day in the atmosphere based on the hydroxyl radical reaction during 12 hours of daylight. Long range atmospheric transport unlikely based on properties of transformation product. Pyridafol is expected to have a low volatility under field conditions based on vapour pressure and to be non-volatile from water and moist soil based on the Henry's law constants.

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Pyridate endpoints	Pyridafol endpoints
Bioaccumulation[4]	Log $K_{ow} \geq 5$	No: 4.01	No: 1.68 (pH 5), 0.52 (pH 7), -1.25 (pH 9)
	BCF ≥ 5000	No: BCF_k = 138 (whole fish; combined for pyridate and transformation products) BCF_{ss} = 129 (whole fish; combined for pyridate and transformation products)	
	BAF ≥ 5000	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 CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in any environment medium is due largely to the quantities of the substance used or released as a result of human activity relative to contributions from natural sources.

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

[4] Bioaccumulation Factors (BAF) are preferred over Bioconcentration Factors (BCF); in the absence of BAF or BCF data, the octanol-water partition coefficient (log K_{ow}) may be used.

Table 25 List of supported uses

Active application rate range	All host crops and use sites: 450–900 g a.i./ha. Higher rates recommended when there are dense and/or mature weed infestations.
Product application rate range	Tough 600 EC Herbicide: 0.75–1.5 L product/ha
Adjuvant	N/A
Efficacy claims	**Weeds suppressed:** common lamb's quarters, common waterhemp, kochia, wild mustard (all with 900 g a.i./ha) **Weeds controlled:** black nightshade (450 g a.i./ha); redroot pigweed (900 g a.i./ha)
Host crops, use sites and timing	Pre-plant and/or pre-emergence (to crop; post-emergence to weeds), as a broadcast spray, in corn (field and sweet), chickpeas, lentils, field peas, canola and mint; Post-emergence to crop and weeds as a broadcast spray in corn (field and sweet), chickpeas and mint.
Application method	Apply in a minimum of 100 L water/ha using ground application equipment. When targeting dense weed populations and/or larger weeds, use higher spray volumes.

Sequential applications	For all crops except mint (2 applications total; to a maximum of 900 g a.i./ha per year) provided the applications are made at least 10–14 days apart
Rotational restrictions	No crops specifically listed. “Tough 600 EC Herbicide offers contact control of susceptible species and has no residual herbicidal activity. Crops rotated following the use of Tough 600 EC Herbicide should not be negatively impacted.”

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

The established American tolerances for pyridate are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180.462. Currently, there are no Codex MRLs[10] listed for pyridate in or on any commodity on the Codex Alimentarius Pesticide Index website.

Table 1 Comparison of Canadian MRLs and American tolerances

Food Commodity	American Tolerance (ppm)	Canadian MRL (ppm)
Dry lentils	None	0.4
Peppermint tops	0.2	
Spearmint tops	0.2	
Meat byproducts of cattle, goats, horses and sheep	None[1]	0.2
Crop subgroup 20A (Rapeseeds)	None	0.05
Dry chickpeas	0.1	
Dry field peas, dry pigeon peas	None	
Eggs	None[1]	
Fat of cattle, goats, hogs, horses, poultry and sheep	None[1]	
Field corn	0.03	
Meat byproducts of hogs and poultry	None[1]	
Meat of cattle, goats, hogs, horses, poultry and sheep	None[1]	
Milk	None[1]	
Sweet corn kernels plus cobs with husks removed	None	

[1] In the United States, as there are no expectations of quantifiable residues in animal matrices, tolerances in meat, milk and eggs are exempted (40 CFR 180.6(a)3).

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

References

A. List of studies/information submitted by registrant

PMRA Document Number	References

1.0 Chemistry

2909750	2015, Process Description - Pyridate (Plant), DACO: 2.11.1,2.11.2,2.11.3 CBI
2909751	2015, Process Description - Pyridate (Lab), DACO: 2.11.1,2.11.2,2.11.3 CBI
2909752	2012, Manufacturing Process, DACO: 2.11.1,2.11.2,2.11.3 CBI
2909757	2011, Validation of Methods of Analysis for the Determination of Pyridate, Isomers, Process Related Impurities and By-products in Pyridate Technical Grade Active Ingredient, DACO: 2.11.4,2.13.1 CBI
2909758	2012, Further Validation of Method OZ10020A to Include Two Additional Process Related By-Products in Pyridate Technical Grade Active Ingredient, DACO: 2.11.4,2.13.1 CBI
2909759	2012, Validation of Method OZ10020A for the Analysis of Process Related By-products in Pyridate Technical Grade Active Ingredient using a Pyridate Surrogate Standard, DACO: 2.11.4,2.13.1 CBI
2909760	2011, Analysis of Technical Pyridate Impurity Profile by LC-MS - Confirmation of Synthetic Impurity Standards and Elucidation of Proposed Impurity Structures, DACO: 2.11.4 CBI
2909763	2015, Analytical Profile of Five Batches of Pyridate Technical Grade Active Ingredient - Produced at [PRIVACY INFO REMOVED], DACO: 2.13.2,2.13.3 CBI
2909766	1988, Color and Appearance of Technical Pyridate, DACO: 2.14.1
2909767	1988, Physical State of Technical Pyridate, DACO: 2.14.2
2909768	1988, Odor of Technical Pyridate, DACO: 2.14.3
2909769	1996, Pyridate: Determination of Physico-Chemical Properties of the Purified Active Substance (Melting and Boiling Points, Ultra-violet/visible, Infra-red, Nuclear Magnetic Resonance and Mass Spectra), DACO: 2.14.12,2.14.4,2.14.5
2909770	1998, Report on Density of Solids, DACO: 2.14.6
2909771	1988, Specific Gravity of Technical Pyridate, DACO: 2.14.6
2909772	1995, Relative Density of Pure Pyridate, DACO: 2.14.6
2909775	1996, Solubility of Pyridate in Water Including Effect on pH, DACO: 2.14.7
2909777	2011, Technical Pyridate Solubility in Organic Solvents, DACO: 2.14.8
2909778	1988, Volatility Assessment of Pyridate and its Major Degradation Product CL-9673, DACO: 2.14.9
2909784	1982, Evaluation of the Partition Coefficient of Pyridate in the System N-Octanol/Water, DACO: 2.14.11
2909785	1996, Pyridate - Determination of 1H-NMR-Spectrum, DACO: 2.13.2
2909786	1988, Stability of Technical Pyridate, DACO: 2.14.13

