Proposed Registration Decision PRD2019-04

Bixafen and F9651-2 Fungicide

(publié aussi en français)

21 May 2019

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

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Canada

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

Catalogue number: H113-9/2019-4E (print version)
H113-9/2019-4E-PDF (PDF version)

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Overview

Proposed Registration Decision for Bixafen and F9651-2 Fungicide

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 Bixafen (F9650) Technical Fungicide, containing the technical grade active ingredient bixafen, and F9651-2 Fungicide, containing the technical grade active ingredients bixafen and tebuconazole, to control foliar diseases on wheat, barley, oats and soybean.

Tebuconazole is currently registered in Canada for foliar and seed treatment uses on wheat, barley, oats, corn, and soybean, as well as use on turf and for industrial uses as a wood preservative. All diseases proposed on the F9651-2 Fungicide label for cereal crops and two diseases proposed for soybean are currently registered for tebuconazole at the rates proposed for F9651-2 Fungicide.

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 bixafen and F9651-2 Fungicide.

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 *Pest Control Products 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.

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

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

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 at Canada.ca/pesticides.

Before making a final registration decision on bixafen and F9651-2 Fungicide, 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 bixafen and F9651-2 Fungicide, 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 Bixafen?

Bixafen is classified as a Group 7 fungicide which inhibits an enzyme involved in energy production in fungi and contributes to the management of diseases of cereals and soybean.

Health Considerations

Can Approved Uses of Bixafen Affect Human Health?

F9651-2 Fungicide, containing bixafen, is unlikely to affect your health when used according to label directions.

Potential exposure to bixafen may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

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

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

In laboratory animals, the technical grade active ingredient bixafen was of low acute toxicity by the oral, dermal and inhalation routes. Bixafen was minimally irritating to the eyes and non-irritating to the skin, and did not cause an allergic skin reaction; consequently, no hazard signal words are required on the label.

The end-use product F9651-2, containing bixafen and tebuconazole, was of moderate acute toxicity via the oral route; consequently, the hazard signal words "WARNING POISON" are required on the label. It was of low toxicity via the dermal and inhalation routes of exposure. It was non-irritating to the eyes and skin and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests were assessed for the potential of bixafen to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment included effects on body weight, the liver and thyroid gland, and blood coagulation. There is low concern for increased susceptibility of the young exposed to bixafen. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water have been determined to be acceptable.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1–2 years old, the subpopulation which would ingest the most bixafen relative to body weight, are expected to be exposed to less than 33% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from bixafen is not of health concern for all population subgroups.

Acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups were less than-15% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was children 1–2 years old.

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

Residue trials conducted throughout the United States and Canada using bixafen on wheat, field corn, sweet corn, sorghum, carrots, radishes, sugar beets, potatoes, soybeans and peanuts, and throughout the European Union on barley are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

New MRLs are not proposed for tebuconazole given that adequate MRLs are currently established for tebuconazole on all proposed crops.

Occupational Risks from Handling F9651-2 Fungicide

Occupational risks have been determined to be acceptable when bixafen is used according to the label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply F9651-2 Fungicide, as well as field workers entering freshly treated fields of wheat (spring, durum and winter), barley, oats and soybeans, can come in direct contact with bixafen residues on the skin. Therefore, the label specifies that handlers mixing/loading and applying F9651-2 Fungicide must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks (gloves are not required inside a closed cab or cockpit). The label also requires that workers do not enter treated fields of wheat (spring, durum and winter), barley, oats and soybeans for 12 hours after application.

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

Potential for bystander exposure is considered minimal and is expected to be significantly less than exposure estimated for workers. Based on the worker assessment, bystander exposure is not of concern.

F9651-2 Fungicide is co-formulated with tebuconazole. Tebuconazole is already registered for use in Canada.

Environmental Considerations

What Happens When Bixafen Is Introduced Into the Environment?

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

Bixafen enters the environment when applied to control foliar diseases of cereal crops and soybeans caused by fungi. On land, bixafen is slow to break down and is not expected to move through the soil and reach groundwater. In water bodies, bixafen will move to sediments where it will remain over time. Bixafen is not expected to be found in the air, or to travel long distances from where it was applied. Bixafen is not expected to build-up in the tissues of organisms.

Bixafen presents negligible risk to wild mammals, birds, bees, beneficial insects, earthworms, invertebrates, marine algae, or aquatic plants. When bixafen is used at labelled application rates, it may pose risks of concern to freshwater diatoms/algae, freshwater fish, amphibians, and terrestrial plants. Therefore, mitigation measures, such as spray buffer zones, are required to minimize potential exposure to organisms in freshwater habitats and non-target terrestrial plants. When bixafen is used in accordance with the label and the required risk reduction measures are applied, the reduced environmental exposure is deemed adequate and risks are considered to be acceptable.

Value Considerations

What Is the Value of F9651-2 Fungicide?

F9651-2 Fungicide contains a combination of active ingredients with different modes of action to control concurrent diseases and manage the development of pathogen resistance.

Both bixafen and tebuconazole have particular strengths against certain diseases which are enhanced by the contribution of the other. The combination of these two active ingredients will control different diseases that co-occur while eliminating the need for tank mixing. F9651-2 Fungicide is an additional fungicide option for cereal and soybean growers that can be used to manage diseases in their crops.

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 Bixafen (F9650) Technical Fungicide and F9651-2 Fungicide to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with bixafen on the skin or through inhalation of spray mists, anyone mixing, loading and applying F9651-2 Fungicide must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks (gloves are not required inside a closed cab or cockpit). The label also requires that workers do not enter treated fields of wheat (spring, durum and winter), barley, oats and soybeans for 12 hours after application. In addition, standard label statements to protect against drift during application are present on the label.

Environment

To minimize exposure and reduce risks to freshwater diatoms/algae, freshwater fish, amphibians, and terrestrial plants, spray buffer zones and precautionary label statements are required. Using vegetative filter strips may also help to reduce contamination of water bodies.

Next Steps

Before making a final registration decision on bixafen and F9651-2 Fungicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization.

Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other Information

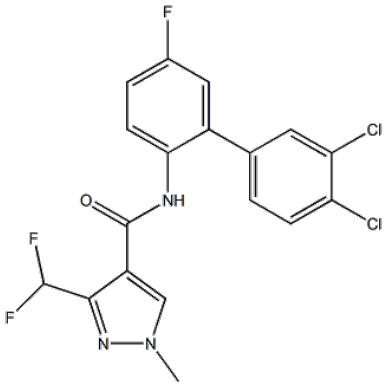
When the Health Canada makes its registration decision, it will publish a Registration Decision on bixafen and F9651-2 Fungicide (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Bixafen and F9651-2 Fungicide

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Bixafen
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	N-(3',4'-dichloro-5-fluoro[1,1'-biphenyl]-2-yl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide
2. Chemical Abstracts Service (CAS)	N-(3',4'-dichloro-5-fluoro[1,1'-biphenyl]-2-yl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide
CAS number	581809-46-3
Molecular formula	$C_{18}H_{12}Cl_2F_3N_3O$
Molecular weight	414.2 g/mol
Structural formula	
Purity of the active ingredient	99.15%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Bixafen (F9650) Technical Fungicide

Property	Result
Colour and physical state	Light brown solid
Odour	No noticeable odour
Melting point	142.9°C
Boiling point or range	Decomposition at 210°C
Relative density	1.51
Vapour pressure at 20°C	4.6×10^{-8} Pa
Henry´s constant at 25°C	9.177×10^{-10} atm·m^3/mol
Ultraviolet (UV)-visible spectrum	Absorption maxima at 210 and 233 nm.
Solubility in water at 20°C	4.9×10^{-4} g/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) Methanol — 32 n-Heptane — 0.056 Toluene — 16 Dichloromethane — 102 Acetone — > 250 Ethyl acetate — 82 Dimethyl sulfoxide — > 250
n-Octanol-water partition coefficient (K_{ow})	3.3
Dissociation constant (pK_a)	No dissociation between pH 1–12.
Stability (temperature, metal)	Stable to elevated temperatures and to metals (aluminium, aluminium acetate, iron, iron citrate).

End-Use Product—F9651-2 Fungicide

Property	Result
Colour	Off-white
Physical state	Liquid
Formulation type	Suspension
Label concentration	340 g/L tebuconazole, 160 g/L bixafen
Container material and description	0.5 L bulk HDPE jugs and HDPE drums with outer metal support
Density	1.14 g/mL
pH of 1% dispersion in water	7.70
Oxidizing or reducing action	Not an oxidizing or reducing substance.

Property	Result
Storage stability	Stable in fluorinated plastic bottles stored at 54°C for 14 days.
Corrosion characteristics	No adverse effects to fluorinated plastic bottles after storage.
Explodability	Not expected to be explosive.

1.3 Directions for Use

For cereals: Apply preventatively, once per season, at rates of 279–364 ml/ha (depending on disease) when conditions are favourable for disease development and disease thresholds are met. Use the high rate for high disease pressure. If early season application is required, use the lower rate. A non-ionic surfactant may be added at 0.25% v/v to improve efficacy. The product may be applied with ground application equipment using a minimum of 100 L water/ha spray volume or with aerial application equipment with a minimum of 45 L water/ha spray volume.

For soybean: Apply at rates of 279–400 ml/ha (depending on disease) when weather conditions are favourable for disease development. Apply up to two times per season on a 10–14 day interval. Use the high rate under high disease pressure. A non-ionic surfactant may be added at 0.125–0.25% v/v to improve efficacy. The product may be applied with ground application equipment using a minimum of 100 L water/ha spray volume.

1.4 Mode of Action

Bixafen restricts the activity of succinate dehydrogenase, an enzyme of complex II within the fungal mitochondrial respiration chain (for energy production) and is classified as a Group 7 fungicide by the Fungicide Resistance Action Committee (FRAC).

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in environmental media, plant and animal matrices by an independent laboratory. Adequate

extraction efficiencies were demonstrated using radiolabelled wheat samples analyzed using plant data-gathering Method 01012 for which the extraction procedure is identical to that of plant enforcement Method 00983. Extraction solvents used in livestock enforcement Method 01063 were similar to those used in the goat and poultry metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled livestock matrices was not required for the enforcement method. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Bixafen (also known as BYF 00587) is a broad spectrum fungicide from the carboxamide fungicide class and pyrazole-carboxamide sub-class. The pesticidal mode of action has been shown to rely on the inhibition of the enzyme succinate dehydrogenase (complex II) within the fungal mitochondrial respiration chain, preventing energy production. A detailed review of the toxicology database for bixafen was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. In addition, mechanistic studies were also provided to investigate the effects observed on hepatic enzyme activation, coagulation time and thyroid hormone levels. The studies in the database were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the potential health hazards associated with bixafen.

Toxicokinetic investigations were conducted in rats with bixafen, radiolabelled with ^{14}C in either the phenyl or pyrazole ring, administered via gavage at various dose levels for different durations. These investigations also included a study with bile duct-cannulated rats.

The radiolabelled test substance was rapidly absorbed and maximum plasma concentrations were achieved within 2–4 hours of dosing for males and females at the single low and repeated low dose levels and within 8 hours at the single high dose level. Based on the radioactivity detected in bile, urine and carcass, oral absorption of bixafen was approximately 88% of the administered dose (AD) in both sexes. The liver and kidneys had the highest levels of residues, with slightly higher levels in females versus males. Based on area under curve (AUC) data, females received a slightly larger systemic dose, likely the result of slower elimination. Noticeably higher levels of residues were observed in female animals at termination compared to males. However, there was no evidence of tissue retention in males or females, as there was ≤3% of the AD found in animals at termination.

At termination, radioactivity from the single low, single high and repeated dose regimens was eliminated predominantly via feces, with minimal elimination via the urine in both sexes. Although still a minor route of excretion, female rats excreted approximately twice the amount of AD in urine compared to males. In bile duct-cannulated animals, males excreted more of the AD via the bile than females. Biliary excretion was the main route of elimination in both sexes.

Parent compound was detected in feces only, and at < 10% of the AD. The main metabolic reaction was the demethylation of the pyrazole ring to form bixafen-desmethyl. Parent compound and bixafen-desmethyl were hydroxylated at different positions. Most of the hydroxy-compounds were conjugated with glucuronic acid. An N-conjugation of bixafen-desmethyl with glucuronic acid was also observed. Conjugation of bixafen with glutathione was a major metabolic reaction in bile. Glutathione conjugation and related metabolites were also found for bixafen-desmethyl. Minor metabolic reactions included cleavage of the amide structure of bixafen forming pyrazole-4-carboxamide and desmethyl-pyrazole-4-carboxamide, which were observed as label-specific metabolites in urine. The oxidation of bixafen-pyrazole-4-carboxamide led to bixafen-pyrazole-4-carboxylic acid. Another minor reaction was the elimination of one of the two chlorine atoms of bixafen-desmethyl-5-hydroxyphenyl and a further conjugation with a methylthio group. In feces, bixafen-desmethyl, bixafen-desmethyl-5-hydroxyphenyl-6-(methylthio), bixafen-5-hydroxyphenyl-6-(methylthio), 4-hydroxyphenyl, bixafen-4-fluoro-5-hydroxyphenyl and bixafen-5-hydroxyphenyl-6-thiol-acetaldehyde were identified.

In acute toxicity studies, technical bixafen was of low acute toxicity via the oral, dermal and inhalation routes in rats. Bixafen was non-irritating to the skin and minimally irritating to the eyes of rabbits. It was not a skin sensitizer in mice by the local lymph node assay (LLNA).

The end-use product F9651-2 fungicide was of moderate acute toxicity via the oral route and of low acute toxicity via the dermal and inhalation routes in rats. It was non-irritating to the eyes and skin of rabbits. F9651-2 was not a skin sensitizer in mice by the LLNA.

In the guideline repeat-dose oral toxicity studies, the primary targets of toxicity for bixafen were the liver in rats, mice and dogs and the thyroid in rats and mice. The rat was the most sensitive species. The effects observed were consistent in both short- and long-term studies. In rodents, males appeared more sensitive to the liver effects than females. Effects in the liver included increased size (rats and mice) and weight (rats, mice and dogs), single cell necrosis (mice and female dogs), and hepatocyte diffuse centrilobular (rats, mice, and female dogs) to panlobular (rats and mice) hypertrophy, as well as increased aspartate aminotransferase (AST) and increased alanine aminotransferase (ALT) in both sexes (mice). In a long-term study, female rats also showed increased incidence of hepatocellular brown pigment and multinucleated hepatocytes. Cholesterol levels were increased in all species. A mechanistic study in the rat showed that increased liver weight was associated with increased liver enzyme activity (phase I and II enzymes) after bixafen administration.

Thyroid gland toxicity consisted of increased incidences of thyroid follicular cell hypertrophy, hyperplasia and colloid alteration. Colloid alteration, as well as thyroid hyperplasia, occurred in rats of both sexes and thyroid follicular cell hyperplasia was observed in female mice. In rats, males appeared more sensitive to thyroid effects than females in subchronic studies (28-day, 90-day and one-generation reproductive toxicity studies), while female mice seemed more sensitive than male mice in a long-term study (18-month). Other effects on the thyroid gland included increased weight, dark and/or pigmented organ, and increased thyroid-stimulating hormone (TSH) levels. In a mechanistic 14-day gavage study in rats, TSH levels were slightly increased in females from the third day of dosing until the end of the study period while, in males, TSH was

increased only at termination. A slight transient decrease in triiodothyronine (T3) was observed in females on days 3 to 7 and a slight decrease in thyroxine (T4) was observed in males at termination. There was evidence of increased clearance of T4, as reflected by the increased glucuronosyltransferase (UDPGT) enzyme activity in both sexes. A recovery study showed that TSH levels returned to normal within 28 days post-dosing, indicating that the effects on the thyroid gland were reversible; however, enlarged liver persisted in female rats.

All species showed body weight effects and pale feces with repeated oral dosing. Increased incidences of stomach squamous hyperplasia, unilateral focal tubular degeneration in testes and focal/multifocal squamous cell hyperplasia in the ovaries were observed in mice. Additional effects in dogs included decreased red blood cell parameters.

Six months into the two-year chronic toxicity/oncogenicity study in rats, several males died from what appeared to be a hemorrhagic syndrome (increased prothrombin and activated partial thromboplastin times). The applicant proposed that the effects were the result of vitamin K deficiency in the diet of the long-term rat study. Altered coagulation times and hemorrhagic syndrome were observed in several studies in rats, but the diet used in the short-term studies was not analysed. Analysis of the long-term diet showed that it contained less than 0.3 ppm of vitamin K3; and thus, was vitamin K deficient. As this was unintentional, the study methodology was modified, the males were removed and the study continued with the female groups using a diet supplemented with 7.1 to 15.7 ppm of vitamin K3 (PMRA No. 2642789). A complementary two-year chronic toxicity/oncogenicity study was initiated in male rats using a diet supplemented with 7.1 to 10.6 ppm of vitamin K3 (PMRA No. 2642790). In these studies, no alteration in coagulation parameters were observed, but the amount of vitamin K was considered excessive and therefore, could have masked any potential effects of bixafen on these parameters (Reference PMRA No. 2914470).