2909787 2018, Request for Waiver for the Requirement of Stability to Metals for Pyridate Technical, DACO: 2.14.13
2909790 2011, Pyridate - Annex I Renewal - Doc J Technical Equivalence, DACO: 2.16 CBI
2909791 2015, Evaluation Report on the Equivalence of Technical Material for the Active Substance Pyridate, DACO: 2.16 CBI
3079983 2020, Establishing Certified Limits for Pyridate Technical, DACO: 2.12.1 CBI
3079984 2019, Analytical Profile of Five Batches of Pyridate Technical Grade Active Ingredient - Produced at [PRIVACY INFO REMOVED], DACO: 2.13.2,2.13.3 CBI
3079985 2019, Amendment to Report: Analytical Profile of Five Batches of Pyridate Technical Grade Active Ingredient - Produced at [PRIVACY INFO REMOVED], DACO: 2.13.2,2.13.3 CBI
2910037 2018, Product Chemistry DACO 3.1.1-3.1.4, 3.5.4, 3.5.5 and 3.5.15 for Tough 600 EC Herbicide, DACO: 3.1.1,3.1.2,3.1.3,3.1.4,3.5.15,3.5.4,3.5.5
2910041 1994, Description of Beginning Materials and Manufacturing Process of Tough 5 EC, DACO: 3.2.1,3.2.2 CBI
2910044 2013, Validation of the Analytical Method used to determine Pyridate within BCP258H an Emulsifiable Concentrate (EC) Formulation, DACO: 3.4.1
2910045 1997, Report on Physico-Chemical Properties, DACO: 3.5.1,3.5.2,3.5.7
2910046 2015, Storage Stability Study for 2 Years at ambient (average warehouse) conditions with specified Physical-Chemical data for BCP258H an Emulsifiable Concentrate (EC) Formulation, DACO: 3.5.10
2910047 2018, Waiver for the Requirement of a Miscibility Study for Tough 600 EC Herbicide, DACO: 3.5.13
2910048 1997, Corrosion Characteristics, DACO: 3.5.14
2910049 1994, Physical and Chemical Characteristics of Tough 5 EC, DACO: 3.5.11,3.5.12,3.5.14,3.5.2,3.5.6,3.5.8,3.5.9
2910050 1997, Physico-chemical Properties, DACO: 3.5.3
2910051 2012, Accelerated Storage Stability Study for 14 days at 54C with specified Physical-chemical data for BCP258H an Emulsifiable Concentrate (EC) Formulation, DACO: 3.5.10,3.5.11,3.5.12,3.5.6,3.5.7,3.5.8,3.5.9

2.0 Human and animal health

2909793 1996, Pyridate TC (in corn oil): Assessment of Acute Oral Toxicity in the Rat, DACO: 4.2.1
2909794 1996, Pyridate TC (in PEG 200): Assessment of Acute Oral Toxicity in the Rat, DACO: 4.2.1
2909795 1987, Acute Oral Toxicity Study with CL 9673 (Phenolform) in Rats, DACO: 4.2.1
2909796 1990, Acute Oral Toxicity Study with CL-9673-*N*-Glucosid in Rats, DACO: 4.2.1
2909797 1994, Dose Toleration Study with Pyridate Technical in the Rat, DACO: 4.2.1
2909799 1987, Acute Oral Toxicity Study with Pyridate Technical in Mice, DACO: 4.2.1
2909800 1988, Acute Oral Toxicity Study with Pyridate Technical in Rats, DACO: 4.2.1
2909801 1996, Pyridate TC (in 1% CMC): Assessment of Acute Oral Toxicity in the Rat, DACO: 4.2.1

2909805 1995, Primary Eye Irritation Study in Albino Rabbits with Pyridate Technical, DACO: 4.2.4
2909807 1995, Primary Dermal Irritation Study in Albino Rabbits with Pyridate Technical, DACO: 4.2.5
2909809 1988, Determination of Skin Irritation and Capacity of Allergenic Sensitization by the Open Epicutaneous Test on Guinea Pigs (OET) with Pyridate Tech., DACO: 4.2.6
2909810 1991, Pyridate Tech: Buehler Delayed Contact Hypersensitivity Study in the Guinea Pig, DACO: 4.2.6
2909813 1991, Pyridate Technical: Toxicity Study by Dietary Administration to CD Rats for 13 Weeks, DACO: 4.3.1
2909815 1986, 1-2 Week Dog Oral Range-finding Toxicity Study, DACO: 4.3.2
2909817 1989, Chronic Toxicity Study in Dogs with Pyridate Technical, DACO: 4.3.2
2909820 1990, Pyridate Technical: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 13 Weeks , DACO: 4.3.2
2909821 1980, Subacute (4-week) Oral Toxicity Study with Pyridate in Mice, DACO: 4.3.3
2909822 1979, Subacute (4-Week) Oral Toxicity Study with Pyridate in Rats, DACO: 4.3.3
2909830 1991, Oncogenicity Study of Pyridate Administered by Dosed Feed to B6C3F1 Mice, DACO: 4.4.3
2909834 1987, Developmental Toxicity (Embryo/Fetal Toxicity and Teratogenic Potential) Study of Pyridate Technical Administered as the Neat Test Substance Orally via Stomach Tube to New Zealand White Rabbits, DACO: 4.5.3
2909835 1992, Embryotoxicity Study (Including Teratogenicity) with Pyridate Technical in the Rabbit, DACO: 4.5.3
2909839 1986, Mutagenicity Evaluation of Pyridate Technical in the Reverse Mutation Assay with *E. coli* strain WP2uvrA , DACO: 4.5.4
2909840 1986, Mutagenicity Evaluation of Pyridate Technical in the Ames Salmonella/Microsome Reverse Mutation Assay, DACO: 4.5.4
2909841 1986, Pyridate Technical - Mutagenicity Evaluation in the Rec Assay with Bacillus Subtilis, DACO: 4.5.4
2909842 1987, Mutagenicity Test on CL 9673, Batch No. 2560714 in the Ames *Salmonella*/Microsome Reverse Mutation Assay, DACO: 4.5.4
2909844 1987, Clastogenic Evaluation of Pyridate Technical in an In Vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells, DACO: 4.5.6
2909846 1986, Clastogenic Evaluation of Pyridate Technical in the In Vivo Mouse Micronucleus Assay, DACO: 4.5.7
2909848 1988, In Vivo - In Vitro Rat Hepatocyte Unscheduled DNA Synthesis Assay, DACO: 4.5.8
2909850 1997, Proposed Metabolic Pathways of Thiocarbonic acid *S*-octyl ester, a Hydrolysis Product of Pyridate, in Mammalians, DACO: 4.5.9
2909851 1997, [14C]-Pyridate and [14C]-SAN 1367H: Comparative Absorption, Distribution and Excretion Studies in the Rat after Intraveneous Administration, DACO: 4.5.9

2909852 1997, SAN 1367 H: [14C]-SAN 1367 H AI - [14C]-Pyridate AI Comparative Rat Metabolism Study, DACO: 4.5.9
2909853 1990, The Absorption, Distribution and Metabolism of [14C]-Pyridate in the Rat (Additional Study), DACO: 4.5.9
2909854 1988, The Disposition of [14C]-Pyridate in the Dog Following Oral Administration, DACO: 4.5.9
2909855 1986, The Absorption, Distribution, Metabolism and Excretion of [14C]-Pyridate in the Rat, DACO: 4.5.9
2909856 1997, [14C]-Pyridate and [14C]-SAN 1367H: Comparative Absorption, Distribution and Excretion Studies in the Rat after Oral Administration, DACO: 4.5.9
2909857 1997, [14C]-Pyridate and [14C]-SAN 1367H: Comparative Absorption, Distribution and Excretion Studies in the Rat after Oral Administration, DACO: 4.5.9
2909858 1997, [14C]-Pyridate and [14C]-SAN 1367H: Comparative Absorption, Distribution and Excretion Studies in the Rat after Oral Administration, DACO: 4.5.9
2909859 1992, CL9673-*N*-glucoside: Absorption, Distribution, Metabolism and Excretion after Single Oral Administration to Rats, DACO: 4.5.9
2909860 2016, Pyridate: Acute Single-Dose Oral Gavage Neurotoxicity Screening Study in Rats, DACO: 4.5.12
2909861 2016, Pyridate: Request for Waiver of Subchronic Neurotoxicity Study, DACO: 4.5.13
2997558 1987, 90 day oral subchronic toxicity study with a 28 day recovery period of pyridate technical, DACO: 4.3.1
2997559 2013, Pyridate Historical Control Data for Mouse Liver Tumours, DACO: 4.4.3
2997561 2012, Mutagenicity Study of Pyridate Technical in the Salmonella Typhimurium Reverse Mutation Assay (In Vitro), DACO: 4.5.4
2997562 2015, Pyridate Neurotoxicity, DACO: 4.5.14
2997563 2019, Request for waiver from the requirement of a Developmental Neurotoxicity Study for Pyridate Technical, DACO: 4.5.14
2997564 1997, Examination of sciatic nerves from the three studies with pyridate technical, DACO: 4.8
2997565 1989, Effects of pyridate technical on the rats spontaneous electroencephalogram, DACO: 4.8
2997566 1989, General pharmacology of pyridate technical, DACO: 4.8
2997567 2019, Certificate of Analysis, DACO: 4.8
2997568 2010, Pyridate and neurotoxicity in dogs, DACO: 4.8
2997569 2012, Pyridate and neurotoxicity, DACO: 4.8
2997570 1987, 90 day dog oral subchronic toxicity study, DACO: 4.3.2
2997571 1980, Sub-acute oral toxicity study with pyridate in Wistar and Sprague Dawley rats, DACO: 4.3.3
3038533 1984, Acute Oral Toxicity (LD50) Study with Pyridate, Techn. in Rats, DACO: 4.2.1
3038534 1984, Acute Dermal Toxicity (LD50) Study with Pyridate, Techn in Rabbits, DACO: 4.2.2