Surviving males from the high dose group within the initial long-term study were used in a mechanistic study, which demonstrated that the addition of 16 ppm of vitamin K3 to the diet significantly lowered both the prothrombin (PT) and the activated partial thromboplastin times (aPTT) to historical control values within two weeks of supplementation (PMRA No. 2642810). As a control group was not used in the mechanistic study, it was difficult to evaluate the role of bixafen on the coagulation parameters. An additional mechanistic study in rats showed that a diet supplemented with 16 ppm of vitamin K3 reduced PT in animals treated with bixafen for 28 days at all doses tested, reaching statistical significance at the mid- and high-dose levels, compared to vitamin K supplemented controls. Although the results of this 28-day study showed a decrease in PT, contrary to what was observed in the long-term study (increases in PT and aPTT), it appears that bixafen may be amplifying the effects resulting from either an excess or deficiency of vitamin K. While the decrease in PT was evident in the vitamin K3 supplemented diet groups, the amount of vitamin K3 supplementation was considered excessive (Reference PMRA No. 2914470), which confounds the interpretation of the studies. Furthermore, in a 90-day dietary toxicology study in rats, increased coagulation times returned to control values after a 4-week recovery period. However, the vitamin K level in the diet used in this study was not assessed. In the absence of a known mechanism of action for bixafen on coagulation, the PMRA concluded that any significant effect on coagulation parameters, regardless of the direction of the change, was treatment-related and adverse.

A repeat-dose dermal toxicity study in the rat did not identify any adverse effects when bixafen was tested up to the limit dose.

There was no evidence of genotoxicity in a battery of in vitro and in vivo genotoxicity studies conducted with bixafen. There was no evidence of oncogenicity after long-term dietary dosing in mice and rats.

There was no evidence of sensitivity of the young in gavage developmental toxicity studies conducted with bixafen in rats or rabbits. In rats, reduced fetal body weight and an increased incidence of multiple skeletal variations were observed at a dose level that produced decreased body weight, body weight gain, and food consumption, as well as clinical signs, in dams. In the rabbit study, there was a reduction in fetal body weight. At the same dose level, decreased body weight gain and food consumption, and increased liver weight were observed in dams. At a high dose level, there was decreased body weight, additional liver toxicity and an increased incidence of abortions, fetal loss and maternal mortality.

In a dietary two-generation reproductive toxicity study in rats, there were no effects on mating, gestation or fertility. Offspring effects consisted of decreased body weight and body weight gain in pups of both generations. At the same dose level, parental toxicity in both generations consisted of increased liver weight and incidence of diffuse centrilobular hypertrophy. Decreased body weight and body weight gain occurred in maternal animals of both generations at premating, gestation and lactation periods. Additional effects in the F0 animals included decreased thymus weight in females and increased kidney and spleen weights in males. There was no evidence of sensitivity of the young.

In an acute neurotoxicity study, rats exposed via gavage to bixafen demonstrated decreased motor activity and body temperature, and, in females, decreased rearing counts. These observations occurred at 4 hours post-dosing, which corresponded to the approximated time of peak bixafen levels in plasma. At the highest dose tested, male animals exhibited decreased body weight gains. There was no evidence of selective neurotoxicity in animals tested with a single dose of bixafen.

Results of the toxicology studies conducted on laboratory animals with bixafen and its associated end-use product are summarized in Appendix I, Tables 2 and 3. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 4.

Incident Reports – Human Health and Domestic Animals

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Bixafen is a new active ingredient pending registration for use in Canada. There have been no incident reports involving this active ingredient received by the PMRA as of 6 September 2018.

3.1.1 *Pest Control Products Act* Hazard Characterization

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

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

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of fetuses or offspring compared to parental animals in the developmental toxicity or reproductive toxicity studies. In developmental toxicity studies, reduced fetal weights (rats and rabbits) and skeletal variations (rats) were observed in the presence of maternal toxicity. In the two-generation rat reproductive toxicity study, decreased body weight and body weight gain occurred at a dose level that also showed maternal toxicity consisting of liver toxicity, and decreased body weight and body weight gain. Overall, endpoints in the young were well-characterized and not considered serious in nature. Therefore, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold.

3.2 Acute Reference Dose (ARfD)

To estimate acute dietary risk, the developmental toxicity study in the rat with a NOAEL of 75 mg/kg bw/day was selected for risk assessment. At the LOAEL of 250 mg/kg bw/day, significantly lower body weight in dams was observed. This effect occurred within the first few days of dosing and is therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to one-fold. Accordingly, the composite assessment factor (CAF) is 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{75 \text{ mg/kg bw/day}}{100} = 0.8 \text{ mg of bixafen/kg bw}$$

3.3 Acceptable Daily Intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 2.0 mg/kg bw/day from the two-year chronic toxicity/oncogenicity study in male rats was selected for risk assessment. Liver and thyroid effects were observed at the study LOAEL of 12.1 mg/kg bw/day. This study provided the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. The CAF is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.0 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg of bixafen/kg bw/day}$$

Cancer Assessment

There was no evidence of carcinogenicity and therefore, no cancer risk assessment is necessary.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Reference Values

Exposure to bixafen is expected to be mainly via the dermal and inhalation routes for chemical handlers and through the dermal route for postapplication workers. Exposure is expected to be short- to intermediate-term in duration, since the product can be applied up to twice during the growing season by farmers and over 30 days per season by custom applicators.

Short- and- Intermediate-term Dermal

For exposures of short- and intermediate-term durations via the dermal route, the NOAEL of 1000 mg/kg bw/day from the 28-day dermal toxicity study in rats was selected for risk assessment. This study assessed the endpoints of concern and no adverse effects were observed. The target Margin of Exposure (MOE) is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of the NOAEL from the 28-day dermal toxicity study in rats and target MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short- and Intermediate-term Inhalation

Repeat-dose inhalation toxicity studies were not available for bixafen. For exposures of short- and intermediate-term duration via the inhalation route, the NOAEL of 13 mg/kg bw/day from the 90-day dietary toxicity study in rats was selected for risk assessment. At the LOAEL of 50 mg/kg bw/day, hepatic centrilobular hypertrophy, thyroid follicular cell hypertrophy and altered coagulation parameters were observed. The MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of the NOAEL from the 90-day dietary toxicity in rats and MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Bixafen belongs to a group of fungicides known as carboxamide fungicides, more specifically it belongs to the pyrazole-carboxamide sub-class. Bixafen shares common metabolites in mammals, plants and soil with other active ingredients of the same class, namely fluxapyroxad, sedaxane and isopyrazam. These metabolites were considered to be of equal or lower toxicity than bixafen, and were

present at very low levels (<0.2 ppm), thus would not have a significant impact in a cumulative assessment. Furthermore, no common mechanism of action for the endpoints of concern has been determined at this time.

3.4.1.1 Dermal Absorption

No chemical-specific dermal absorption data were submitted. Dermal absorption data are not required as the dermal endpoint is based on a dermal study.

3.4.2 Occupational Exposure and Risk

Individuals have potential for exposure to F9651-2 Fungicide during mixing, loading and application. Exposure to workers mixing, loading and applying F9651-2 Fungicide is expected to be short- to intermediate-term duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders and applicators applying F9651-2 Fungicide to wheat (spring, durum and winter), barley, oat and soybean fields using groundboom and aerial application equipment.

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

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

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

Dermal and inhalation exposure estimates were compared to the relevant bixafen toxicological reference value (no observable adverse effect level [NOAEL] = 1000 mg/kg bw/day for dermal and 12.9 mg/kg bw/day for inhalation) to obtain the margins of exposure (MOEs); the target MOE is 100. Tables 3.4.2.1.1 and 3.4.2.1.2 present the AHETF unit exposure values and estimates of exposure and risk, respectively. Acceptable MOEs were calculated for workers who wear the proposed PPE, use the engineering controls, and follow the restrictions on the product label.

TABLE 3.4.2.1.1 AHETF Unit Exposure Estimates for Mixer/Loaders and Applicators Handling F9651-2 Fungicide (µg/kg a.i. handled)			
Scenario		**Dermal**	**Inhalation[1]**
Mixer/loader AHETF estimates			
A	Open Mix/Load Liquids (Single layer, CR gloves)	58.50	0.63
Applicator AHETF estimates			
B	Open Cab Groundboom Liquid Application (Single layer, CR gloves)	25.40	1.68
C	Aerial Closed Cockpit liquid application (single layer)	2.67	0.00969
Mixer/loader + applicator AHETF estimates			
A+B	Open Mix/Load Liquids and Open Cab Groundboom Liquid Application (Single layer, CR gloves)	83.90	2.31

[1] Light inhalation rate

TABLE 3.4.2.1.2 Mixer/Loader/Applicator Risk Assessment for Chemical Handlers								
Exposure scenario	**Dermal Unit exposure (µg/kg a.i. handled)[1]**	**Inhalation Unit exposure (µg/kg a.i. handled)[1]**	**ATPD (ha/day)[2]**	**Rate (kg a.i./ha)**	**Dermal exposure (µg/kg bw/day)[3]**	**Inhalation exposure (µg/kg bw/day)[3]**	**Dermal MOE (target 100)[4]**	**Inhalation MOE (target 100)[5]**
PPE: (Single layer, CR gloves except in closed cab or cockpit)								
Farmer (M/L/A)	83.90	2.31	107	0.064	7.18	0.20	139240	65238
Custom (M/L)	58.50	0.63	360		16.85	0.18	59354	71098
Custom (A)	25.40	1.68	360		7.32	0.48	26662	136702
Custom (M/L/A)	83.90	2.31	360		24.16	0.67	41385	19390
Aerial (M/L)	58.50	0.63	400	0.0582	17.02	0.18	58742	70365
Aerial (A)	2.67	0.00969	400		0.78	0.003	1287051	4574809

[1] Unit exposure based on AHETF from Table 3.4.2.1.1
[2] Default Area Treated Per Day tables (2015)
[3] Exposure = (Unit exposure [µg/kg a.i.] x ATPD [ha] x Rate [kg/ha]) / (80 kg bw x 1000 µg/mg)
[4] Based on dermal NOAEL = 1000 mg/kg bw/day, target MOE = 100
[5] Based on inhalation NOAEL = 13 mg/kg bw/day, target MOE = 100

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Bixafen has a vapour pressure of 4.6×10^{-8} Pa at 20°C and is considered to be non-volatile and therefore only a dermal assessment is required.

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

Dermal exposure to workers entering treated areas is estimated by coupling default dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients.

The exposure estimates were compared to the bixafen dermal toxicological reference value (NOAEL = 1000 mg/kg bw/day) to obtain the MOE; the target MOE is 100. Since these values exceed the target MOE of 100 (Table 3.4.2.2.1) for wheat (spring, durum and winter), barley, oats and soybeans, the level of postapplication exposure is not of health concern.

TABLE 3.4.2.2.1 Postapplication Exposure and Risk Estimate for Bixafen on Day 0 After the Last Application

Re-entry activity	Peak DFR (µg/cm^2)[1]	Transfer coefficient (cm^2/hr)[2]	Dermal exposure (mg/kg bw/day)[3]	MOE (target 100)[4]	REI[5]
Hand weeding	0.1996	70	0.0014	715701	12 hours
Scouting	0.1996	1100	0.0220	45545	12 hours

[1] Calculated using the default peak residue value of 25% and a default daily dissipation rate of 10%
[2] Transfer coefficients obtained from the PMRA Agricultural TCs Table (12.22.2016)
[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 1000 mg/kg bw/day, target MOE = 100
[5] Minimum REI is 12 hours to allow residues to dry

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

F9651-2 Fungicide is not a domestic class product; therefore, a residential handler assessment was not required.

3.4.3.2 Postapplication Exposure and Risk

F9651-2 Fungicide is not a domestic class product; therefore, a residential postapplication exposure assessment was not required.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application to agricultural crops is permitted 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.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition in plant products for risk assessment is bixafen and the metabolite bixafen-desmethyl, and for enforcement is bixafen. The residue definition for both risk assessment and enforcement in livestock matrices is bixafen and the metabolite bixafen-desmethyl. The data gathering/enforcement analytical methods are valid for the quantitation of bixafen and bixafen-desmethyl residues in crop and livestock matrices. The residues of bixafen

and bixafen-desmethyl are stable in representative matrices from five crop categories (high water, high oil, high protein, high starch and high acid content) for up to 24 months when stored in a freezer at -18°C. Therefore, bixafen and bixafen-desmethyl residues are considered stable in all frozen crop matrices and processed crop fractions for up to 24 months. Storage stability data were not submitted for animal matrices; however, these data are not required since all tissue, milk and egg samples were analyzed within 30 days of collection in the dairy cattle and laying hen feeding studies.

The raw agricultural commodities, wheat grain, barley grain, soybean seed, sorghum grain, field corn grain, potato tubers, sugar beet roots and peanut nutmeats were processed and bixafen residues concentrated in the following processed commodities: field corn refined oil (1.8×), meal (1.4×) and flour (1.4×), and refined peanut oil (2.2×).

Adequate feeding studies were carried out to assess the anticipated residues in livestock matrices resulting from the proposed uses. Crop field trials conducted throughout Canada, the United States and Europe using end-use products containing bixafen at approved or exaggerated rates are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic analysis for bixafen: 100% crop treated, default processing factors (where available), and residues in/on crops and animal commodities at the recommended MRL levels. The basic chronic dietary exposure from all supported bixafen food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 33% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to bixafen from food and drinking water is 10.8% (0.002164 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1–2 years of age at 32.5% (0.006506 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for bixafen: 100% crop treated, default processing factors, and residues in/on crops and animal commodities at the recommended MRL levels. The refined acute dietary exposure (food alone) for all supported bixafen registered commodities is estimated to be 7.3% (0.009066 mg/kg bw/day) of the ARfD for the general population (95^{th} percentile, deterministic). Aggregate exposure from food and drinking water is 7.4% of the ARfD for the general population and is, therefore, acceptable. The highest exposure and risk estimate is for children 1–2 years of age at 14.4% (0.014495 mg/kg bw/day) of the ARfD.

3.5.3 Drinking Water

The residue definition for drinking water includes bixafen only.

Estimated environmental concentrations (EECs) of bixafen in groundwater were calculated using the Pesticide Water Calculator (PWC v1.52) model to simulate leaching through a layered soil profile over a 100-year period. The concentrations calculated using PWC are average concentrations in the top 1 m of the water table. EECs of bixafen in surface water were also calculated using the PWC model over a 50-year period, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The largest EECs across all modelled scenarios are reported in Table 3.5.1.1 below. The Level 1 EEC estimates cover all regions of Canada and are expected to allow for future use expansion into other crops at the modelled application rate.

Table 3.5.1.1 Level 1 Estimated Environmental Concentrations of Bixafen in Potential Drinking Water Sources

Crop/use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Soybeans: 2 applications at 64 g a.i./ha with an interval of 10 days, total 128 g a.i./ha/year	1.6	1.6	3.0	1.5

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

3.5.4 Aggregate Exposure and Risk

The aggregate risk for bixafen consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.5 Maximum Residue Limits

Table 3.5.1.2 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Sorghum	3.0
Crop group 15: Cereal grains, except sorghum and rice	0.4
Crop subgroup 1A: Root vegetables	0.3
Fat, meat and meat byproducts of cattle, goats, horses and sheep	0.2
Milk	0.05
Dry soybeans	0.04
Crop subgroup 1C: Tuberous and corm vegetables; eggs; fat, meat and meat byproducts of hogs and poultry; peanuts	0.01

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 the Canada.ca website.

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

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Bixafen is highly persistent under laboratory and field conditions, and biotransformation of bixafen occurs very slowly in the environment. Only minor transformation products were produced in soil during laboratory studies of less than one year. In a laboratory soil biotransformation study using loam soil under anaerobic conditions, the DT_{50} value for bixafen was 819 days. Under aerobic conditions in four soils (loam, sandy loam, and silt loam), the DT_{50} values for bixafen were 96–1773 days. Non-extracted residues were observed exceeding 10% of applied amounts of bixafen in soil studies.

Hydrolysis and phototransformation are also not expected to be important routes of environmental transformation. Bixafen is stable to hydrolysis at environmentally relevant pH values, and phototransformation half-lives for bixafen under continuous irradiation were approximately 109 days and 81 days in soil and water, respectively. Bixafen is sparingly soluble in water. Volatilization from water or moist soils is also not expected as the vapour pressure and Henry's law constant for bixafen are relatively low.

The adsorption K_{oc} values for bixafen (3858–5812 mL/g in five soils) indicate that it is expected to exhibit slight mobility in a variety of soil types. Bixafen meets four of the eight criteria of leaching potential, so there is a suggestion of potential leaching, but when aerobic soil half-lives are considered with K_{oc} values, the resulting Groundwater Ubiquity Score (GUS) values indicate that bixafen is a non-leacher.

Moreover, results from two terrestrial field dissipation studies relevant to Canada (in Alberta and New Jersey) showed that bixafen residues were detected mainly in the 0 to 15 cm layers. The number of detections and amounts of bixafen in each layer decreased with soil depth. There were substantially lower concentrations measured in the 15 to 30 cm layers, only a few detections in the 30 to 45 cm layers, and just two detections in the 45 to 60 cm layer. Representative half-lives/DT_{50} values were 550 and 748 days in Alberta and 300 and 100 days in New Jersey.

Overall, taking into consideration results from laboratory studies and terrestrial field dissipation studies, in addition to the assessment of mobility using GUS scores and the criteria of leaching potential, bixafen has low potential to leach to ground water. From conservative multi-year modelling estimates, environmental concentrations of bixafen in surface and ground water are expected to be low.

If bixafen was to reach water bodies, it has been observed that bixafen readily partitions to sediment in two laboratory water-sediment systems under aerobic conditions. The amount of bixafen remaining in the water phase was 10% to 18% after 59 days and was generally less than 10% at study termination (118 days), at which point there was approximately 74–89% of applied radioactivity in sediment, with the majority identified as bixafen. Total system half-lives for bixafen ranged from 1144–6793 days.

Carryover into the next growing season was more significant in Alberta (62% and 82%) than in New Jersey (15% and 19%). However, a carry-over statement for bixafen is not required for foliar applications on the F9651-2 Fungicide label to protect sensitive organisms in the environment, as bixafen is strongly bound to soil, is a non-leacher, and, in general, there is very little systemic uptake of bixafen by rotational crops. There is also evidence of even lower uptake of aged bixafen residues by rotational crops compared with fresh residues. However, it is noted that a carry-over statement is required for tebuconazole, and, therefore, a carry-over statement will be included on the label for F9651-2 Fungicide.