3038535 1989, 4-Hour Aerosol Inhalation Toxicity Study (LC50) with Pyridate, Techn. in Rats, DACO: 4.2.3
3038536 1976, Irritant Effects of CL 11.344 on Rabbit Eye Mucosa, DACO: 4.2.4
3038537 1976, Irritant Effects on CL 11.344 on Rabbit Skin, DACO: 4.2.5
3038540 1978, CL 11.344: 3-Months Feeding Study in Dogs Oral Application, DACO: 4.3.2
3038541 1982, 12 Months Oral (Feeding) Toxicity Study with Technical Pyridate in Beagle Dogs, DACO: 4.3.2
3038542 1983, Maximum Tolerated Dose of Pyridate in Dogs, DACO: 4.3.2
3038543 1988, Pyridate 3 Week Dermal Toxicity Study in Rats, DACO: 4.3.5
3038544 1983, Two-Year Feeding Study with Pyridate in Rats, DACO: 4.4.1
3038545 1983, Two-Year Feeding Study with Pyridate in Rats, DACO: 4.4.1
3038546 1990, Lifespan Oral Carcinogenicity Study of Pyridate in Rats, DACO: 4.4.2
3038547 1990, Life-Span (104 wk) Oral Carcinogenicity Study with Pyridate in Mice, DACO: 4.4.3
3038548 1983, Pyridate Technical - 80 Week Feeding Study in Mice, DACO: 4.4.3
3038549 1982, Multigeneration Study with Pyridate in Rats, DACO: 4.5.1
3038550 1986, Embryotoxicity (Including Teratogenicity) Study with Pyridate Technical in the Rat, DACO: 4.5.2
3038551 1985, Embryotoxicity (Including Teratogenicity) Study with Pyridate Technical in the Rabbit, DACO: 4.5.3
3038552 1978, Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of CL 11.344, DACO: 4.5.4
3038553 1978, CL 11344 Cell Transformation Test, DACO: 4.5.4
3038554 1981, Evaluation of Pyridate in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay, DACO: 4.5.5
3038555 1978, Micronucleus Test on CL 11.344, DACO: 4.5.7
3038556 1980, Mutagenicity Evaluation of Pyridate in the Test for Loss of X or Y Chromosomes in *Drosophilia melanogaster*, DACO: 4.5.8
3038557 1980, Mutagenicity Evaluation of Pyridate in the Somatic Cell Mutation Assay, DACO: 4.5.8
2910053 1994, Acute Oral Toxicity Study with Lentagran 600 EC (Tough 5EC) in Rats, DACO: 4.6.1
2910054 1994, Acute Dermal Toxicity Study with Lentagran 600 EC (Tough 5 EC) in Rats, DACO: 4.6.2
2910055 1994, 4-Hour, Acute Inhalation Toxicity Study with Lentagran 600 EC (Tough 5 EC) in Rats, DACO: 4.6.3
2910056 1994, Acute Eye Irritation/Corrosion Study with Lentagran 600 EC (Tough 5 EC) in the Rabbit, DACO: 4.6.4
2910057 1994, Primary Skin Irritation/Corrosion Study with Lentagran 600 EC (Tough 5 EC) in the Rabbit (4-Hour Semi-Occlusive Application), DACO: 4.6.5
2910058 1994, Contact Hypersensitivity to Lentagran 600 EC (Tough 5 EC) in Albino Guinea Pigs Maximization-Test, DACO: 4.6.6
1913109 2009, Agricultural Handler Exposure Scenario Monograph: Open Cab Groundboom Application of Liquid Sprays, Report Number AHE1004, DACO: 5.3,5.4

2910064 2014, Dermal Absorption of [14C]-pyridate, formulated as pyridate 600 g/L EC, by male Sprague-Dawley Rats, DACO: 5.8

2910065 2014, In-Vitro Human Skin Penetration of [14C]-Pyridate, Formulated as [Pyridate 600 g/L EC], DACO: 5.8

2910066 2014, In-Vitro Rat Skin Penetration of [14C]-Pyridate, Formulated as [Pyridate 600 g/L EC], DACO: 5.8

3139691 2014, Dermal absorption of [14C]-pyridate, formulated as pyridate 600 g/L EC], by male Sprague-Dawley rats, DACO: 5.8 CBI

3139692 2014, Dermal absorption of [14C]-pyridate, formulated as pyridate 600 g/L EC], by male Sprague-Dawley rats, DACO: 5.8 CBI

1200352 Residues – Summaries, DACO: 7.1

1200360 1983, Residues of Pyridate & Its Main Metabolites CL 9673 and Conjugated CL 9673 in Lentagran WP and Lentagran EC Treated Corn, DACO: 7.4.2

1200372 1983, Residues of Pyridate & Its Main Metabolites CL 9673 and Conjugated CL 9673 in Lentagran WP and Lentagran EC Treated Corn, DACO: 7.4.6

1200373 1984, Study on Uptake of CL 9673 from Soil by Succeeding Crops. Residue analysis of CL 9673 in Soil and in Rape, Turnip & Ray Grass Succeeding Lentagran WP Treated Corn, DACO: 7.4.3

1208305 1987, Residues of Pyridate and Its Main Metabolites, Free CL 9673 and Hydrolyzable CL 9673 in Sweet Corn Treated with 2 and 4 kg Pyridate 45 WP/ha and with 2 kg Pyridate 45 WP/ha Plus Atrazine 90 WP and Cyanazine (480 g/L), Respectively, DACO: 7.4.1, 7.4.2

1208872 1986, Residues of Pyridate and Its Main Metabolites, Free CL 9673 and Hydrolyzable CL 9673 in Corn Treated with 2 and 4 kg Pyridate 45 WP/ha and with 2 kg Pyridate 45 WP/ha Plus Atrazine 90 WP and Cyanazine (480 g/L), DACO: 7.4.1, 7.4.2

1211051 Summaries: Food, Feed and Tobacco Residue Studies. Tables 1-11 Residues of Lentagran: Austria, France, England, DACO: 7.1,7.4.2

1213932 1987, Residues of Pyridate and Its Main Metabolites Free CL 9673 and Hydrolyzable CL 9673 Conjugates in Field Corn Treated with 2,0 & 4,0 kg Pyridate 45WP/ha, DACO: 7.4.2

1213938 1987, Residues of Pyridate and Its Main Metabolites...in Field Corn Treated with 2,0 & 4,0 kg Pyridate 45WP/ha (897), DACO: 7.4.6

1214446 1988, Plant Metabolism Study of 14C-Pyridate in Broccoli Pot Trial Under Combined Greenhouse & Outdoor Conditions, DACO 6.3

1214449 1988, Plant Metabolism Study of 14C-Pyridate in Corn Pot Trial Under Combined Greenhouse & Outdoor Conditions, DACO 6.3

1223052 1988, Storage Stability Studies on Residues of Pyridate and Its Main Metabolites CL-9673 and Hydrolyzable CL-9673 Conjugates in Wheat Grain and Whole Green Plants of Cabbage, Corn, Alfalfa and Rape, DACO 7.3

1223053 1988, Storage Stability Study on 14C-Pyridate and Metabolites in Peanuts, Corn, Broccoli and Alfalfa, DACO 7.3

2909863 2018, Metabolism/Toxicokinetic Studies Summary for Pyridate Technical, DACO: 6.1

2909864 1989, The Excretion of [14C]-Pyridate in the Laying Hen and Broiler Chicken, DACO: 6.2

2909865 1987, Distribution and Excretion of 14C-Pyridate After Repeated Oral Administration to Laying Hens, DACO: 6.2

2909866 1987, Distribution, Degradation and Excretion of 14C-Pyridate after Repeated Oral Administration to a Lactating Goat, DACO: 6.2

2909867 1989, The Disposition of [14C]-Pyridate in the Lactating Cow, DACO: 6.2

2909868 1984, Examination of Residues of 14C-Pyridate and the main Metabolite 14C-CL 9673 in Spring Barley and Maize in a Greenhouse Pot Trial, DACO: 6.3

2909869 1988, Plant Metabolism Study of 14C-Pyridate in Peanut Pot Trial under Combined Greenhouse and Outdoor Conditions, DACO: 6.3

2909870 1987, 14C-Pyridate: Corn Metabolism in a Model Study under Outdoor Conditions, DACO: 6.3

2909871 1984, Rice Metabolism Study of 14C-Pyridate in a Greenhouse Trial, DACO: 6.3

2909994 2018, Comprehensive Summary for Pyridate Technical and Tough 600 EC Herbicide, DACO: 12.7

2910036 2018, Comprehensive Summary for Pyridate Technical and Tough 600 EC Herbicide, DACO: 12.7

2910067 2018, Cross Reference for the Requirement of Metabolism Data for Tough 600 EC Herbicide, DACO: 6.1,6.2,6.3

2910068 2018, Food, Feed and Tobacco Residue Summary, DACO: 7.1

2910069 1992, Method of Analysis for Determination of Residues of Pyridate and its main metabolites CL-9673 and hydrolysable CL-9673 conjugates in plant materials, DACO: 7.2.1

2910071 2012, Validation of an Analytical Method for the Determination of Pyridate, Pyridafol (CL 9673) and CL 9673-hydrolysable Conjugates in Plant Material, DACO: 7.2.1,7.2.2,7.2.3B

2910072 2012, Development and Validation of a Monitoring Method of Pyridate Analysis in Six Different Matrices of Animal Origin (Eggs, Bovine Meat, Milk, Fat, Liver and Kidney), DACO: 7.2.2

2910073 2012, Independent Laboratory Validation of an Analytical Method for the Determination of Residues of Pyridate and Pyridafol (CL 9673) in Food of Animal Origin, DACO: 7.2.3A

2910074 2014, Independent Laboratory Validation (ILV) of an Analytical Method for the Determination of CL9673-*O*-glucoside in Different Matrices of Animal Origin, DACO: 7.2.3A

2910075 2012, Independent Laboratory Validation (ILV) of an Analytical Method for the Determination of Pyridate, Pyridafol (CL 9673) and CL 9673-hydrolysable Conjugates in Plant Material, DACO: 7.2.3A

2910076 2002, Stability of Residues of Pyridate (SAN 319) in Deep Freeze Stored Analytical Specimens of Milk and Animal Tissues (Muscle, Fat, Liver, Kidney), DACO: 7.3

2910077 1996, Storage stability study on residues of Pyridate in whole plants of maize, rape, field pea and green plant of onion under deep freeze conditions, DACO: 7.3

2910081 2018, Magnitude and Decline of Pyridate and Metabolite Residues on Canola Following Application of Pyridate 600 EC, DACO: 7.4.1,7.4.2

2910086 2018, Magnitude and Decline of Pyridate and Metabolite Residues on Chickpea Following Application of Pyridate 600 EC, DACO: 7.4.1,7.4.2

2910088 1996, Pyridate: Magnitude of the Residue on Garbanzo Beans, DACO: 7.4.1

2910090 1994, Residues of Pyridate and its main metabolites free CL-9673 and hydrolysable CL-9673 conjugates in field pea treated with 2.0 kg Lentagran WP/ha, DACO: 7.4.1
2910092 1990, Residues of Pyridate and its main metabolites free CL 9673 and hydrolysable Cl 9673 conjugates in field pea treated with 2.0 kg Lentagran WP/ha, DACO: 7.4.1
2910093 2018, Magnitude and Decline of Pyridate and Metabolite Residues on Lentil Following Application of Pyridate 600 EC, DACO: 7.4.1,7.4.2
2910094 2018, Rationale to Support Crop Groupings, Application Timings and Pre-Harvest Intervals, DACO: 7.4.1
2910102 1996, Pyridate: Magnitude of the Residue on Mint, DACO: 7.3,7.4.1,7.4.5
2910103 1996, Pyridate: Magnitude of the Residue on Pea (succulent), DACO: 7.3,7.4.1
2910104 1985, Confined Accumulation Studies on Rotational Crops with 14C-pyridate, DACO: 7.4.3
1200374 1985, Confined Accumulation Studies on Rotational Crops with 14C-pyridate, DACO: 7.4.2
2910105 1998, Study on Processed Food (Corn-oil, Peanut oil) from 14C-Pyridate Metabolism Studies in Peanuts and Corn, DACO: 7.4.5
2910106 1989, Analysis of Corn RAC and Processed Fractions for CL9673, DACO: 7.4.5
2910107 1989, Feeding Study in the Lactating Cow, DACO: 7.5
2910108 1989, Feeding Study in the Laying Hen, DACO: 7.5
3100304 2020, Discussion of the Freezer Storage Stability of Pyridate and its Metabolites Supporting the Plant Metabolism Studies, DACO: 6.3
3105157 1995, Validation of an Analytical Method for Determination of Residues of Pyridate and its Main Metabolite CL-9673 in Foods of Animal Origin, DACO: 7.2.3A
3105158 2020, Discussion of the Freezer Storage Stability of Pyridate and its Metabolites Supporting the Plant Residue Studies, DACO: 7.3
3105159 1997, Crop Residue Study Including Adjuvant Bridging with SAN-319H 450 EC 361 LZ on Sweet Corn, DACO: 7.2.1,7.3,7.4.1,7.4.2
3105160 2020, Request for waiver from the requirement of a Residue Study in Zone 7 for Sweet Corn with Tough 600 EC, DACO: 7.4.1
3105161 2020, Request for waiver from the requirement of a Confined Crop Rotation Residue Study with Replanting Dates of 60-270 and 270-365 days with Tough 600 EC, DACO: 7.4.3