No transformation products were tracked during field studies in Alberta and New Jersey, likely because only minor transformation products were observed during aerobic soil studies. However, there is evidence from a field rotational crop study in Germany that the transformation product, Bixafen-desmethyl, will accumulate in soil over time and may become a major transformation product.

A sharp reduction in the concentrations for bixafen occurred over the first 1 to 2 months in New Jersey that cannot be explained by aerobic soil degradation, volatilization, or abiotic transformation. It is noted that mass balances for bixafen residues in the New Jersey soil were estimated as lower than 57% at day 15 and lower than 40% at day 29. There is therefore uncertainty associated with the half-life values obtained from the New Jersey field study. Mass balances for bixafen residues in Alberta were between 77% and 100% up to day 274.

The potential for bioaccumulation of bixafen in fish is low. The maximum estimated $BCF_{k,g,l}$ was 454, and depuration of bixafen from fish reached over 99% after 14 days.

Bixafen fate data is summarized in Appendix I, Tables 7, 8, and 9.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. 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 = 1 for most species, 0.4 for acute risk to pollinators, and 2 for glass plate studies using the standard beneficial arthropod test species, *Typhlodromus pyri* and *Aphidius rhopalosiphi*; LOC = 1 is used for higher tier tests of the standard arthropod test species and for other arthropod test species).

If the screening level RQ is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ 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.

4.2.1 Risks to Terrestrial Organisms

A risk assessment for bixafen was conducted for terrestrial organisms. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 of EC_{50} (LC_{50}) values are typically used to adjust the toxicity values for terrestrial invertebrates, birds, and mammals when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints. A summary of terrestrial toxicity data for bixafen is presented in Appendix I, Table 10. The screening level risk assessment for bixafen is presented in Appendix I, Table 11 (for terrestrial organisms other than birds and mammals) and Appendix I, Table 12 (for birds and mammals).

Earthworms: The risk quotients for earthworms resulting from chronic exposure to bixafen are well below the level of concern for survival and reproduction at the screening level. The use of bixafen is not expected to pose chronic risk to earthworms.

Beneficial arthropods: The risk to predatory and parasitic arthropods was assessed at the screening level using maximum cumulative in-field EECs on plant surfaces, calculated from direct spray on a field. The in-field EEC on plant surfaces from the cumulative maximum application rate for soybeans is 96 g a.i./ha.

Refinement of the risk assessment was done for off-field exposure due to spray drift. Based on crops and type of equipment used, spray drift factors are applied to in-field exposure values to obtain off-field exposure values. The F9651-2 Fungicide label allows for aerial applications to oats, barley, and wheat. For a ‘medium’ droplet size, the maximum spray drift deposition at one metre downwind from the point of application is 23% of the in-field application rate. Off-field exposure from drift is a conservative estimate as it considers the method of application that produces the greatest amount of spray drift deposition. The off-field EEC from the proposed use on cereals is 13.4 g a.i./ha (58.2 g a.i./ha × 0.23) for plant surfaces.

The in-field RQs for the predatory arthropods, *Chrysoperla carnea* and *Typhlodromus pyri*, resulting from chronic exposure to bixafen do not exceed the level of concern at the screening level. The risk quotient for the parasitic arthropod, *Aphidius rhopalosiphi*, was only slightly higher than the level of concern (LOC = 2) at the screening level for in-field exposure from direct overspray (RQ = 2.7), however, off-field exposure did not exceed the level of concern (RQ = 0.38). The use of bixafen is therefore not expected to pose a chronic risk to soil-dwelling invertebrates under realistic exposure scenarios.

Bees: Bixafen may be found on pollen and nectar as spray droplets are deposited onto open flowers during foliar application. The highest exposures for bees are expected to be from direct foliar applications during bloom, versus systemic exposures. Applications during bloom may result in exposure to adult forager bees, and also to bees in the hive, from contaminated pollen and nectar being brought back to the hive for consumption.

Based on the Tier 1 risk assessment, risks were not of concern for adult bees from acute contact (RQ = 0.0031) and oral (RQ = 0.031) exposures and also for adult (RQ = 0.45) and larval (RQ = 0.39) bees from chronic exposure.

Birds and mammals: To assess the risk to birds and mammals, the concentration of bixafen on various food items is used to determine the amount of pesticide in the diet, or estimated daily exposure (EDE). Because exposure is dependent on the body weight of the organism and the amount and type of food consumed, a set of generic body weights is used to represent a range of bird (20, 100, 1000 g) and mammal (15, 35 and 1000 g) species, and specialized feeding guilds are considered for each category of animal weights (herbivore, frugivore, insectivore, granivore). Also, as animals may consume large quantities of a given food if they encounter an abundant or desirable food source, it is assumed that the diet is comprised entirely (100%) of a particular dietary item.

A screening level assessment is initially carried out to identify uses that do not pose a risk to non-target organisms, groups of organisms that are not expected to be at risk, and areas where there may be a potential for concern and for which further characterization of the risk is required. The screening level risk assessment is based on simple methods, conservative exposure scenarios, and sensitive toxicity endpoints. For this assessment, EDEs are based on EECs that were calculated with maximum residue concentrations from the nomogram. At the screening level, only one feeding guild for each category of bird and mammal weights is selected. The selected feeding guilds are relevant to each specific size of bird or mammal and based on the most conservative residue values. A diet consisting of 100% plant material is not considered realistic for small and medium sized birds (20 and 100 g) and small mammals (15 g) and, therefore, was not included in the determination of EDEs. The most conservative exposure estimate for these categories of bird and mammal weights is associated with a diet comprised of 100% small insects.

Bixafen is expected to pose negligible risk to birds and mammals, as acute and reproduction exposures did not exceed the level of concern at the screening level. The risk quotients for birds and mammals resulting from acute exposures ranged from 0.02 to 0.16, while RQs from reproduction exposures to bixafen ranged from 0.13 to 0.33.

Terrestrial vascular plants: The risk to terrestrial vascular plants was assessed using maximum cumulative in-field EECs on plant or soil surfaces, calculated from a direct spray on a field. The in-field EECs on plant and soil surfaces from the cumulative maximum application rate for soybeans are 96 g a.i./ha and 128 g a.i./ha, respectively. As described for beneficial arthropods, off-field exposure is due to spray drift. The off-field EEC from the proposed aerial use on cereals is 13.4 g a.i./ha (58.2 g a.i./ha × 0.23) for plant surfaces.

The screening level risk quotients for terrestrial plants following exposure to bixafen exceeded the level of concern. With respect to seedling emergence, the level of concern was exceeded at the screening level for in-field exposure (RQ = 79) and also for off-field exposure due to drift (RQ = 8.2). With respect to vegetative vigour, the level of concern was exceeded at the screening level for in-field exposure (RQ = 4.7), but off-field exposure did not exceed the level of concern (RQ = 0.66).

Risk to non-target terrestrial plants is predominantly to seedling emergence, however, risk concern is reduced because applications of bixafen are likely to occur between mid-June and end of August, when most non-target terrestrial plants are expected to be past the early-life stage. When the risk is further refined to off-field exposures due to spray drift, the risk to seedling emergence is low.

Standard label statements and spray buffer zones (2 to 3m for field sprayer; 50 to 65m for aerial) are required to mitigate the impact of bixafen in F9651-2 Fungicide on sensitive non-target plants in terrestrial habitats. While significant carry-over of bixafen is expected, a carry-over statement for bixafen is not required for foliar applications on the F9651-2 Fungicide label as there is expected to be low off-field risk to non-target plants. Moreover, bixafen is strongly bound to soil, is a non-leacher, and, in general, there is very little systemic uptake of bixafen by rotational crops. There is also evidence of even lower uptake of aged residues by rotational crops compared with fresh residues. However, it is noted that a carry-over statement is required for tebuconazole (co-formulated in this product with bixafen), and, therefore, a carry-over statement will be included on the label for F9651-2 Fungicide.

4.2.2 Risks to Aquatic Organisms

A risk assessment for bixafen was conducted for freshwater and marine aquatic organisms based on available toxicity data. A summary of aquatic toxicity data is presented in Appendix I, Table 13. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 of EC_{50} (LC_{50}) values are typically used for aquatic plants, invertebrates, and fish species when calculating RQs. No uncertainty factors are applied to chronic NOEC endpoints.

At the screening level, EECs in the aquatic environment were calculated based on a cumulative maximum rate of 128 g a.i./ha and directly sprayed on a 15-cm deep water body representing a seasonal pond suitable for amphibians, and a 80 cm deep water body representing a permanent pond for aquatic organisms. For marine organisms, the EEC in water was also based on an application rate of 128 g a.i./ha to an 80 cm deep water body. It was assumed that bixafen was instantaneously and completely mixed within the water body. The resulting EECs were 0.0853 mg a.i./L for a water body of 15 cm in depth and 0.0160 mg a.i./L for a water body of 80 cm in depth (Appendix I, Table 14).

For groups where the LOC is exceeded (thus, if RQ≥1), a refined Tier 1 assessment is conducted to determine risk resulting from spray drift and runoff separately. Exposure resulting from spray drift was considered by applying spray drift factors associated with various application methods as described in Section 4.2.1 and the resulting EECs are summarized in Appendix I, Table 15.

Exposure through surface run-off was estimated using the PWC model, which simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. The water body consists of a 1 ha wetland with an average depth of 80 cm and a drainage area of 10 ha.

EECs in a scaled down version of the permanent water body described above, but having a water depth of 15 cm, was also modelled to assess the risk to amphibians, as a risk was identified at the screening level. EECs in pore water were also generated to assess the risk to sediment-dwelling organisms. The most conservative EECs obtained from the modelling are reported in Appendix I, Table 16.

The screening level risk quotients for bixafen are summarized in Appendix I, Table 14. The risk quotients for the Tier 1 refined assessment of bixafen are presented in Appendix I, Table 15 (spray drift) and Appendix I, Table 16 (runoff).

Invertebrates: The acute (RQ = 0.030) and chronic (RQ = 0.30) risk quotients for freshwater pelagic invertebrates (*Daphnia magna*) do not exceed the level of concern at the screening level. As well, the acute RQs for two saltwater benthic invertebrates, mysid shrimp (RQ < 0.13), and marine oyster (RQ < 0.09), in addition to the chronic risk quotient for mysid shrimp (RQ = 0.18), all do not exceed the level of concern at the screening level.

The chronic risk quotient for freshwater benthic invertebrates (chironomid/midge) is equal to the level of concern (1.0) at the screening level. As well, the acute risk quotient for estuarine amphipods is exceeded when cumulative applications for marine ecosystems are considered (RQ < 1.5). These acute and chronic risk exposures are further characterized using refinements for drift and runoff.

Fish: The RQ for marine fish (sheepshead minnow; RQ = 1.1) resulting from acute exposure to bixafen exceeds the level of concern at the screening level. As well, the RQs for freshwater fish resulting from acute (RQs = 2.2 and 1.5, respectively, for rainbow trout and fathead minnow) and chronic early-life stage (RQ = 3.5 for fathead minnow) exposures to bixafen exceed the level of concern at the screening level. The acute and chronic risks to freshwater and marine fish are further characterized using refinements for drift and runoff.

Amphibians: Due to lack of amphibian specific data, data from freshwater fish studies are used as surrogate data with a further safety factor of 10 applied. Using acute and chronic endpoints from surrogate studies with freshwater fish, along with the EEC for bixafen in a 15 cm deep body of water, the RQs for amphibians resulting from acute and early-life stage exposure to bixafen exceed the level of concern at the screening level (RQs = 12 and 19, respectively). The acute and chronic risks to amphibians are further characterized using refinements for drift and runoff.

Algae: The risk quotients resulting from acute exposure to bixafen do not exceed the level of concern for freshwater green (RQ = 0.47) and bluegreen (RQ < 0.04) algae, nor for marine diatoms (RQ = 0.21). Thus, the use of bixafen is not expected to pose a risk to these taxonomic groups of algae. However, the level of concern is exceeded for acute exposures to freshwater diatoms (RQ = 2.0), so the risk to this algal group is further characterized using refinements for drift and runoff.

Aquatic vascular plants: The RQs for two species of aquatic vascular plants resulting from acute exposure to bixafen do not exceed the level of concern at the screening level (RQs < 0.08 and <0.04), and no further characterization is needed. The use of bixafen is not expected to pose a risk to aquatic vascular plants.

Tier 1: Refined Aquatic Risk Assessment

Assessment of potential risk from spray drift

The EEC used during the screening level assessment assumed direct application to water bodies. Refined EECs for ground boom (field sprayer) and aerial applications were calculated using a maximum percent drift deposition at one metre downwind (6% for ground and 23% for aerial) from the point of application for an ASAE 'medium' droplet size. Although 'medium' was not formally specified on the proposed product label, this is the droplet size typically used for fungicides.

The screening level EECs for fresh water bodies 80 and 15 cm deep (0.0160 and 0.0853 mg a.i./L, respectively) were based on the maximum annual proposed use on soybeans (2 applications at 64 g a.i./ha with a 10-day interval), as were the screening level EECs for marine water bodies 80 cm deep (0.0160 mg a.i./L). For ground use, once drift is taken into account, these values become 0.00096 mg a.i./L for the 80 cm depth and 0.0051 mg a.i./L for the 15 cm depth.

Since aerial use is only approved for use on cereals (1 application at 58.2 g a.i./ha), this is the rate used to refine for drift. Once aerial drift is taken into account, the screening level values (0.00728 mg a.i./ha for the 80 cm depth and 0.0388 for the 15 cm depth) become 0.00167 mg a.i./L for the 80 cm depth and 0.00892 mg a.i./L for the 15 cm depth.

The risk quotients obtained using the EECs corrected for maximum drift from aerial and ground boom use at one meter from the point of application are presented in Appendix I, Table 15.

The refined risk quotients indicate that the level of concern from bixafen exposure due to spray drift is not exceeded for fish, freshwater diatoms, benthic invertebrates, or estuarine amphipods from either ground or aerial applications. However, the LOC is still exceeded for amphibians from both ground (RQ = 1.1, chronic) and aerial (RQ = 1.2, acute; RQ = 1.9, chronic) applications.

Assessment of potential risk from runoff

The screening level risk quotients for aquatic organisms following exposure to bixafen exceeded the level of concern for freshwater and marine fish (acute and chronic), amphibians (acute and chronic), freshwater diatoms (acute), freshwater benthic invertebrates (chronic), and estuarine amphipods (acute). In order to further characterize the risk, exposure from runoff into a body of water directly adjacent to the application field was determined using EECs predicted by the PWC model.

The risk quotients for exposure to bixafen through runoff are provided in Appendix I, Table 16. These were calculated based on the same toxicity endpoints as for the screening level assessment, but using modelled EECs for a timeframe reflecting the exposure duration of the toxicity tests. The level of concern is still exceeded for freshwater fish, amphibians, freshwater diatoms, and estuarine amphipods. The revised risk quotients range from <1.3 (estuarine amphipods, acute) to 3.3 (amphibians, chronic). These risk quotients only slightly exceed the level of concern. Given the conservatisms that are imbedded in the modelling, the overall concern is thus expected to be low. In addition, the exposure from runoff would be further reduced if the best practices included on the product label are implemented.

Tier 1 summary

Spray buffer zones are required to mitigate potential effects on aquatic organisms from drift of F9651-2 Fungicide into adjacent freshwater habitats. The spray buffer zones are specific to the methods of application and are up to 1 m using field sprayers and up to 10 m for aerial applications. Runoff into freshwater habitats is mitigated using precautionary label statements and may be further reduced by including a vegetative strip between the treated area and the edge of the water body.

Incident Reports – Environment

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Bixafen is a new active ingredient pending registration for use in Canada. There have been no incident reports involving this active ingredient received by the PMRA as of 6 September 2018.

5.0 Value

Cereal and soybean growers use many different strategies to reduce disease incidence, such as crop rotation, balanced fertility, use of resistant crop varieties, removal of alternate hosts, and the use of thresholds to time fungicide applications. Cereals are usually only sprayed once or twice per season. Soybeans may receive additional fungicide treatments throughout the season depending on the risk of disease development or the diseases present.

Tebuconazole is currently used by cereal and soybean growers to treat foliar diseases. The addition of bixafen allows growers to target additional diseases that may be present at the time of treatment. Where both active ingredients are effective against the same disease, the combination of the two modes of action helps delay the development of pathogen resistance. The registration of F9651-2 Fungicide provides cereal and soybean growers with an additional tool for managing diseases in their crops.

A total of 23 efficacy trials conducted on wheat were reviewed to support disease claims on cereals and eight trials were reviewed to support claims on soybean. The individual active ingredients were tested separately and combined to determine the contribution of each to efficacy. In many cases, the contribution of one active ingredient was significantly better than the other, but in general, both active ingredients reduced disease symptoms. Scientific rationales

were reviewed to support certain claims currently registered on the tebuconazole precedent label; for these use claims the contribution of bixafen could not be determined. The addition of a non-ionic surfactant often improved the level of efficacy of the product on both wheat and soybean. Treatments applied with ultra-low volume sprays to simulate aerial application demonstrated equivalent levels of efficacy on cereal crops compared to ground application equipment. The results of efficacy trials conducted on wheat were applied to other cereal crops based on their susceptibility to the disease and pathogen. The supported use claims are listed in Appendix I, Table 19.

F9651-2 Fungicide did not cause injury to wheat or soybean when applied as proposed, with or without a surfactant, or when applied at a rate 1.3× higher than proposed. Adverse effects are not expected as a result of application to cereal crops or soybean.

Use claims on the F9651-2 Fungicide label for control or suppression of foliar diseases of cereal crops and soybean are supported according to the use directions on the label. Details of the supported uses are summarized in Appendix I, Table 19.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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 (those that meet all four criteria outlined in the policy, (in other words, persistent in air, soil, water, or sediment, bio-accumulative, primarily a result of human activity, and toxic as defined by the *Canadian Environmental Protection Act*).

During the review process, bixafen and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria, as summarized in Appendix I, Table 17. The PMRA has reached the following conclusions:

- Bixafen does not meet all TSMP Track 1 criteria and is not considered a Track 1 substance. See Appendix I, Table 17 for comparison with Track 1 criteria.
- No Track 1 substances resulting from the use of bixafen have been detected in soils from laboratory or field studies.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical, and formulants and contaminants in the end-use product, are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list

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

[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of*

is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including Regulatory Directive DIR99-03, Regulatory Directive DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade bixafen and the end-use product, F9651-2 Fungicide, do not contain any formulants or contaminants of environmental concern identified in the *Canada Gazette.*
- The use of formulants in registered pest control products is assessed on an ongoing basis through the PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The submitted toxicology database is adequate to characterize the potential health hazards associated with bixafen. In short- and long-term toxicity studies with laboratory animals, the primary targets of toxicity were the liver, thyroid gland and coagulation parameters. Bixafen was not genotoxic and there was no evidence of carcinogenicity in rodents after long-term dosing. Impaired fetal growth (rats and rabbits) and effects on fetal skeletal development (rats) were observed in the presence of maternal toxicity in developmental toxicity studies. In reproductive toxicity studies, bixafen did not have adverse effects on fertility, mating, or gestation. Impaired growth was observed in pups at dose levels that also caused maternal toxicity. This risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Mixers, loaders and applicators handling F9651-2 Fungicide and workers entering treated fields of wheat (spring, durum and winter), barley, oats and soybeans are not expected to be exposed to levels of bixafen that will result in health risks of concern when F9651-2 Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is bixafen in plant products and bixafen and the metabolite bixafen-desmethyl in animal matrices. The proposed use of bixafen on wheat, barley, oats and soybeans does not constitute a health risk of concern for chronic or acute dietary exposure (food and drinking

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Pest Control Product Formulants and Contaminants of Health or Environmental Concern and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613*. Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New *Pest Control Products Act*.

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

water) to any segment of the population, including infants, children, adults and seniors and is therefore considered acceptable. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of bixafen.

Commodity	Recommended MRL (ppm)
Sorghum	3.0
Crop group 15: Cereal grains, except sorghum and rice	0.4
Crop subgroup 1A: Root vegetables	0.3
Fat, meat and meat byproducts of cattle, goats, horses and sheep	0.2
Milk	0.05
Dry soybeans	0.04
Crop subgroup 1C: Tuberous and corm vegetables; eggs; fat, meat and meat byproducts of hogs and poultry; peanuts	0.01

7.2 Environmental Risk

The use of F9651-2 Fungicide containing the active ingredient, bixafen, at the proposed label rates does not pose a risk of concern to wild mammals, birds, bees, beneficial insects, earthworms, freshwater invertebrates, marine algae and fish, or aquatic plants. When bixafen is used at labelled application rates, it may pose risks of concern to freshwater diatoms/algae, freshwater fish, marine invertebrates, amphibians, and terrestrial plants. Risks to these organisms can be mitigated with spray buffer zones and precautionary label statements. Using vegetative filter strips may also help to reduce contamination of freshwater habitats. When bixafen is used in accordance with the label and the required risk reduction measures are applied, the reduced environmental exposure is deemed adequate and risks are considered to be acceptable.

7.3 Value

The active ingredients bixafen and tebuconazole have been shown to be effective against foliar diseases of cereal crops and soybean. The combination of these active ingredients allows growers to target multiple diseases simultaneously. Where both active ingredients are effective against the same disease, the combination of the two modes of action helps delay the development of pathogen resistance. The registration of F9651-2 Fungicide provides cereal and soybean growers with an additional tool for managing diseases in their crops. Based on the information provided, the value is supported for the registration of F9651-2 Fungicide to control or suppress diseases on cereal crops and soybean.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Bixafen (F9650) Technical Fungicide, containing the technical grade active ingredient bixafen, and the end use product F9651-2 Fungicide, containing the technical grade active ingredients bixafen and tebuconazole, for use on wheat, barley, oats and soybean to control foliar diseases.

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

List of Abbreviations

µg	microgram(s)
♂	males
♀	females
↑	increased
↓	decreased
<	less than
>	greater than
≥	greater than or equal to
°C	Celsius
AB	Alberta
abs	absolute
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
AHETF	Agricultural Handlers Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AOPWIN	Atmospheric Oxidation Program for Microsoft Windows
aPTT	activated partial thromboplastin time
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
ASAE	American Society of Agricultural Engineers
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	area under curve
BAF	bioaccumulation factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BC	British Columbia
BCF	bioconcentration factor
$BCF_{k,g,l}$	bioconcentration factor based on kinetic (k) analysis, normalized to a 5% lipid (l) content in fish tissue, and corrected for growth (g) dilution
BROD	7-benzoxyresorufin O-debenzylase
bw	body weight
bwg	body weight gain
BYF 00587	code used for bixafen
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
cm	centimetres
C_{max}	maximum plasmatic concentration
CYP	cytochrome
d	day(s)

DAT	days after treatment
DEEM–FCID	Dietary Exposure Evaluation Model
DFOP	double first-order in parallel
DFR	dislodgeable foliar residue
DIR	directive
DT_{50}	dissipation time 50% (the dose required to observe a 50% 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
EDE	estimated daily exposure
EEC	estimated environmental concentration
ELS	early life stage
ER_{25}	effective rate on 25% of the population
EU	Europe
F0	parental generation
F1	first generation
F2	second generation
fc	food consumption
FDA	The *Food and Drugs Act*
FIR	food ingestion rate
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GD	gestation day
GIT	gastrointestinal tract
GUS	groundwater ubiquity score
ha	hectare(s)
HAFT	highest average field trial
HB	hemoglobin
HCT	hematocrit
HDPE	high-density polyethylene
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
hr	hour(s)
IC_{25}	inhibition concentration on 25% of the population
IC_{50}	inhibition concentration on 50% of the population
IORE	indeterminate order rate equation
IUPAC	International Union of Pure and Applied Chemistry
K+CWHR	kernels plus cob with husks removed
K_d	soil-water partition coefficient
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration required to kill 50% of the test group
LD_{50}	lethal dose required to kill 50% of the test group

LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOEL	lowest observed effect level
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)
m^3	metres cubed
M	multisite (mode of action)
MB	Manitoba
mg	milligram
mL	millilitre
M/L/A	Mixer/Loader/Applicator
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
mo	month
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
°N	degrees North
NAFTA	North American Free Trade Agreement
NC	not calculated
NOAEL	no observed adverse effect level
NOAEC	no observed adverse concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOI	notice of intent
NZW	New Zealand white
OC	organic carbon content
ON	Ontario
P	host plant defense induction (mode of action)
Pa	Pascal
PBI	plantback interval
PCPA	*Pest Control Product Act*
PEI	Prince Edward Island
pH	measure of the acidity or basicity of an aqueous solution
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PROD	7-pentoxyresorufin O-depentylase
PT	prothrombin time

PWC	Pesticide in Water Calculator
QC	Québec
RAC	raw agricultural commodity
RBC	red blood cell
REI	restricted entry interval
rel	relative
RQ	risk quotient
RTI	re-treatment interval
SFO	single first-order
SHD	single high dose
SK	Saskatchewan
SLD	single low dose
$t_{1/2}$	half-life
T1, T2	tautomers 1 and 2
T3	triiodothyronine
T4	thyroxine
TC	transfer coefficient
TGAI	technical grade active ingredient
t_{max}	time to reach maximum plasmatic concentration
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TSH	thyroid-stimulating hormone
TWA	time weighted average
UDPGT	uridine diphosphate glucuronosyltransferase
UK	United Kingdom
US	United States
UV	ultraviolet
v/v	volume per volume dilution
Vitamin K3	menadione
wk(s)	week(s)
wt(s)	weight(s)

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte(s)	Method Type	LOQ		Reference (PMRA Document Number)
Soil / Sediment	00952	Bixafen	HPLC-MS/MS	0.005 ppm		2642817
Soil / Sediment	00952/M001	Bixafen-desmethyl	HPLC-MS/MS	0.005 ppm		2642751
Water	01073	Bixafen	HPLC-MS/MS	0.05 µg/L		2642740
Plant	01366	Bixafen -pyrazole-4-carboxamide (M43) and Bixafen - desmethyl-pyrazole-4-carboxylic acid (M44)	Data-gathering (HPLC-MS/MS)	0.01 ppm per analyte (expressed as parent equivalents)	Orange fruit, tomato fruit, potato tuber, dry bean seed, soybean seed	2643810, 2643805
	01012	Bixafen and Bixafen-desmethyl	Data-gathering (HPLC-MS/MS)	0.01 ppm per analyte (expressed as parent equivalents)	Wheat grain, straw, green material; head lettuce; turnip	2643807, 2643808
	00983	Bixafen	Enforcement method (HPLC-MS/MS)	0.01 ppm	Wheat green material and grain; orange fruit; rape oilseed	2643809, 2643804
Animal	01036	Bixafen and Bixafen-desmethyl	Data-gathering method (HPLC-MS/MS)	0.01 ppm per analyte (expressed as parent equivalents)	Egg yolk, egg white, milk, skim milk, cream, muscle, kidney, poultry liver, cattle liver, fat	2642755
	01063	Bixafen and Bixafen-desmethyl	Enforcement method (HPLC-MS/MS)	0.01 ppm per analyte (expressed as parent equivalents)	Egg, milk, muscle, kidney, fat, liver	2642756, 2642737

Table 2 Toxicity Profile of F9651-2 (containing 13.8% bixafen and 30.4% tebuconazole)

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

Study Type/Animal/PMRA No.	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA No. 2643780	$LD_{50♀}$ = 550 mg/kg bw Moderate toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA No. 2643781	$LD_{50♂♀}$ > 5000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA No. 2643782	LC_{50} > 2.09 mg/L Low toxicity
Primary dermal irritation NZW rabbits PMRA No. 2643784	MAS = 0/8, $MIS_{at\ 1\ hour}$ = 0.67/8 Non-irritating
Primary eye irritation NZW rabbits PMRA No. 2643783	MAS = 0/110, $MIS_{at\ 1\ hour}$ = 2/110 Non-irritating
Dermal sensitization (LLNA) CBA/J mice PMRA No. 2643785	Not a dermal sensitizer

Table 3 Toxicity Profile of Bixafen (F9650) Technical Fungicide

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

Study Type/Animal/PMRA No.	Study Results
Toxicokinetic Studies	
The absorption, distribution, metabolism, and elimination (ADME) of bixafen were investigated in rats studies. **Doses:** Single dose of 2 or 50 mg/kg bw via gavage in 0.5% aqueous tragacanth with dichlorophenyl-UL-^{14}C radiolabelled bixafen and sacrificed at 72 hours (4/sex/group), or 2 mg/kg bw/day for 14 days with non-radiolabelled bixafen and 1 day with dichlorophenyl-UL-^{14}C radiolabelled bixafen and sacrificed at 72 hours (4/sex/group), or bile duct-cannulated animals dosed at 2 mg/kg bw in 0.5% aqueous tragacanth and sacrificed at 48 hours (5/sex/group). **Absorption:** Approximately 93-107% of the AD was recovered based on the measurement of the total radioactivity in excreta (urine, bile and feces) and organs and tissues at sacrifice. The radioactivity was rapidly absorbed and the maximum plasma concentrations were achieved at 2 hours for ♂ and 4 hours for ♀ in the SLD and repeated dose groups and 8 hours for the SHD groups. In bile duct-cannulated rats, ~ 87% of the AD was absorbed by ♂ and 89% by ♀ based on the recoveries in bile, urine and carcass (excluding GIT). **Distribution:** For all dose regimens, at the 72 hour sacrifice, ~ 0.1-3.0% of the AD was found in the ♂ and ♀ (including GIT residues) or 0.1-1.6% (excluding GIT residues). The liver and kidneys had the highest levels of residues. Levels in tissues were generally higher in ♀. There was no evidence of tissue retention in ♂ or ♀. In bile duct-cannulated rats (48 hour sacrifice), there were high residue levels in ♀ (~32% of the AD excluding GIT residues and 43% of the AD including GIT residues) compared to ♂ (~2.7% of the AD excluding GIT residues and 9% of the AD including GIT residues). AUC was greater in ♀ animals (up to twofold at the low dose) compared to ♂ animals. **Elimination:** At the 72 hour sacrifice, ~93-99% of SLD and SHD were eliminated in urine and feces (106% in the repeated dose group). In bile duct-cannulated rats, ~91% and 63% of the AD was eliminated by the 48 hour sacrifice in ♂ and ♀, respectively. Biliary excretion (~83% in ♂ and 56% of the AD in ♀ at 48 hours after dosing) was the major route of excretion with minor amounts in urine (<3% of the AD at 72 hours after dosing). Female rats excreted approximately twice the amount of the administered radioactivity in urine than ♂ [SLD 1.41% (♂) vs 2.87% (♀) and SHD 0.69% (♂) versus 1.67% (♀)]. Based on AUC data ♀ animals showed slower elimination compared to ♂ animals. **Metabolism:** The primary metabolic reaction was the demethylation of the pyrazole ring forming bixafen-desmethyl. Parent compound and bixafen-desmethyl were hydroxylated at different positions. Most of the hydroxy compounds were conjugated with glucuronic acid. An N-conjugation of bixafen-desmethyl with glucuronic acid was also observed. Conjugation of Bixafen with glutathione was a major metabolic reaction in bile. The glutathione conjugation and related metabolites were also found for bixafen-desmethyl. A minor metabolic reaction was the cleavage of the amide structure of bixafen forming pyrazole-4-carboxamide and desmethyl-pyrazole-4-carboxamide which were observed as label specific metabolites in urine. An oxidation of bixafen-pyrazole-4-carboxamide led to bixafen-pyrazole-4-carboxylic acid. Another minor reaction was the elimination of one of the two chlorine atoms of bixafen-desmethyl-5-hydroxyphenyl and a further conjugation with a methylthio group. (PMRA No. 2642798).	
Doses: Single dose of 2 mg/kg bw pyrazole-5-^{14}C labelled bixafen in 0.5% aqueous tragacanth and sacrificed at 72 hours (4 ♂).	

Study Type/Animal/PMRA No.	Study Results
Absorption: Rapid absorption and distribution with plasma t_{max} at ~3 hours and plasma C_{max} of 0.42 µg/mL. The major route of excretion was via feces (>93% of the AD), radioactivity in the urine accounted for <4.4% of the AD. **Distribution:** At sacrifice, the remaining concentration in mean equivalent concentration was negligible and the highest concentration was found in the liver (0.0266 µg/g; 0.0715% of the AD*) followed by thyroid gland (0.0093 µg/g; <0.0001% of the AD), adrenal gland (0.0083 µg/g; 0.0001% of the AD) and kidney (0.0066 µg/g; 0.0029% of the AD).*Based on dose normalised concentration ([radioactivity per g tissue/radioactivity per g bw]). **Metabolism:** Parent compound was detected in feces only (8.57% of the AD). The predominant metabolic reaction was the demethylation of the pyrazole ring forming bixafen-desmethyl. Both the parent compound and bixafen-desmethyl were hydroxylated at different positions, especially in the fluoro-phenyl ring. Elimination of the fluorine atom and subsequent hydroxylation was also detected. Rearrangement (migration) of the fluorine atom on the phenyl ring was also detected following hydroxylation reactions. Conjugation of bixafen with glutathione was a major metabolic reaction and led to an intermediate glutathione conjugate, which was further degraded to cysteine conjugates and methylthio-, methylsulfinyl- and thiol-acetaldehyde compounds. The glutathione conjugate and related metabolites were also found for bixafen-desmethyl. A minor metabolic reaction, observed as label specific metabolites in urine, was the cleavage of the molecule forming pyrazole-4-carboxamide and desmethyl-pyrazole-4-carboxamide. An oxidation of bixafen-pyrazole-4-carboxamide led to bixafen-pyrazole-4-carboxylic acid. Cleavage can also occur to generate biphenyl derivatives that represented up to 4% of the AD. Another minor reaction was the elimination of one of the two chlorine atoms of bixafen-desmethyl-5-hydroxyphenyl and a further conjugation with a methylthio group. **In urine:** Bixafen-desmethyl-pyrazole-4-carboxamide (2.78% of the AD), bixafen-pyrazole-4-carboxamide (0.97% of the AD); **In feces:** Bixafen (8.57% of the AD), bixafen-desmethyl (10.47% of the AD), bixafen-desmethyl-5-hydroxyphenyl-6-(methylthio) (14.13% of the AD), bixafen-5-hydroxyphenyl-6-(methylthio) and 4-hydroxyphenyl (10.34% of the AD), bixafen-4-fluoro-5-hydroxyphenyl and bixafen-5-hydroxyphenyl-6-thiol-acetaldehyde (6.97% of the AD). (PMRA No. 2642799).
Doses: Single doses of 10, 50, 500 or 1000 mg/kg bw of unlabelled bixafen in 0.5% aqueous methylcellulose (3/sex/group; 1 ♂ served as control). **Absorption:** C_{max} of bixafen (F9650) was reached between 5.33 and 7.33 hours post-dose. At ≥500 mg/kg bw, the increase in C_{max} was not proportional (sub-linear) to the dose and t_{max} was shorter in ♂ compared to ♀ (about 1.7-fold). (PMRA No. 2642800).
Doses: Single dose of 3 mg/kg bw pyrazole-5-^{14}C labelled bixafen in 0.5% aqueous tragacanth (9 ♂). **Distribution:** Radioactivity was detected in all organs and tissues and decreased rapidly between 8 and 48 hours. In most organs and tissues the residues were < LOD or < LOQ at 72 to 168 hours after dosing. At the end of the test period, liver and nasal mucosa showed residues above the LOD but below 0.05 mg/kg. **Metabolism:** Parent compound and the metabolites bixafen-desmethyl-5-hydroxyphenyl-6-sulfoxide and bixafen-5-hydroxyphenyl-6-sulfoxide were identified in feces. Bixafen-desmethyl-pyrazole-4-carboxamide and bixafen-pyrazole-4-carboxylic acid were identified in urine. **Elimination:** No significant expiration of ^{14}C-labelled volatiles was observed. (PMRA No. 2642801).
Doses: Single dose of 3 mg/kg bw dichlorophenyl-UL-^{14}C labelled bixafen in 0.5% aqueous tragacanth (8 ♂). **Absorption:** Absorption was rapid (t_{max} approximately 1 hour). **Distribution:** Maximum concentrations in the organs and tissues were observed between 1 and 8 hours after dosing. The low radioactivity concentration in blood