3.0 Environment

2909875 2011, Pyridate and CL-9673: Determination of Residues of Pyridate and the metabolite CL-9673 in Soil - Method Validation, DACO: 8.2.2.1
2909876 2016, Independent Laboratory Validation of Belchim Method OZ/10/012 - Pyridate and CL-9673: Determination of Residues of Pyridate and the Metabolite CL-9673 in Soil, DACO: 8.2.2.1
2909878 2007, Validation of the Analytical Method CL9673/Water/SJ/07/1 for the Analysis of CL 9673 in Water, DACO: 8.2.2.3

3038560 2018, Independent Laboratory Validation of Belchim Method OZ/10/012 - Pyridate and CL-9673: Determination of Residues of Pyridate and the Metabolite CL-9673 in Soil, DACO: 8.2.2.1

3038561 2018, Independent Laboratory Validation for the Determination of Pyridate and Pyridafol in Surface and Ground Water, DACO: 8.2.2.3

2909880 1997, (14C)-SAN 1367 H: Hydrolytic Stability, DACO: 8.2.3.2

2909881 1997, Pyridate: Hydrolysis as a Function of pH, DACO: 8.2.3.2

2909882 1992, Photodegradation Study of 14C-Pyridate on Soil, DACO: 8.2.3.3.1

2909883 1990, Photodegradation Study of 14C-Pyridate on a Silty Loam Soil, DACO: 8.2.3.3.1

2909886 1992, Photodegradation Study of 14C-Pyridate in Water at pH 5, 7 and 9, DACO: 8.2.3.3.2

2909892 2016, Aerobic Transformation of Pyridate in One Soil, DACO: 8.2.3.4.2

2909895 1995, Metabolism and Degradation of 14C-Labelled Pyridate in Four Soils, DACO: 8.2.3.4.2

2909896 2002, Degradation of [Pyridazine-4,5-14C]- Labelled NOA 402989 in One Soil Incubated Under Aerobic Conditions, DACO: 8.2.3.4.2

2909898 1996, Pyridate: Rate of Degradation of 14C-CL-9869 in Three European Soils under Laboratory Conditions, DACO: 8.2.3.4.2

2909899 1992, 14C-Pyridate: Degradation and Metabolism in One Soil Incubated Under Anaerobic Conditions, DACO: 8.2.3.4.4

2909901 1997, Route and Rate of Degradation of 14C-Labelled SAN 1367 H AI in Water/Sediment Systems, DACO: 8.2.3.5.4

2909902 2012, [14C]-Pyridate: Degradation and Retention in Two Water-Sediment Systems, DACO: 8.2.3.5.4

2909903 2016, Anaerobic Transformation of Pyridate in Sediment/Water Systems, DACO: 8.2.3.5.6

2909906 2012, Pyridate: Estimate of Adsorption Coefficient (Koc) on Soil by HPLC (OECD 121), DACO: 8.2.4.2

2909908 2012, [14C]-CL-9673: Adsorption to and Desorption from Five Soils, DACO: 8.2.4.2

2909923 2011, Effects of pyridate technical (Acute Contact and Oral) on Honey Bees (*Apis mellifera* L.) in the Laboratory, DACO: 9.2.4.1,9.2.4.2

2909925 1997, A Semi-Field Evaluation of the Effects of Lentagran 600 EC (SAN 319H 600 EC) on the Honey Bee *Apis mellifera*, DACO: 9.2.4.3

2909926 2000, SAN 319 EC 600 (A 9921 A): A Laboratory Study to Evaluate the Effects on the Green Lacewing *Chrysoperla carnea* Steph. (Neuroptera, Chrysopidae), DACO: 9.2.5

2909929 1997, A Laboratory Study to Evaluate the Side-Effects of the Herbicide Lentagran 600 EC (SAN 319 H 600 EC) on the Predatory Mite *Typhlodromus pyri*, DACO: 9.2.5

2909930 2000, A-9921 A: Extended Toxicity Test with the Predacious Mite *Typhlodromus pyri* Scheuten (Acari: Phytoseiidae), DACO: 9.2.5

2909932 1996, A semi-field study to evaluate the side-effects of the herbicide Lentagran 600 EC (SAN 319 H 600 EC) on adult *Coccinella septempunctata*, DACO: 9.2.5

2909933 1997, Lentagran 600 EC (A-9921 A): Determination of Side-Effects on the Aphid Parasitoid, Aphidius spp. (Hymenoptera, Aphidiidae) Using an Extended Laboratory Test, DACO: 9.2.6

2909935 2000, Acute Toxicity of NOA 406847 Metabolite of SAN 319) to *Daphnia magna*, DACO: 9.3.2