Study Type/Animal/PMRA No.	Study Results
during the study indicated a fast distribution within the body with highest levels in liver, kidney, fat and several glands (adrenal, pituitary, thyroid, salivary, harderian, infraorbital). A rapid decline of the radioactivity concentrations in all organs and tissues was observed between 1 and 48 hours after administration. **Elimination:** The majority of radioactivity was eliminated via feces. During the 1-48 hour time interval tissue residues dropped by at least one order of magnitude. No significant expiration of ^{14}C-labelled volatiles was detected. **Metabolism:** The unchanged parent compound bixafen was detected as a major component in feces extract. Bixafen-desmethyl-5-hydroxyphenyl-6-sulfoxide and bixafen-5-hydroxyphenyl-6-sulfoxide were identified as metabolites in feces. In urine, no parent compound was detected. (PMRA No. 2642802).	
Acute oral toxicity Wistar rats PMRA No. 2642766	$LD_{50♀}$ > 2000 mg/kg bw Low toxicity
Acute dermal Wistar rats PMRA No. 2642767	$LD_{50♂♀}$ > 2000 mg/kg bw Low toxicity
Acute inhalation Wistar rats PMRA No. 2642768	$LC_{50♂♀} \geq$ 2.0 mg/L of respirable particles Low toxicity
Primary eye irritation NZW rabbits PMRA No. 2642769	MAS = 0.22/110, $MIS_{at\ 1\ hour}$ = 2/110 Minimally irritating
Primary dermal irritation NZW rabbits PMRA No. 2642770	MAS = 0/8, MIS = 0/8 No signs of irritation in any of the animals tested. Non-irritating
Dermal sensitization (LLNA) CBA/J mice PMRA No. 2642772	Not a dermal sensitizer
28-Day toxicity (dietary)	No NOAEL established, range-finding study.

Study Type/Animal/PMRA No.	Study Results
C57BL/6J mice PMRA No. 2642774	≥81/103 mg/kg bw/day ♂/♀: ↑ liver size, ↑ liver wt, hepatocyte centrilobular hypertrophy, focal coagulative necrosis, ↓ total protein, ↓ albumin, ↑ AST; ↑ ALT (♀) 305/424 mg/kg bw/day ♂/♀: mortality days 7–14; ↓ bw, ↓ fc, ↓ albumin, ↑ cholesterol (♀) Decedents: ↓ bw, ↓ fc, ↓ motor activity, cold to touch, hunched posture; tremor, piloerection (♀).
28-Day toxicity (dietary) Wistar rats PMRA No. 2642773	No NOAEL established, range-finding study. ≥ 25/28 mg/kg bw/day ♂/♀: ↑ rel liver wt, minimal to slight hepatic centrilobular hypertrophy; P450 CYP2B and CYP3A induction (♂); ↑ abs liver wt, induction of BROD, PROD (associated with ↑ liver wt (♀)) 137/138 mg/kg bw/day ♂/♀: ↓ bwg, ↓ bilirubin, ↑ liver wt; ; ↓ bw, ↑ prothrombin time, thyroid hypertrophy of follicular cells (♂); dark liver, enlarged liver, ↑ platelets, ↑ cholesterol (♀)
90-Day toxicity (dietary) C57BL/6J mice PMRA No. 2642777	NOAEL = 34/43 mg/kg bw/day ♂/♀ LOAEL = 88/110 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↑ liver wt, hepatocellular hypertrophy, ↑ incidence stomach squamous hyperplasia; ↓ cholesterol, ↑ incidence of unilateral focal tubular degeneration in testes, ↑ ALT (♂); ↑ incidence of focal/multifocal squamous cell hyperplasia ovaries (♀)
90-Day toxicity (dietary) Wistar rats PMRA No. 2642776	NOAEL = 13/15 mg/kg bw/day ♂/♀ LOAEL = 50/59 mg/kg bw/day ♂/♀ Effects at the LOAEL: enlarged liver, minimal to slight hepatic centrilobular hypertrophy, minimal to slight thyroid follicular cell hypertrophy; ↑ rel liver wt (♂); ↑ liver wt, ↓ prothrombin time (♀) At the end of a 28-day recovery period in the high dose level group (130/153 mg/kg bw/day in ♂/♀), all effects observed returned to control values except for enlarged liver in ♀
90-Day toxicity (gavage) Beagle dogs PMRA No. 2642779	NOAEL= 300 mg/kg bw/day LOAEL= 1000 mg/kg bw/day Effects at the LOAEL: ↓ bwg, enlarged hepatocytes with vacuolated cytoplasm; ↓ bw, ↓ RBC, ↓ HB on Days 58 and 86, ↓ HCT on Days 58 and 86 (♂); single cell liver necrosis and ovarian cysts in one animal (not same) (♀)
12-Month toxicity (gavage) Beagle dogs PMRA No. 2642787	NOAEL= 100 mg/kg bw/day LOAEL= 1000 mg/kg bw/day Effects at the LOAEL: ↑ liver wt; ↓ RBC, ↓ HB, ↓ HCT (transient 3–6 mo) (♂); ↓ bw, ↓ bwg, slight hepatocellular hypertrophy, liver pigmentation, minimal single cell liver necrosis, ↑ ALP, ↑ cholesterol, pale feces (♀)
28-Day toxicity (dermal)	NOAEL= 1000 mg/kg bw/day LOAEL= not determined

Study Type/Animal/PMRA No.	Study Results
Wistar rats PMRA No. 2642781	No adverse effects at the highest dose tested.
80-Week oncogenicity (dietary) C57BL/6J mice PMRA No. 2642788	NOAEL= 6.7/8.6 mg/kg bw/day ♂/♀ LOAEL= 20/26 mg/kg bw/day in ♂/♀ Effects at the LOAEL: ↑ liver wt, dark liver; hepatocyte centrilobular hypertrophy, hepatocellular single cell degeneration/necrosis, small thymus (♂); minimal to slight thyroid follicular cell hyperplasia (♀) No evidence of oncogenicity.
2-Year dietary combined chronic toxicity/oncogenicity Wistar rats (♀) PMRA No. 2642789	NOAEL= 2.81 mg/kg bw/day ♀ LOAEL= 17 mg/kg bw/day ♀ Effects at the LOAEL: ↑ liver wt, enlarged liver, dark liver, ↓ bilirubin (18 and 24 mo), ↑ multinucleated hepatocytes, ↑ hepatocellular brown pigment, ↑ minimal to slight diffuse centrilobular to panlobular hepatocellular hypertrophy, ↑ dark thyroid, ↑ minimal to slight diffuse follicular cell hypertrophy, ↑ minimal to slight thyroid colloid alteration No evidence of oncogenicity.
2-Year dietary combined chronic toxicity/oncogenicity Wistar rats (♂) PMRA No. 2642790	NOAEL= 2.0 mg/kg bw/day ♂ LOAEL= 12 mg/kg bw/day ♂ Effects at the LOAEL: ↓ bilirubin, ↑ minimal to slight diffuse centrilobular to panlobular hepatocellular hypertrophy, ↑ incidence of minimal to moderate alteration of the thyroid colloid No evidence of oncogenicity.
One-generation reproductive toxicity (dietary) Wistar rats PMRA No. 2642786	No NOAEL established, range-finding study. Parental toxicity: ≥ 36 mg/kg bw/day ♂: ↑ liver wt, ↑ thyroid wt (♂) 110/125 mg/kg bw/day ♂/♀: ↑ liver wt (♀) 326/368 mg/kg bw/day ♂/♀: ↓ bw, ↓ bwg, ↓ thymus wt; ↑ aPTT (♂) Reproductive toxicity: No treatment-related adverse effects Offspring toxicity: 371 mg/kg bw/day: ↓ bw from PND4, ↓ bwg
Two-generation reproductive toxicity (dietary)	Parental toxicity: NOAEL= 26/31 mg/kg bw/day ♂/♀

Study Type/Animal/PMRA No.	Study Results
Wistar rats PMRA No. 2642785	LOAEL= 169/194 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↑ liver wt, ↑ incidence of minimal to slight centrilobular and diffuse hypertrophy; ↑ F0 kidney wt, ↑ F0 spleen wt (♂); ↓ F0 and F1 bw (pre-mating, gestation and lactation), ↓ F0 and F1 bwg (pre-mating), ↓ F0 thymus wt (♀) Reproductive toxicity: NOAEL= 169/194 mg/kg bw/day ♂/♀ LOAEL= Not determined No adverse effects at the highest dose tested. Offspring toxicity: NOAEL= 31 mg/kg bw/day LOAEL= 194 mg/kg bw/day Effects at the LOAEL: ↓ pup bw and bwg in F1 (PND 7-21) and F2 (PND 14-21) No evidence of sensitivity of the young.
Developmental toxicity (gavage) Sprague-Dawley rats PMRA No. 2642784	Maternal toxicity: NOAEL= 75 mg/kg bw/day LOAEL= 250 mg/kg bw/day Effects at the LOAEL: ↓ bw at GD 6-8, ↓ bwg at GD 18-21, ↓ fc, piloerection, soiling around nose, mouth and abdomen. Developmental toxicity: NOAEL= 75 mg/kg bw/day LOAEL= 250 mg/kg bw/day Effects at the LOAEL: ↓ fetal bw, incomplete ossification of 5th sternebrae and/or unossified 5th sternebrae and unossified 7th cervical centrum, extra ossification points on the 14th thoracic vertebra, shortened 14th ribs and bipartite or dumbbell-shaped thoracic centra No treatment-related malformations. No evidence of sensitivity of the young.
Developmental toxicity (gavage) NZW rabbits	Maternal toxicity: NOAEL= 25 mg/kg bw/day LOAEL= 100 mg/kg bw/day

Study Type/Animal/PMRA No.	Study Results
PMRA No. 2642783	Effects at the LOAEL: ↓ bwg, ↓ fc, hair loss, ↓ or no excreta, ↑ liver wt, ↑ vaginal discharge Developmental toxicity: NOAEL= 25 mg/kg bw/day LOAEL= 100 mg/kg bw/day Effects at the LOAEL: ↓ fetal bw No treatment-related malformations. No evidence of sensitivity of the young.
Bacterial reverse mutation test *S.* typhimurium (TA 1535, TA 1537, TA 98, TA 100, TA 102 strains) PMRA No. 2642791	Negative
In vitro gene mutation assay Chinese Hamster V79 cells PMRA No. 2642792	Negative
Chromosomal aberration assay Chinese Hamster V79 cells PMRA No. 2642793	Negative
In vivo mammalian cytogenetics (micronucleus test) NMRI mice PMRA No. 2642794	Negative
Acute oral neurotoxicity study (gavage) Sprague-Dawley rats	Systemic toxicity: NOAEL= 250 mg/kg bw LOAEL= 1000 mg/kg bw based on ↓ motor activity (total and ambulatory) at 4 hours; ↓ body temperature at 4 hours, ↓ rearing counts (♀)

Study Type/Animal/PMRA No.	Study Results
PMRA No. 2642796	No evidence of selective neurotoxicity.
28-Day oral (dietary) Wistar rats (♂) PMRA No. 2642775	Supplemental study (mechanistic) This study was designed to determine if administration of bixafen results in changes to blood coagulation parameters when the diet contains 16 ppm of vitamin K3. ≥162 mg/kg bw/day: ↑ rel liver wt, ↑ rel thyroid wt, dark livers, ↓ prothrombin times ≥375 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↑ liver wt, ↑ rel thyroid wt, enlarged liver, ↑ nasal discharge The level of vitamin K3 added to the diet is considered to be significantly higher than the recommended level. From the data presented in this study, an effect of bixafen on coagulation time cannot be excluded.
Comparison of the effect of bixafen on blood coagulation parameters with vitamin K3 supplemented and vitamin K3 deficient diets (dietary) Wistar rats (♂) PMRA No. 2642810	Supplemental study (mechanistic) This study was designed to compare the effect of vitamin K supplementation on blood coagulation parameters of rats dosed with 1000 ppm of bixafen for 6 months. Male rats administered bixafen in vitamin K3 deficient diet (containing <0.3 ppm of vitamin K3) at a concentration of 1000 ppm of bixafen for approximatively six months exhibited a hemorrhagic syndrome (increased PT and aPTT values) and a high rate of mortality in the original two-year chronic toxicity/onocogenicity study. The addition of 16 ppm of vitamin K to the diet significantly lowered these values after two weeks compared to the previous time point. There was no control group fed with the vitamin K deficient diet (<0.3 ppm of vitamin K3), which would have been helpful to evaluate the role of bixafen on coagulation parameters.
14-day toxicity (gavage) (hepatic enzymes and thyroid hormones investigations) Wistar rats PMRA No. 2642765	Supplemental study (mechanistic) This study was designed to investigate the changes in the thyroid gland following treatment with 150 mg bixafen/kg bw/day by measuring plasma thyroid hormone levels (TSH, T3 and T4) and liver enzyme induction. Thyroid: bixafen induced slight ↑ in serum TSH. Higher TSH values were observed in ♀ on study Days 3, 7 and 14 while in ♂ a significant increase was observed only after 14 days. A slight transient reduction of T3 was also observed in ♀ on study Days 3 and 7 and a slight decrease in T4 was observed in ♂ on study Day 14. Liver: liver weight was increased in both sexes after administration of the test substance for 14 days. There was an increase in BROD activity in both sexes compared to controls. In addition, a slight ↑ was also observed in mean UDPGT activity in both sexes. The test substance slightly induced both phase I and II hepatic enzymes after 14 days of bixafen administration.

Table 4 Toxicology Reference Values for Use in Health Risk Assessment for Bixafen

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary	Developmental toxicity study in rat	NOAEL= 75 mg/kg bw/day Decreased body weight in dams between GD 6–8	100
	ARfD = 0.8 mg/kg bw		
Repeated dietary	2-Year dietary chronic toxicity/oncogenicity study in rat	NOAEL= 2.0 mg/kg bw/day Liver and thyroid effects	100
	ADI = 0.02 mg/kg bw/day		
Short- and Intermediate – term dermal	28-Day dermal toxicity study in rat	NOAEL= 1000 mg/kg bw/day No adverse effects at the highest dose tested	100
Short- and Intermediate-term inhalation[2]	90-Day toxicity study in rat	NOAEL= 13 mg/kg bw/day Liver and thyroid effects	100
Cancer	There was no evidence of oncogenic potential of bixafen in rodents		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 5 Integrated Food Residue Chemistry Summary

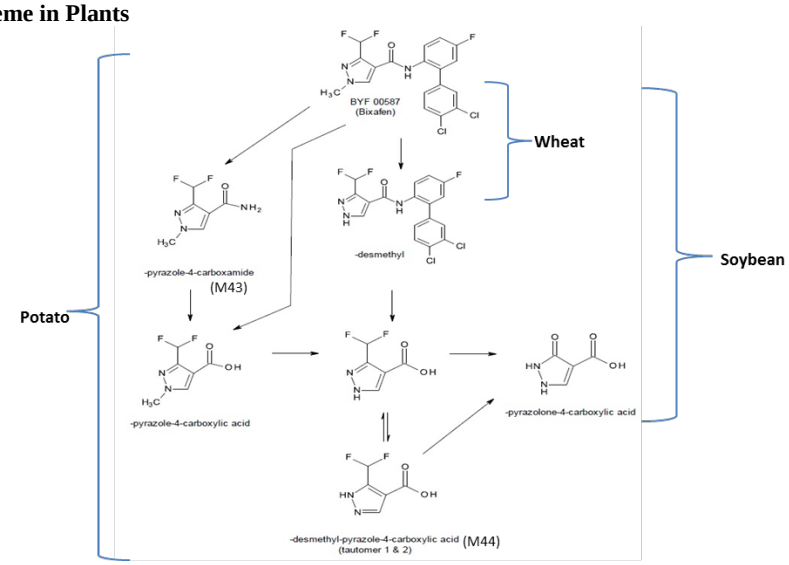
NATURE OF THE RESIDUE IN SOYBEANS			**PMRA No. 2642741 & 2642748**	
Radiolabel Position	[pyrazole-5-^{14}C]-bixafen (PY-label) and [dichlorophenyl-UL-^{14}C]-bixafen (PH-label)			
Test Site	Climate controlled greenhouse in a planting container filled with a sandy loam soil.			
Treatment	Foliar treatments			
Total Rate	Three applications at a target rate of 60 g a.i./ha per application, for actual total rates of 188 g a.i./ha (PY-label) and 187 g a.i./ha (PH-label). Forage and hay samples were harvested at the specified PHIs (see below) after the second application at the end of flowering (BBCH 69) at rates totalling 127-128 g a.i/ha. Seed and straw samples were collected at the specified PHIs (see below) after the third foliar application when approx. 80% of the pods were ripe (BBCH 88) for total rates (both labels) of 187-188 g a.i./ha.			
Formulation	Emulsifiable concentrate			
Preharvest interval	Forage and hay: 5 and 29 days, respectively, after the second application. Seed and straw: 26 days after the third application.			
Matrices	**PHI (days)**	**[^{14}C-PY] TRRs (ppm)**	**[^{14}C-PH] TRRs (ppm)**	
Forage	5 after the 2nd application	5.32	3.98	
Hay		4.00	2.81	
Straw	26 after the third application	12.90	9.52	
Seed		0.024	0.005	
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C-PY]**	**[^{14}C-PH]**	**[^{14}C-PY]**	**[^{14}C-PH]**
Forage Hay Straw	Bixafen		Bixafen-desmethyl	

Seed	Bixafen, bixafen-desmethyl-pyrazole-4-carboxylic acid and bixafen-pyrazolone-4-carboxylic acid	None	None

NATURE OF THE RESIDUE IN WHEAT			**PMRA No. 2642746 & 2642747**	
Radiolabel Position	[pyrazole-5-^{14}C]-bixafen (PY-label) and [dichlorophenyl-UL-^{14}C]-bixafen (PH-label)			
Test Site	The crop was grown in the vegetation area of the test facility under natural light and temperature conditions.			
Treatment	Foliar treatments.			
Total Rate	Two applications at 128-132 g a.i./ha per application for a total rate of 286 g a.i./ha.			
Formulation	Emulsifiable concentrate			
Preharvest interval	Forage: 9 days after the first application. Hay, straw and grain: 9 (hay) and 50 days (grain and straw) after the 2nd application.			
Matrices	**PHI (days)**	**[^{14}C-PY] TRRs (ppm)**	**[^{14}C-PH] TRRs (ppm)**	
Forage	9 after the 1st application	1.67	1.57	
Hay	9 after the 2nd application	6.57	7.64	
Straw	50 after the 2nd application	24.27	22.85	
Grain		0.162	0.229	
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C-PY]**	**[^{14}C-PH]**	**[^{14}C-PY]**	**[^{14}C-PH]**
Forage Hay Straw Grain	Bixafen		Bixafen-desmethyl	

NATURE OF THE RESIDUE IN POTATOES			**PMRA No. 2642750 & 2642749**	
Radiolabel Position	[pyrazole-5-^{14}C]-bixafen (PY-label) and [dichlorophenyl-UL-^{14}C]-bixafen (PH-label)			
Test Site	The crop was grown in a greenhouse under natural light and temperature conditions.			
Treatment	Foliar treatments.			
Total Rate	Three applications with the first application made at BBCH 61 (beginning of flowering), and the second application made at BBCH 70 (first berries visible). Leaves were harvested after the second application with rates totaling 486-490 g a.i./ha. The third application was made at BBCH 97 (leaves and stems dead, stems bleached and dried) and tubers were harvested after the third application for a total applied rate to the plants of 724-733 g a.i./ha.			
Formulation	Emulsifiable concentrate			
Preharvest interval	Leaves: 30 days after the second application. Tubers: 7 days after the third application.			
Matrices	**PHI (days)**	**[^{14}C-PY] TRRs (ppm)**	**[^{14}C-PH] TRRs (ppm)**	
Leaves	30 after the 2nd application	24.38	21.77	
Tubers	7 after the 3rd application	0.003	0.002	
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C-PY]**	**[^{14}C-PH]**	**[^{14}C-PY]**	**[^{14}C-PH]**
Leaves Tubers	Bixafen		Bixafen-desmethyl, M43; bixafen-pyrazolone-4-carboxylic acid; bixafen-pyrazole-4-carboxylic acid	Bixafen-desmethyl

Proposed Metabolic Scheme in Plants

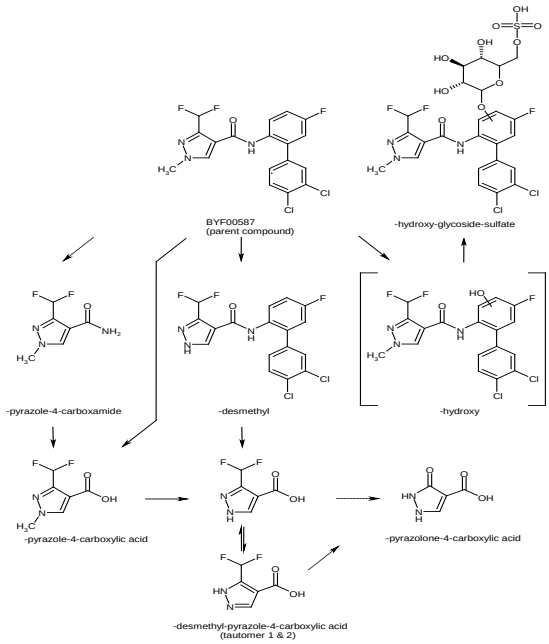


The metabolism of bixafen in three diverse crops was determined to be similar. In all three crops and their associated matrices, the major residue observed was unchanged bixafen, thereby indicating that following foliar application and uptake/distribution, limited metabolism of the active substance occurs. When metabolism occurred, the mechanism involves *N*-desmethylation of the pyrazole amide moiety, generating the minor metabolite bixafen-desmethyl, which was observed in all crops, all matrices. In addition, minor metabolites specific to the [pyrazole-5-^{14}C]-label, bixafen-pyrazolone-4-carboxylic acid and bixafen-desmethyl-pyrazole-4-carboxylic acid (M44), the latter of which results from the cleavage of bixafen-desmethyl by hydrolysis or photolysis, were observed in soybean seed and potatoes; in potatoes, bixafen-pyrazole-4-carboxamide (M43) and bixafen-pyrazole-4-carboxylic acid were observed as minor components.

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Wheat, Swiss chard and Turnips		**PMRA No. 2642763, 2642762, 2642685**			
Radiolabel Position		[pyrazole-5-^{14}C]-bixafen (PY-label) and [dichlorophenyl-UL-^{14}C]-bixafen (PH-label)			
Test site		Sandy loam soil in planting containers located in a vegetation area during the first rotation and the first period of the second rotation until day 191 after application. Subsequently, the planting containers were moved into a greenhouse for the remainder of the study duration.			
Formulation		Emulsifiable concentrate			
Application rate and timing		Bare soil was treated with 785 g a.i./ha (PY-label) and 847 g a.i./ha (PH-label) and aged for 30 (first rotation), 138 (second rotation) and 285 days (third rotation). Wheat forage and hay were harvested at BBCH 29-30 and 75, respectively. Wheat straw and grain, Swiss chard and turnip matrices (leaves and root) were harvested at maturity. Soil was also sampled at 30 days after treatment (DAT), 138 DAT, 285 DAT and 418 DAT.			
Metabolites Identified		**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Matrices	**PBI (days)**	**[^{14}C- PY-label]**	**[^{14}C- PH-label]**	**[^{14}C- PY-label]**	**[^{14}C- PH-label]**
Wheat forage	30	Bixafen, bixafen-desmethyl, M43, bixafen pyrazole-4-carboxylic acid	Bixafen, bixafen-desmethyl,	M44 (T2), bixafen pyrazolone-4-carboxylic acid	None detected
	138	Bixafen, bixafen-desmethyl		M43. bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid	
	285	Bixafen, bixafen-desmethyl , M43		None detected	
Wheat hay	30	Bixafen, bixafen-desmethyl	Bixafen, bixafen-desmethyl	M43	None detected
	138			M43, bixafen pyrazole-4-carboxylic acid	
	285	Bixafen, bixafen-desmethyl, M43		None detected	
Wheat straw	30	Bixafen, bixafen-desmethyl		M44 (T1 & T2), M43, bixafen pyrazole-4-carboxylic acid	None detected

	138			M44 (T1 & T2), M43	
	285			M43	
Wheat grain	30	Not determined; TRRs were too low			
	138				
	285				
Swiss chard	30	Bixafen, M44 (T1 & T2), M43, bixafen hydroxy-glycoside-sulfate	Bixafen, bixafen hydroxy-glycoside-sulfate	Bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid	None detected
	138	Bixafen, bixafen-desmethyl, M44 (T1), bixafen hydroxy-glycoside-sulfate		M43, M44 (T2), bixafen pyrazolone-4-carboxylic acid, bixafen-desmethyl	Bixafen-desmethyl
	285	Bixafen, M44 (T1), bixafen-hydroxy-glucoside-sulfate		M44 (T2), M43, bixafen-desmethyl	Bixafen-desmethyl
Turnip leaves	30	Bixafen, M43	Bixafen, bixafen-desmethyl	M44 (T1 & T2), bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid, bixafen-desmethyl	None detected
	138	Bixafen, M44 (T1)		M44 (T2), M43, bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid, bixafen-desmethyl	
	285	Bixafen, M43		M44 (T2), bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid, bixafen-desmethyl	
Turnip roots	30	Bixafen, bixafen-desmethyl		M44 (T2), M43, bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid	None detected
	138			Bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid	
	285			Bixafen pyrazolone-4-carboxylic acid, bixafen pyrazole-4-carboxylic acid	
Soil	30	Bixafen		Bixafen-desmethyl	
	138				
	285				
	418				

Proposed Metabolic Scheme in Rotational Crops



The results of the confined rotational crop studies indicate that the metabolism of bixafen in secondary crops is similar to that observed in primary crops with the major observed compound being unchanged bixafen. Bixafen-desmethyl was observed in all matrices at varying levels, but tended to be more prevalent in wheat matrices at levels higher than bixafen, but lower than that of bixafen in Swiss chard, turnip leaves and turnip roots. Other metabolites observed at lower levels included bixafen-hydroxy-glycoside-sulfate in Swiss chard (14.6-38.3% of the TRR; 0.007-0.016 ppm) and the five pyrazole metabolites (bixafen-pyrazole-4-carboxylic acid, bixafen-desmethyl-pyrazole-4-carboxylic acid [M44] [tautomers 1 and 2], bixafen-pyrazolone-4-carboxylic acid, and bixafen-pyrazole-4-carboxamide [M43]), which were observed in all RACS and all rotational intervals. In aged soil samples, bixafen was the only major metabolites observed and bixafen-desmethyl was the only minor metabolite observed.

NATURE OF THE RESIDUE IN LAYING HEN | **PMRA No. 2642744 & 2642745**

Six and five laying hens were dosed orally with [^{14}C-bixafen] at 25.7 ppm [pyrazole-5-^{14}C]-bixafen (PY-label)-32.52 ppm [dichlorophenyl-UL-^{14}C]-bixafen (PH-label), respectively, in the feed by gelatin capsule once daily for 14 days. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The hens were euthanized 24 hours after administration of the final dose and the following tissue samples were collected at sacrifice: muscle (leg and breast), liver, kidney, fat (subcutaneous) and skin (without fat).

Matrices	[pyrazole-5-^{14}C]-bixafen (PY-label)		[dichlorophenyl-UL-^{14}C]-bixafen (PH-label)	
	TRRs (ppm)	% of Administered Dose	TRRs (ppm)	% of Administered Dose
Excreta	13.0	88.3	18.6	92.5
Muscle	0.033	0.05	0.037	0.05
Fat	0.234	0.1	0.365	0.03
Liver	0.639	0.05	0.807	0.06
Eggs: Days 1-14	0.776	1.15	0.640	0.98

Metabolites identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[^{14}C- PY-label]	[^{14}C- PH-label]	[^{14}C- PY-label]	[^{14}C- PH-label]
Muscle	Bixafen, bixafen-desmethyl		None	
Fat				
Liver	Bixafen-desmethyl		Bixafen, bixafen-desmethyl-hydroxypyrazole	Bixafen, bixafen-5-hydroxyphenyl-6-cysteinyl, bixafen-desmethyl-glycoside, bixafen-desmethyl-hydroxy-pentoside, bixafen-desmethyl-hydroxypyrazole
Eggs: Days 1-6/7	Bixafen, bixafen-desmethyl		None	Bixafen-desmethyl-hydroxy-pentoside

Days 7/8-14		Bixafen-desmethyl-hydroxypyrazole	Bixafen-desmethyl-glycoside, bixafen-desmethyl-hydroxy-pentoside, bixafen-desmethyl-hydroxypyrazole

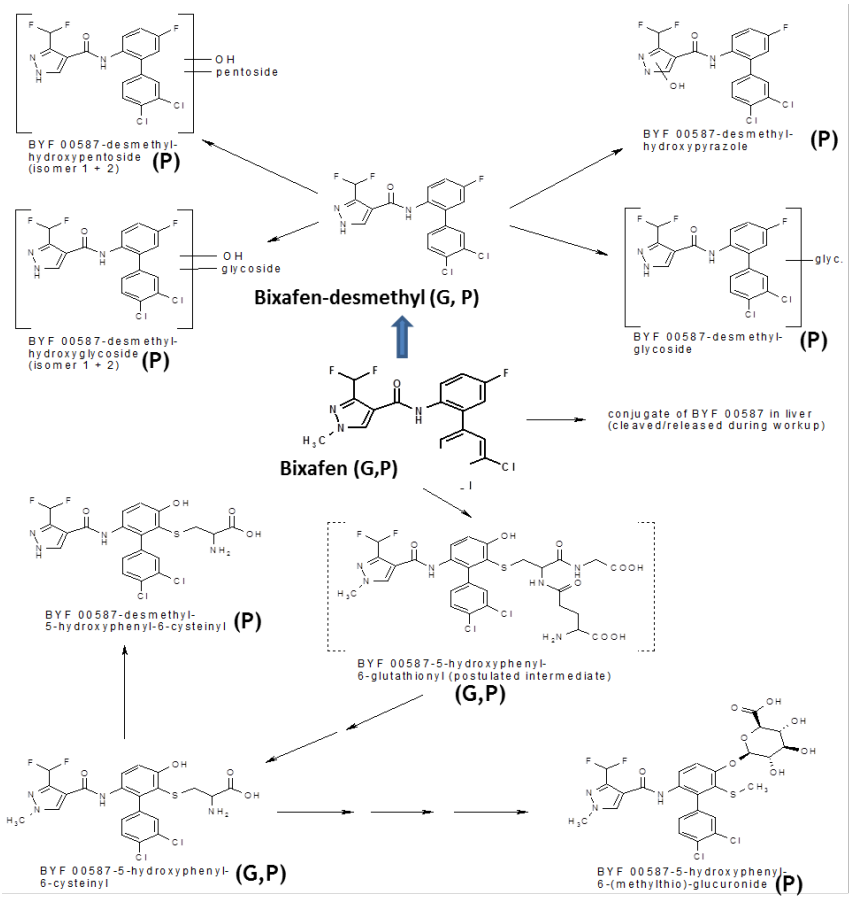
NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA No. 2642742 & 2642743**

A single goat per radiolabel was dosed orally once per day over 5 days with 46.08 mg bixafen per kg feed per day of either [dichlorophenyl-UL-^{14}C]-bixafen (PH-label) or 34.7 mg per kg feed per day of [pyrazole-5-^{14}C]-bixafen (PY-label). Total radioactive residues (TRRs) were determined in the excreta (faeces and urine - collected every 24 hours) and in milk, which was collected daily once in the morning and once in the afternoon and directly before sacrifice. The morning milk samples were pooled separately from the evening milk samples. The animals were sacrificed ~24 hours after the final dose the following tissue samples were collected: muscle (round [both labels] and loin [PY-label only]), liver, kidney and fat (omental and perirenal).

Matrices	**[dichlorophenyl-UL-^{14}C]-bixafen (PH-label)**		**[pyrazole-5-^{14}C]-bixafen (PY-label)-**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Urine (cumulative over 5 days)	1.95	5.62	0.806	1.75
Feces (cumulative over 5 days)	13.50	82.08	17.63	71.88
Muscle (total; loin + round)	0.047	0.134	0.057	0.17
Fat (total; perirenal + omental)	0.611	0.70	0.466	0.553
Kidney	0.143	0.004	0.203	0.007
Liver	0.737	0.166	1.178	0.278
Milk (cumulative over 5 days)	0.040	0.275	0.037	0.094

Metabolites identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C-PY-label]**	**[^{14}C-PH-label]**	**[^{14}C-PY-label]**	**[^{14}C-PH-label]**
Milk: Morning Pool	Bixafen & bixafen-desmethyl		Bixafen-desmethyl-N-glucuronide (isomer 2)	Bixafen-desmethyl-N-glucuronide (isomers 1 & 2)
Evening Pool				
Muscle	Bixafen & bixafen-desmethyl		None	
Fat	Bixafen & bixafen-desmethyl		None	
Liver	Bixafen & bixafen-desmethyl		Bixafen-desmethyl-5-hydroxyphenyl-6-cysteinyl, bixafen-desmethyl-N-glucuronide (isomers 1 & 2)	Bixafen-desmethyl-N-glucuronide (isomers 1 & 2)
Kidney	Bixafen & bixafen-desmethyl		Bixafen-desmethyl-N-glucuronide (isomers 1 & 2)	

Proposed Metabolic Scheme in Livestock:



G = goat; P = poultry.

The results indicate that metabolism of bixafen in both laying hen and lactating goat are similar. When ingested orally, bixafen is primarily excreted (>73% of the administered dose). The nature of the residue was not determined in the excreta. When retained in the tissues, the distribution of residues appears to reflect a preferred secretion of bixafen-derived compounds into the developing eggs and fatty tissues of poultry. Characterization of tissue-retained residues indicated that bixafen metabolism in both animals proceeds via demethylation of the pyrazole ring yielding the bixafen-desmethyl metabolite. Further minor biochemical reactions included substitution of the fluorine atom by a hydroxy group and an adjacent glutathione conjugation, an unspecified hydroxylation of an aromatic ring and conjugation with various sugar molecules, hydroxylation of the pyrazole ring, and in the goat, subsequent hydrolysis of the glutathione conjugate resulting in the exclusive minor liver metabolite, bixafen-5-hydroxy-phenyl-6-cysteinyl. No evidence of cleavage of bixafen between the pyrazole and phenyl rings was detected in either organism.