2909937 2011, Pyridate Technical: A Study on the Acute Toxicity to *Daphnia magna*, DACO: 9.3.2

2909939 1991, 48-Hour Acute Toxicity of CL 9673 Technical to *Daphnia magna* (OECD-Immobilization Test), DACO: 9.3.2

2909940 1992, Influence of Pyridate Technical on the Reproduction of *Daphnia magna*, DACO: 9.3.3

2909941 1991, Influence of CL 9673 Technical on the Reproduction of *Daphnia magna*, DACO: 9.3.3

2909943 1995, CL-9673 Technical - Acute Toxicity to Mysids (*Mysidopsis bahia*) Under Flow-Through Conditions, DACO: 9.4.2

2909947 2000, Acute Toxicity Test of NOA 406847 (Metabolite of SAN 319) to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, DACO: 9.5.2.1

2909948 1993, CL 9673 Technical: 96-Hour Acute Toxicity Study (LC50) in the Rainbow Trout under Flow-Through Conditions, DACO: 9.5.2.1

2909949 1991, Acute Flow-Through Toxicity of CL-9673 to Bluegill (*Lepomis macrochirus*), DACO: 9.5.2.2

2909954 2011, CL 9673: A Study on the Toxicity to Early-Life Stages of Rainbow Trout, DACO: 9.5.3.1

2909958 1986, An Acute Oral Toxicity Study with the Bobwhite, DACO: 9.6.2.1

2909963 1987, Pyridate Technical: A One-Generation Reproduction Study with the Bobwhite (*Colinus virginianus*), DACO: 9.6.3.1

2909965 1987, Pyridate Technical: A One-Generation Reproduction Study with the Mallard (*Anas platyrhynchos*), DACO: 9.6.3.2

2909966 2016, Pyridate: An Acute Oral Toxicity Study with the Zebra Finch, DACO: 9.6.2.3

2909969 2000, Toxicity of NOA 406847 (Metabolite of SAN 319) to Green Algae, DACO: 9.8.2

2909970 1991, Acute Toxicity of CL 9673 Technical to *Selenastrum capricornutum* (OECD - Algae Growth Inhibition Test), DACO: 9.8.2

2909971 2013, Toxicity of CL 9673 to *Anabaena flos-aquae* in an Algal Growth Inhibition Test (Revised Final Report No. 1 - 2nd Original), DACO: 9.8.2

2909972 2013, Toxicity of CL9673 to *Anabaena flos-aquae* in an Algal Growth Inhibition Test (Final Report - 2nd Original), DACO: 9.8.2

2909973 2013, Toxicity of CL9673 to *Anabaena flos-aquae* in an Algal Growth Inhibition Test (Expert Statement), DACO: 9.8.2

2909974 2017, Pyridate: A 96-Hour Toxicity Test with the Freshwater Diatom (*Navicula pelliculosa*), DACO: 9.8.2

2909978 1997, Growth inhibition test of SAN 1367 H tech. to blue algae (*Anabaena flos-aquae*) under static conditions, DACO: 9.8.2

2909979 2017, Pyridate: A 96-Hour Toxicity Test with the Marine Diatom (*Skeletonema costatum*), DACO: 9.8.3

2909980 2016, Pyridate 600 EC - Seedling Emergence Test, DACO: 9.8.4

2909981 2016, Pyridate 600 EC - Vegetative Vigor Test, DACO: 9.8.4

2909982 2001, A Toxicity Test to Determine the Effects of SAN 319 (A 9921 A) on Seedling Emergence of Six Species of Plants, DACO: 9.8.4

2909983 2001, A Toxicity Test to Determine the Effects of SAN 319 (A 9921 A) On Vegetative Vigor of Six Species of Plants, DACO: 9.8.4

2909986 1997, Acute Toxicity Test of SAN 1367 H tech. to the Duckweed *Lemna gibba* G3 under Static Conditions, DACO: 9.8.5

2909987 2001, Effects of SAN 1367 A (metabolite of SAN 319) on Reproduction and Growth of Earthworms *Eisenia fetida* in Artificial Soil, DACO: 9.8

2909988 2014, Effects of CL9673 (Pyridafol) on Reproduction and Growth of Earthworms *Eisenia fetida* in Artificial Soil with 5% Peat, DACO: 9.8

2910111 1992, Dissipation of Pyridate Residues from an Iowa Loam and an Illinois Sandy Loam Corn Field Treated with Tough 3.75 EC Herbicide, DACO: 8.3.2,8.3.2.2

2910112 1992, Dissipation of Pyridate Residues from a Wisconsin Silt Loam Cabbage Field Treated with Tough 3.75 EC Herbicide, DACO: 8.3.2,8.3.2.2

2910113 1992, Dissipation of Pyridate Residues from a California Sandy Loam Cabbage Field Treated with Tough 3.75 EC Herbicide, DACO: 8.3.2,8.3.2.2

2910120 2011, Terrestrial Soil Dissipation of Pyridate and its Metabolite CL-9673 after one Application of Lentagran 450 g/kg WP on Bare Soil in Northern France, 2010-2011, DACO: 8.3.2,8.3.2.3

2910121 1996, Residues of Pyridate and its Main Metabolites CL-9673 and CL-9673-O-methyl in Soil Treated with 2.5 kg Lentagran 45 WP/ha, DACO: 8.3.2,8.3.2.3

2910124 2001, Field Soil Dissipation and Mobility of Residues of SAN 1367 H and its O-Methyl Metabolite in Bare Soil and Cropped Soil Following Application of A-11897 A (SAN 1367 H 490 SC) in Northern Germany, DACO: 8.3.2,8.3.2.3

2910125 2011, Terrestrial Soil Dissipation of Pyridate and its Metabolite CL-9673 after one Application of Lentagran 450 g/kg on Bare Soil in Germany, 2010-2011, DACO: 8.3.2,8.3.2.3