FREEZER STORAGE STABILITY	**PMRA No. 2643811, 2643812 & 2643814; 2643813**

Plant matrices:

Bixafen and bixafen-desmethyl - Dry bean seed, orange fruit, wheat, potato tuber, lettuce head and rape seed

The freezer storage stability data indicate that residues of bixafen and bixafen-desmethyl are stable at ≤-18°C for up to 24 months.

M43 and M44 - Orange fruit, tomato fruit, potato tuber, dry bean seed and soybean seed

The freezer storage stability data indicate that residues of the metabolites M43 and M44 are stable at ≤-18°C for up to 24 months.

Data are available for representative high water (wheat green material, lettuce), high oil (rape seed), high protein (dry bean seed), high starch (wheat grain and potato tuber), and high acid (orange fruit) crops for bixafen and bixafen-desmethyl. Data are also available for representative high water (tomato fruit), high oil (soybean seed), high protein (dry bean seed), high starch (potato tuber) and high acid (orange fruit) crops for metabolites bixafen-pyrazole-4-carboxamide (M43) and bixafen-desmethyl-pyrazole-4-carboxylic acid (M44). Therefore, storage stability can be extrapolated to all crops and processed commodities for up to 24 months.

Animal matrices: Storage stability data were not submitted for animal matrices; however, these data are not required since all tissue, milk and egg samples were analyzed within 30 days of collection in the dairy cattle and laying hen feeding studies.

CROP FIELD TRIALS AND RESIDUE DECLINE ON WHEAT	PMRA No. 2643803

Field trials were conducted on wheat in 2014 and 2015 in Canada and the United States. Trials were conducted in North America Growing Regions 2 (1 trial), 4 (1 trial), 5 (4 trials), 6 (1 trial), 7 (5 trials), 7A (1 trial), 8 (4 trials), 11 (3 trials) and 14 (6 trials) for a total of 26 trials. An emulsifiable concentrate formulation of bixafen was applied twice as foliar broadcast sprays at rates of 109-116 g a.i./ha/ application for seasonal application rates of 219-231 g a.i./ha. The timing of the first application was based on approximate crop growth stage (BBCH 25) with the second application occurring 30 to 35 days prior to normal harvest for wheat grain and straw, 18-27 days for hay and 8-19 days for forage. An adjuvant was included in the spray mixtures at 18 of the 26 trials. Residue decline behavior was determined at 2 sites where forage samples were collected at 0, 3, 6-7, 9-10, and 13-15 days after the first application, and grain and straw samples were collected at 25-27, 30, 35, 41, and 44-46 days after the last treatment.

Residue decline data show that residues of bixafen, bixafen-desmethyl and total bixafen demonstrated a decreasing trend in forage and residues of bixafen and total bixafen remained relatively constant in grain and straw with longer PHIs. Decline behavior could not be evaluated for bixafen-desmethyl in grain as residues at all PHIs were non quantifiable.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Wheat Forage	219-231	8-19*	25	3.18	0.91	1.119	0.87
Wheat Hay		18-27	25	2.56	0.972	1.013	0.738
Wheat Grain		25-35	26	0.107	0.036	0.0755	0.149
Wheat Straw			26	3.58	1.49	1.755	0.980
Bixafen-desmethyl							
Wheat Forage	219-231	8-19*	25	0.297	0.106	0.122	0.066
Wheat Hay		18-27	25	0.644	0.187	0.221	0.166
Wheat Grain		25-35	26	0.0233	0.0183	0.0185	0.0045
Wheat Straw			26	0.793	0.354	0.391	0.178
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Wheat Forage	219-231	8-19*	25	3.4	1.0	1.2	0.88
Wheat Hay		18-27	25	3.2	1.1	1.2	0.9
Wheat Grain		25-35	26	0.11	0.04	0.05	0.03
Wheat Straw			26	4.2	1.9	2.2	1.1

HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.
*At only 1 of trials were forage samples collected at 19 days. PHIs for forage at the remaining trials ranged from 8-12 days.

CROP FIELD TRIALS AND RESIDUE DECLINE ON BARLEY	PMRA No. 2934416, 2934417, 2934418 & 2934419

Field trials were conducted on barley in 2006 and 2007 in representative growing regions in Northern Europe (Northern France [4 trials], Sweden [1 trial], United Kingdom [2 trials], Germany [2 trials], Belgium [1 trial]) and Southern Europe (France [4 trials], Italy [3 trials], Spain [2 trials], Portugal [1 trial]) for a total of 20 trials. An emulsifiable concentrate (EC) formulation of bixafen was applied twice as foliar broadcast sprays at a rate of 125 g a.i./ha/application for seasonal application rates of 250 g a.i./ha. The timing of the first application was based on approximate crop growth stage BBCH 37-41 with the second application occurring at BBCH 61-71, with PHIs of 0 days for forage and 34-66 days for grain and stover. Adjuvant use was not specified.

Residue decline data show that residues of bixafen, bixafen-demethyl and total bixafen demonstrated a declining trend in forage with longer PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Barley Forage	250	0	20	7	3.5	3.65	1.2
Barley Grain		34-66	20	0.34	0.07	0.090	0.08
Barley Straw			20	10	1.7	2.9	2.6
Bixafen-desmethyl							
Barley Forage	250	0	20	0.25	0.09	0.102	0.061
Barley Grain		34-66	20	0.04	0.01	0.017	0.011
Barley Straw			20	1.4	0.18	0.27	0.3
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Barley Forage	250	0	20	7.25	3.6	3.76	1.2
Barley Grain		34-66	20	0.38	0.09	0.11	0.09
Barley Straw			20	11.4	1.9	3.17	2.9

HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON SORGHUM **PMRA No. 2643802**

Field trials were conducted on grain sorghum in 2014 in the United States in North America Growing Regions 4 (1 trial), 5 (3 trials), 6 (2 trials), 7 (1 trial) and 8 (2 trials) for a total of 9 trials. An emulsifiable concentrate formulation of bixafen was applied twice as foliar broadcast sprays at rates of 112-115 g a.i./ha/ application for seasonal application rates of 224 to 230 g a.i./ha. The timing of the applications was approximately 50 and 30 days prior to normal harvest of the sorghum RACs. Forage samples were harvested at PHIs of 9-10 days, while grain and stover samples were harvested following the second application at PHIs of 27-35 days. An adjuvant was included in the spray mixtures at 6 of the 9 sites. At the decline trial, forage and grain/stover samples were harvested at PHIs of 0, 5, 10, 15 and 20 days, and 20, 25, 30, 35 and 40 days, respectively.

Residue decline data show that residues of bixafen and total bixafen in forage, grain and stover samples, and residues of the desmethyl metabolite in grain and stover, decreased with longer PHIs. Residues of the desmethyl metabolite in forage remained similar over longer PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Forage	224-230	9-10	9	1.26	0.359	0.558	0.371
Grain		27-35	9	1.78	0.246	0.438	0.555
Stover			9	3.83	0.720	1.194	1.15
Bixafen-desmethyl							
Forage	224-230	9-10	9	0.777	0.17	0.259	0.232
Grain		27-35	9	0.112	0.061	0.686	0.030
Stover			9	1.45	0.278	0.471	0.438
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Forage	224-230	9-10	9	1.6	0.8	0.83	0.5
Grain		27-35	9	1.9	0.28	0.5	0.58
Stover			9	4.4	1.4	1.6	1.2

HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON FIELD CORN | **PMRA No. 2643801**

Field trials were conducted on field corn in 2014 in Canada and the United States in North America Growing Regions 1 (1 trial), 2 (1 trial), 5 (12 trials), 6 (1 trial) and 11 (1 trial) for a total of 16 trials. An emulsifiable concentrate formulation of bixafen was applied twice as foliar broadcast sprays at rates of 108.4-117.8 g a.i./ha/application for seasonal application rates of 217-230 g a.i./ha. The first application was applied 47 to 68 days prior to field corn harvest and the last application occurred 27-32 days prior to harvest. Field corn forage was harvested 8-11 days after the first treatment, while field corn grain and stover were harvested 27-32 days after the last treatment. An adjuvant was included in the spray mixtures at 12 of the 16 sites. At the decline trials, forage samples were collected at 0, 5, 10, 14-15, and 20 days after the first treatment and grain and stover samples were harvested at 19-20, 24-25, 30-31, 33-35 and 40 days after the last treatment.

Residue decline data show that in corn forage, residues of bixafen and total bixafen declined with increasing PHIs and residues of the desmethyl metabolite remained relatively constant. In field corn stover, all residues remained at a similar level with increasing PHIs. Residue decline behavior could not be evaluated in field corn grain given that all residues were non quantifiable at all PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Field Corn Forage	217-230	9-11	14*	1.11	0.374	0.442	0.293
Field Corn Grain		27-32	16	<0.01	<0.01	<0.01	NA
Field Corn Stover			16	2.45	1.785	1.614	0.798
Bixafen-desmethyl							
Field Corn Forage	217-230	9-11	14*	0.126	0.055	0.0709	0.0387
Field Corn Grain		27-32	16	<0.01	<0.01	<0.01	NA
Field Corn Stover			16	0.378	0.183	0.188	0.105
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Field Corn Forage	217-230	9-11	14*	1.20	0.383	0.46	0.32
Field Corn Grain		27-32	16	<0.02	<0.02	<0.02	NA
Field Corn Stover			16	3.21	2.1	1.79	0.85

HAFT = Highest Average Field Trial, SD = Standard Deviation, NA = not applicable.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.
*Forage samples at two of the 16 trial sites were inadvertently collected at later PHIs of 29 and 30 days; as such, the residue values for these sites were not included in the summary table above.

CROP FIELD TRIALS AND RESIDUE DECLINE ON SWEET CORN	PMRA No. 2643793

Field trials were conducted on sweet corn in 2014 in Canada and the United States in North America Growing Regions 1 (1 trial), 2 (1 trial), 3 (1 trial), 5 (4 trials), 10 (1 trial), 11 (2 trials) and 12 (1 trial) for a total of 11 trials. An emulsifiable concentrate formulation of bixafen was applied twice as foliar broadcast sprays at rates of 109.4-115.2 g a.i./ha/application for seasonal application rates of 222.9-229.5 g a.i./ha. The first and second applications were applied approximately 48-54 and 29-32 days prior to normal fresh sweet corn harvest, respectively. Sweet corn forage, kernels plus cob with husk removed (K+CWHR) and stover samples were collected at PHIs of 29-32 days following the second application. An adjuvant was included in the spray mixtures at 8 of the 11 sites. At the decline trials, forage, K+CWHR and stover samples were collected at 18, 25, 30, 35 and 39 days after the last treatment.

Residue decline data show that in sweet corn forage, all residues tended to remain the same with increasing PHIs. In sweet corn stover, all residues declined over longer PHIs. Residue decline behavior could not be evaluated in K+CWHR given that all residues were non quantifiable at all PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Forage	222.9-229.5	29-32	11	0.352	0.145	0.159	0.101
K+CWHR			11	<0.01	<0.01	<0.01	NA
Stover			11	0.639	0.237	0.282	0.197
Bixafen-desmethyl							
Forage	222.9-229.5	29-32	11	0.142	0.0392	0.0516	0.041
K+CWHR			11	<0.01	<0.01	<0.01	NA
Stover			11	0.207	0.0695	0.081	0.06
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Forage	222.9-229.5	29-32	11	0.45	0.15	0.20	0.13
K+CWHR			11	<0.02	<0.02	<0.02	NA
Stover			11	0.79	0.33	0.36	0.224

HAFT = Highest Average Field Trial, SD = Standard Deviation, NA = not applicable.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON RADISH	PMRA No. 2643800

Field trials were conducted on radish in the 2014 and 2015 season in Canada and the United States in North America Growing Regions 1 (1 trial), 3 (2 trials), 5 (2 trials) and 10 (1 trial) for a total of 6 trials. An emulsifiable concentrate formulation of bixafen was applied four times as foliar broadcast sprays at rates of 55.3-57.8 g a.i./ha/application for seasonal application rates of 224-229 g a.i./ha. All applications were made at 4-7 day re-treatment intervals. Radish roots and tops were harvested 6-8 days after the last application. For the decline trial, radishes (roots and tops) were harvested immediately prior to the last application (-0 days) and immediately after the last application (0), and 3, 6, 10, and 13 days following the last application.

For radish samples collected from the decline trial, bixafen and total bixafen residues remained relatively constant in the radish roots but residues of the desmethyl metabolite increased slightly in this same matrix with increasing PHIs; in radish tops, residues of bixafen, the desmethyl metabolite and total residues showed an overall decreasing trend with increasing PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Radish Roots	224-229	6-8	6	0.096	0.062	0.057	0.029
Radish Tops			6	1.26	0.905	0.857	0.389
Bixafen-desmethyl							
Radish Roots	224-229	6-8	6	0.017	0.012	0.013	0.003
Radish Tops			6	0.276	0.118	0.156	0.075

Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Radish Roots	224-229	6-8	6	0.111	0.075	0.069	0.030
Radish Tops			6	1.53	1.04	1.012	0.450

HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON CARROTS **PMRA No. 2643799**

Field trials were conducted on carrots in the 2014 season in Canada and the United States in North America Growing Regions 1 (1 trial), 3 (1 trial), 5 (4 trials), 6 (1 trial) and 10 (3 trials) for a total of 10 trials. An emulsifiable concentrate formulation of bixafen was applied four times as foliar broadcast sprays at rates of 54.56-61.42 g a.i./ha/application for seasonal application rates of 225.06-235.79 g a.i./ha. Adjuvants were included in the spray mixtures at 7 of the 10 trial sites. All applications were made at 4-7 day re-treatment intervals, with the first and second applications made 21-24 days and 16-19 days, respectively, prior to normal carrot root harvest, and the third and fourth applications made 11-14 days and 6-9 days, respectively, prior to normal harvest. Carrot roots were harvested 6-9 days after the last application. For the decline trial, carrot root samples were collected immediately prior to the last application (-0 days), immediately after the last application (0 days) and 4, 7, 11 and 14 days following the last treatment.

Residue decline data show that bixafen and total bixafen residues in carrot roots increased with increasing PHIs. Residues of the desmethyl metabolite were all <LOQ at all PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Carrot Root	225.06-235.79	6-9	10	0.171	0.046	0.0551	0.050
Bixafen-desmethyl							
Carrot Root	225.06-235.79	6-9	10	<0.01	<0.01	<0.01	NA
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Carrot Root	225.06-235.79	6-9	10	0.180	0.055	0.065	0.05

HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON SUGAR BEETS **PMRA No. 2643798**

Field trials were conducted on sugar beets in the 2014 season in Canada and the United States in North America Growing Regions 5 (5 trials), 7 (1 trial), 7A (4 trials), 8 (1 trial), 9 (1 trial) and 10 (1 trial) for a total of 13 trials. An emulsifiable concentrate formulation of bixafen was applied four times as foliar broadcast sprays at rates of 55.2-58.3 g a.i./ha/application for seasonal application rates of 223-229 g a.i./ha. Adjuvants were included in the spray mixtures at 9 of the 13 trial sites. The first application was made 27-29 days prior to sugar beet harvest and subsequent applications were made at 6-8 day intervals with the last application occurring 6-8 days prior to harvest of mature sugar beets (6-8 day PHIs). For the decline trial, sugar beet root and leaf samples were collected immediately prior to the last application (-0 days), immediately after the last application (0 days) and 4, 7, 10 and 14 days following the last treatment.

Residue decline data show that bixafen and total bixafen residues remained relatively constant in sugar beet roots and tops, whereas bixafen-desmethyl increased at longer PHIs in tops, and were non quantifiable over all PHIs in roots.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Root	223-229	6-8	13	0.057	0.030	0.031	0.015
Tops (leaves)			13	3.2	1.1	1.48	0.808

Bixafen-desmethyl							
Root	223-229	6-8	13	<0.01	<0.01	<0.01	NA
Tops (leaves)			13	0.061	0.011	0.022	0.017
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Root	223-229	6-8	13	0.068	0.040	0.041	0.015
Tops (leaves)			13	3.2	1.2	1.5	0.82

HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON POTATOES **PMRA No. 2643797**

Field trials were conducted on potatoes in the 2014 and 2015 seasons in Canada and the United States in North America Growing Regions 1 (5 trials), 2 (1 trial), 3 (1 trial), 5 (4 trials), 9 (1 trial), 10 (1 trial), 11 (6 trials) and 14 (1 trial) for a total of 20 trials. An emulsifiable concentrate formulation of bixafen was applied four times as foliar broadcast sprays at rates of 53.7-62.2 g a.i./ha/application for seasonal application rates of 223.5-232.6 g a.i./ha. Adjuvants were included in the spray mixtures at 15 of the 20 trial sites. The first application was applied 26-30 days prior to potato harvest with subsequent applications made at 5-9 day intervals with the last application occurring 6-8 days prior to harvest (in other words, 6-8 day PHIs for potato tuber samples). For the two decline trials, potato tuber samples were collected immediately prior to the fourth application (-0 days), and at 0, 2-4, 7, 10-11 and 14 days after the last treatment.