3038595 2012, [14C]-CL-9673: Aqueous Photolysis and Quantum Yield Determination in Sterile Buffer Solutions, DACO: 8.6

3038605 2018, Pyridate - Toxicity to Honey Bee Larvae (*Apis mellifera* L.) after Repeated Exposure under In Vitro Laboratory Conditions, DACO: 9.2.4

3038606 2017, Pyridate - technical - Assessment of Effects on the Adult Honey Bee, *Apis mellifera* L., in a 10 Day Chronic Feeding Test under Laboratory Conditions, DACO: 9.2.4

3038615 2018, Pyridate: A 96-Hour Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*), DACO: 9.4.4

3038618 2018, Pyridate: A 96-Hour Flow-Through Acute Toxicity Test with the Rainbow Trout (*Oncorhynchus mykiss*), DACO: 9.5.2.1

3038623 1984, Accumulation and Elimination of 14C-Pyridate by Bluegill Sunfish in a Dynamic Flow-Through System, DACO: 9.5.6

3038629 2014, Toxicity of Pyridate technical to *Anabaena flos-aquae* in an Algal Growth Inhibition Test, DACO: 9.8.2

3038632 2014, Toxicity of BCP258H to *Anabaena flos-aquae* in an Algal Growth Inhibition Test, DACO: 9.8.2

3038634 2014, Toxicity of BCP 209H to *Pseudokirchneriella subcapitata* in an Algal Growth Inhibition Test, DACO: 9.8.2

3038635 2013, Toxicity of BCP258H to *Pseudokirchneriella subcapitata* in an Algal Growth Inhibition Test, DACO: 9.8.2
3038636 2014, Toxicity of BCP258H to *Pseudokirchneriella subcapitata* in an Algal Growth Inhibition Test, DACO: 9.8.2
3038641 2002, A Toxicity Test to Determine the Effects of A 8985 A on Seedling Emergence of Six Species of Plants, DACO: 9.8.4
3038642 2002, A Toxicity Test to Determine the Effects of A 8985 A on Vegetative Vigour of Six Species of Plants, DACO: 9.8.4
3038646 2013, Toxicity of BCP258H to the Aquatic Plant *Lemna gibba* in a Semi-Static Growth Inhibition Test, DACO: 9.8.5
3038648 2013, Toxicity of BCP 209H to the Aquatic Plant *Lemna gibba* in a Semi-Static Growth Inhibition Test, DACO: 9.9
3038655 2012, Toxicity of HHAC 062 to *Anabaena flos-aquae* in an Algal Growth Inhibition Test, DACO: 9.9
3038656 2012, Toxicity of 6-chloro-4-methoxy-3-phenylpyridazine (CL9869) to the Aquatic Plant *Lemna gibba* in a Semi-Static Growth Inhibition Test, DACO: 9.9
3038662 2013, Toxicity of BCP 209H to *Pseudokirchneriella subcapitata* in an Algal Growth Inhibition Test, DACO: 9.9
3038664 2012, Acute Toxicity of HHAC 062 to *Daphnia magna* in a Static 48-Hour Immobilisation Limit-Test, DACO: 9.9
3153901 2018, Pyridate: A 10-Day Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Whole SED, DACO: 9.4.6

4.0 Value

2910027 2018, Summary of Value for Tough 600 EC Herbicide, DACO: 10.1, 10.2, 10.2.1, 10.2.2, 10.2.3 ,10.2.3.1, 10.2.3.2(B), 10.2.3.3(B), 10.2.3.4(B), 10.2.4, 10.3, 10.3.1, 10.3.2, 10.3.2(A), 10.3.3, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4
2910030 2018, Appendix 4: Trial Reports for Post-Emergent Efficacy Evaluations of Tough 600 EC Herbicide - Corn, DACO: 10.2.3.1, 10.2.3.3(B)
2910031 2018, Appendix 5: Trial Reports for Post-Emergent Crop Tolerance Evaluations of Tough 600 EC Herbicide - Corn, DACO: 10.2.3.1, 10.2.3.3(B)
2910032 2018, Appendix 6: Trial Reports for Post-Emergent Efficacy Evaluations of Tough 600 EC Herbicide - Chickpeas, DACO: 10.2.3.1, 10.2.3.3(B)
2910033 2018, Appendix 7: Trial Reports for Post-Emergent Crop Tolerance Evaluations of Tough 600 EC Herbicide - Chickpeas, DACO: 10.2.3.1, 10.2.3.3(B)
2910034 2018, Appendix 8: Trial Reports for Post-Emergent Efficacy Evaluations of Tough 600 EC Herbicide - Non-Crop Areas, DACO: 10.2.3.1, 10.2.3.3(B)
2910035 2018, Appendix 9: Trial Reports for Pre-Plant Crop Tolerance Evaluations of Tough 600 EC Herbicide - Canola, Corn, Soybean, Wheat, Chickpea, Field Pea and Lentil, DACO: 10.2.3.1, 10.2.3.3(B)
2998725 2019, Updated Efficacy Trials and Summary for Tough 600 EC Herbicide, DACO: 10.2.3.3(B)
2998727 2019, Updated Efficacy Trials and Summary for Tough 600 EC Herbicide, DACO: 10.2.3.3(B)
3074493 2020, Request for waiver from the requirement of studies to address damage of Tough 600 EC Herbicide to rotational crops, DACO: 10.3.3

B. Additional information considered

i) Published information

1.0 Human and animal health

3179297 Okubo T., Yokoyama Y., Kano K., Soya Y., Kano I., 2004, Estimation of estrogenic and antiestrogenic activities of selected pesticides by MCF-7 cell proliferation assay, Arch Environ Contam Toxicol. 2004. 46 (4):445-53., DACO: 4.8