Decline behavior could not be determined in potato tubers given that all residues were non quantifiable at all tested PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Potato Tubers	223.5-232.6	6-8	20	0.0105	<0.01	0.01	0.0001
Bixafen-desmethyl							
Potato Tubers	223.5-232.6	6-8	20	<0.01	<0.01	<0.01	NA
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Potato Tubers	223.5-232.6	6-8	20	0.02	<0.02	<0.02	0.0001

HAFT = Highest Average Field Trial, SD = Standard Deviation NA = not applicable.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON SOYBEANS **PMRA No. 2643795**

Field trials were conducted on soybeans in the 2014 season in Canada and the United States in North America Growing Regions 2 (2 trials), 4 (3 trials) and 5 (16 trials) for a total of 21 trials. An emulsifiable concentrate formulation of bixafen was applied twice as foliar broadcast sprays at rates of 108-121 g a.i./ha/application for seasonal application rates of 219-233 g a.i./ha. Adjuvants were included in the spray mixtures at 15 of the 21 trial sites. The first application was applied 30-39 days prior to normal soybean harvest, with the subsequent applications made at 11-14 day retreatment intervals (RTIs) with mature soybean seed samples harvested at 18-27 day PHIs. For the two decline trials, soybean seed samples were harvested 9, 14-15, 20, 25-26, and 28-30 days after the last treatment.

In the decline trials, at one site, residues of bixafen and bixafen-desmethyl were <LOQ at all sampling intervals; at the second site, quantifiable residues of bixafen and total bixafen observed at the earliest 9-day PHI were non quantifiable at the subsequent and longer PHIs. Decline behavior of the M44 metabolite could not be determined in soybean seed given that all residues were non quantifiable at all tested PHIs.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Soybean seed	219-233	18-27	21	0.029	<0.01	<0.013	NA
Bixafen-desmethyl							
Soybean seed	219-233	18-27	21	<0.01	<0.01	<0.01	NA

Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Soybean seed	219-233	18-27	21	0.034	<0.02	0.022	0.0051
M44							
Soybean seed	219-233	18-27	21	<0.01	<0.01	<0.01	NA

HAFT = Highest Average Field Trial, SD = Standard Deviation NA = not applicable.
Values based on per-trial averages. For computation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS AND RESIDUE DECLINE ON PEANUTS — **PMRA No. 2643794**

Field trials were conducted on peanuts in the 2014 season in the United States in North America Growing Regions 2 (8 trials), 3 (1 trial), 5 (3 trials), 6 (2 trials) and 8 (1 trial) for a total of 15 trials. An emulsifiable concentrate formulation of bixafen was applied four times as foliar broadcast sprays at rates of 54-58 g a.i./ha/application, at 11-14 day RTIs, for total seasonal application rates of 219.7 – 229.1 g a.i./ha, with peanut nutmeat and hay harvested at 12-16 day PHIs. Adjuvants were included in the spray mixtures at 11 of the 15 trial sites. Residue decline behavior was evaluated at a single trial site where samples were harvested prior to the fourth application (-0 days), immediately following the fourth application (day 0), and at 6, 14, 21, and 28 days after the fourth and final application.

In the decline trial, in peanut hay, total bixafen residues demonstrated a declining trend with longer PHIs. There were no quantifiable residues of M44 at any sampling interval in hay. No quantifiable residues of bixafen, bixafen-desmethyl or M44 were observed in peanut nutmeats at any sampling interval.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)				
			n	HAFT	Median	Mean	SD
Bixafen							
Nutmeat	219.7 – 229.1	12-16	15	<0.01	<0.01	<0.01	NA
Hay				4.42	2.52	2.4	1.36
Bixafen-desmethyl							
Nutmeat	219.7 – 229.1	12-16	15	<0.01	<0.01	<0.01	NA
Hay				1.04	0.399	0.499	0.27
Total Bixafen Residues (Bixafen + bixafen-desmethyl, expressed as bixafen equivalents)							
Nutmeat	219.7 – 229.1	12-16	15	<0.02	<0.02	<0.02	NA
Hay				5.3	3.0	2.9	1.6
M44							
Nutmeat	219.7 – 229.1	12-16	15	<0.01	<0.01	<0.01	NA

RESIDUE DATA IN ROTATIONAL CROPS - RADISH, LETTUCE AND WINTER WHEAT — **PMRA No. 2643787, 2643789, 2643788**

Study 1: Three European field trials for bixafen uptake into rotational crops turnip, lettuce and wheat, were conducted during the 2006 growing season in Germany. At each trial location for the 30-day plant-back interval (PBI), an emulsifiable concentrate formulation of bixafen was applied to bare soil at the rate of 281 g ai/ha followed by incorporation (maximum 8 cm depth) to avoid photo-degradation. At each trial location for the other plant-back intervals, bixafen was applied as two foliar applications at the rates of 156 g ai/ha + 125 g ai/ha, with a 14-day re-treatment interval (RTI), for a total of 281 g ai/ha to winter barley as the primary crop. An adjuvant was not added to the spray mixture. Mature barley was harvested 296 days after planting and threshed, with the straw ploughed under in order to capture all possible residues. Turnip and lettuce were seeded into the treated plots at PBIs of 27-30 days, 61 days and 314-328 days, and winter or spring wheat were seeded into treated plots at PBIs of 28, 140 and 300 days. Crops were harvested at early (14 days prior to normal harvest for turnip [roots and tops] and lettuce or at BBCH 29-30 – green material – for wheat) and at normal harvest maturity (BBCH 49 for turnip [roots and tops] and lettuce and BBCH 89 for wheat grain and straw).

The results from this study indicated that residues of bixafen and the desmethyl metabolite were non quantifiable (i.e., <LOQ) in all crop matrices, at all PBIs, with the exception of bixafen residues of 0.05 ppm in one lettuce sample from the 30-day PBI plot.

Study 2: Three European field trials for bixafen uptake into rotational crops carrots, lettuce and wheat, were conducted in Spain during the 2006 growing season. At each trial location, for the 32-day plant-back interval, an emulsifiable concentrate formulation of bixafen was applied to bare soil at the rate of 281 g ai/ha followed by incorporation (maximum 8 cm depth) to avoid photo-degradation. At each trial location for the other plant-back intervals, bixafen was applied as two foliar applications at the rates of 156 g ai/ha + 125 g ai/ha, with a 15-day RTI, for a total of 281 g ai/ha to winter barley as the primary crop. An adjuvant was not added to any spray mixture. Mature barley was harvested 185 days after planting and threshed, with the straw was ploughed under in order to capture all possible residues. Carrots and lettuce were seeded into the treated plots at PBIs of 32, 70 and 302 days. Winter wheat was seeded into treated plots at PBIs of 32, 184 and 278 days. Crops were harvested at early harvest (14 days prior to normal harvest for carrot [tops and rootrs]

and lettuce or at BBCH 29-30 – green material – for wheat) and at normal harvest maturity (BBCH 49 for carrot and lettuce and BBCH 89 for wheat grain and straw).

The results from this study indicated that residues of bixafen and the desmethyl metabolite were non quantifiable (in other words, <LOQ) in all crop matrices, at all PBIs, with the exception of bixafen-desmethyl residues of 0.02 ppm in one wheat straw sample from the 32-day PBI plot.

Study 3: Three European field trials for bixafen uptake into rotational crops turnip, lettuce and wheat were conducted Northern France during the 2006 growing season. At each trial location, for the 30-PBI, an emulsifiable concentrate formulation of bixafen was applied to bare soil at the rate of 281 g ai/ha followed by incorporation (maximum 8 cm depth) to avoid photo-degradation. At each trial location for the other PBIs, bixafen was applied as two foliar applications at the rate of 156 g ai/ha + 125 g ai/ha, with a 15-day PBI, for a total of 281 g ai/ha to winter barley as the primary crop. An adjuvant was not added to the spray mixture. Mature barley was harvested 279 days after planting and threshed, with the straw ploughed under in order to capture all possible residues. Turnip and lettuce were seeded into treated plots at PBIs of 30, 60 and 298-331 days. Wheat was seeded into treated plots at PBIs of 30, 120 and 298 days. Crops were harvested at early harvest (14 days prior to normal harvest for turnip [roots and tops] and lettuce or at BBCH 30 – green material – for wheat) and at normal harvest maturity (BBCH 49 for turnip [roots and tops] and lettuce and BBCH 89 for wheat grain and straw).

The results from this study indicated that residues of bixafen and the desmethyl metabolite were non quantifiable (i.e., <LOQ) in all crop matrices, at all PBIs.

Based on the results of the field accumulation studies, a plant-back interval of 0-days for the proposed crops wheat, oats, barley and soybeans, and of 30 days for all non-labelled crops is required.

PROCESSED FOOD AND FEED - WHEAT			**PMRA No.2643803**
Test Site	One trial in North America Growing Region 5.		
Treatment	Two broadcast foliar applications made 34 days apart at rates of 553.3 and 573.7 g a.i./ha per application, including an adjuvant in both spray application mixtures.		
Total Rate	1.127 kg a.i./ha		
End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)		
Preharvest interval	30 days after the last application		
Processed Commodity:	**Average Processing Factor (Analyte)**		
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**
Aspirated grain fractions	206x	48x	176x
Bran	0.8x	1.1x	0.88x
Flour	0.12x	0.52x	0.23x
Middlings	0.18x	0.52x	0.29x
Shorts	0.18x	0.52x	0.39x
Germ	0.57x	1.4x	0.72x

PROCESSED FOOD AND FEED - BARLEY			**PMRA No. 2643791**
Test Site	Four trials in Europe (1 trial in Sweden, 2 in Germany and 1 in Northern France).		
Treatment	Two foliar applications at 250 g a.i./ha per application with 14-29 day RTIs.		
Total Rate	500 g a.i./ha		
End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)		
Preharvest interval	35-46 days after the last application.		
Processed Commodity:	**Average Processing Factor (Analyte)**		
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**
Malt	0.86x	2x	0.8x
Malt culms	0.72x	2x	0.8x
Beer	<0.05x	<0.50x	0.2x
Brewer's yeast	0.18x	<0.50x	0.3x
Brewer's grain	0.92x	1.50x	1.1x
Hops draff	0.67x	1.0x	0.7x
Pearl barley	0.21x	0.50x	0.3x
Pearl barley rub-off	4.11x	3x	4x

PROCESSED FOOD AND FEED - SOYBEANS		**PMRA No.2643795**
Test Site	One trial site in North America growing region 5.	
Treatment	Two foliar broadcast spray applications applied with a 34-day RTI at rates of 556-	

	574 g a.i./ha per application. An adjuvant was included in both spray applications.			
Total Rate	1.13 kg a.i/ha			
End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)			
Preharvest interval	34 days following the last application			
Processed Commodity:	**Average Processing Factor (Analyte)**			
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**	**M44**
Aspirated grain fractions	308x	2.6x	253x	1.1x
Refined oil	0.34x	NC	<0.46x	NC
Hulls	2.4x	NC	2.2x	NC
Meal	<0.22x	NC	<0.36x	NC
NC = not calculated as residues in both the RAC and processed commodity were each <0.01 ppm.				
PROCESSED FOOD AND FEED – SUGAR BEETS			**PMRA No.2643798**	
Test Site	A single trial site located in North America Region 5.			
Treatment	Four foliar broadcast spray applications with RTIs of 6-8 days, at rates of 279-287 g a.i/ha per application. An adjuvant was included in all spray applications.			
Total Rate	1.128 kg a.i/ha			
End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)			
Preharvest interval	6 days			
Processed Commodity:	**Average Processing Factor (Analyte)**			
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**	
Refined sugar	0.28x	<0.72x	0.31x	
Dried pulp	1.1x	10.7x	10.9x	
Molasses	0.83x	0.72x	0.82x	
PROCESSED FOOD AND FEED – POTATOES			**PMRA No.2643797**	
Test Site	A single processing trial in North America region 11.			
Treatment	Four foliar broadcast spray applications at rates of 272.1-284.6 g a.i./ha per application at 6-8 day intervals. All spray applications contained an adjuvant.			
Total Rate	1.12 kg a.i./ha			
End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)			
Preharvest interval	7 days			
Processed Commodity:	**Average Processing Factor (Analyte)**			
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**	
Wet peel	1.2x	NC	1.1x	
Granules/flakes	NC	NC	NC	
Chips	NC	NC	NC	
NC = not calculated as residues in both the RAC and processed commodity were each <0.01 ppm.				
PROCESSED FOOD AND FEED – SORGHUM			**PMRA No.2643802**	
Test Site	One trial with two treated plots in North America Region 8.			
Treatment	Two foliar spray applications at 560.5-562.7 g a.i/ha per application at 20-21 day RTIs. An adjuvant was included in both spray applications.			
Total Rate	1.121-1.143 kg a.i./ha			
End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)			
Preharvest interval	30-31 days			
Processed Commodity:	**Average Processing Factor (Analyte)**			
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**	
Aspirated grain fractions	26x	18.2x	26x	
Syrup	0.17x	0.037x	0.15x	
PROCESSED FOOD AND FEED – FIELD CORN			**PMRA No.2643801**	
Test Site	One trial site located in North America Region 5.			
Treatment	Two foliar broadcast sprays at rates of 558-562 g a.i/ha with a 20-day RTI. An adjuvant was included in both spray mixtures.			
Total Rate	1.120 kg a.i/ha			

End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)		
Preharvest interval	27 days		
Processed Commodity:	**Average Processing Factor (Analyte)**		
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**
AGF	153x	2.3x	81x
Starch, grits, germ, refined oil (dry milling)	0.9x	NC	0.9x
Refined oil (wet milling)	1.8x	NC	1.4x
Flour, meal	1.4x	NC	1.2x
NC = not calculated as residues in both the RAC and processed commodity were each <0.01 ppm.			

PROCESSED FOOD AND FEED – PEANUT				**PMRA No. 2643794**
Test Site	One trial in North America Region 2.			
Treatment	Four foliar broadcast sprays at rates of 285.3-286.0 g a.i/ha per application with 13-15 day RTIs. No adjuvants were added to the spray mixtures.			
Total Rate	1.143 kg a.i/ha			
End-use product/formulation	EC 125 emulsifiable concentrate formulation (guarantee - 125 g/L bixafen)			
Preharvest interval	14 days			
Processed Commodity:	**Average Processing Factor (Analyte)**			
	Bixafen	**Bixafen-desmethyl**	**Total Bixafen (bixafen + bixafen-desmethyl)**	**M44**
Meal	0.6x	NC	0.7x	NC
Refined oil	2.2x	NC	1.8x	NC
NC = not calculated as residues in both the RAC and processed commodity were each <0.01 ppm.				

LIVESTOCK FEEDING – Dairy cattle	**PMRA No.2642761**
Lactating dairy cows were administered bixafen at dose levels of 5.7, 16.0 and 54.3 ppm in the feed for 29 consecutive days. The dose levels of 5.7, 16.0 and 54.3 represent 3x, 9x and 30x, respectively, the estimated more balanced diet (MBD) to beef cattle and 1x, 2.8x and 9.4x, respectively, for dairy cattle.	

Commodity	**Feeding Level (ppm)**	**Highest Residues* (ppm)**	**MBD (ppm)**
			Beef/Dairy
Whole milk	5.7	0.046	5.76
Fat		0.209	
Liver		0.69	
Kidney		0.152	
Muscle		0.065	

*Total bixafen residues = the sum of bixafen plus the metabolite bixafen-desmethyl, converted to and expressed as bixafen equivalents (the residue definition in livestock matrices). Given that the feeding level in the study corresponds to the dietary burden for dairy cattle, it was not necessary to calculate anticipated residues.

LIVESTOCK FEEDING – Laying hens	**PMRA No.2642760**
Laying hens were administered bixafen at dose levels of 1.38, 4.34 and 15.0 ppm in the feed for 28 consecutive days. The dose levels of 1.38, 4.34 and 15.0 ppm represent 13.8x, 43.4x and 150x, respectively, the estimated MBD to poultry.	

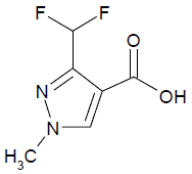
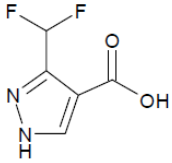
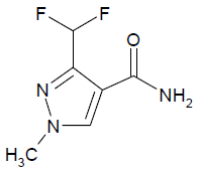
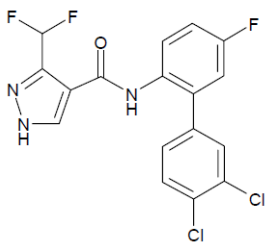
Commodity	**Feeding Level (ppm)**	**Highest Residues (ppm)**	**MBD (ppm)**	**Anticipated Residue at MBD (ppm)**
Whole Egg	15.0	0.23	0.1	0.002
Fat		0.09		0.002
Liver		0.05		0.002
Muscle		<0.02		NC
NC = not calculated since residues were non quantifiable.				

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

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT Primary: Soybeans, wheat and potatoes Rotational: Wheat, Swiss chard, turnip		Bixafen	
RESIDUE DEFINITION FOR RISK ASSESSMENT Primary: Soybeans, wheat and potatoes Rotational: Wheat, Swiss chard, turnip		Bixafen and bixafen-desmethyl	
METABOLIC PROFILE IN DIVERSE CROPS		Similar in primary crops (soybeans, wheat and potatoes) and rotational crops (wheat, Swiss chard, turnip).	
ANIMAL STUDIES			
ANIMALS		**Ruminant and Poultry**	
RESIDUE DEFINITION FOR ENFORCEMENT		Bixafen and bixafen-desmethyl	
RESIDUE DEFINITION FOR RISK ASSESSMENT			
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)		The metabolic profile is similar in all three animals.	
FAT SOLUBLE RESIDUE		Yes	
DIETARY RISK FROM FOOD AND WATER			
Basic chronic dietary exposure analysis **ADI = 0.02 mg/kg bw/day** **Estimated chronic drinking water concentration = 1.5 µg/L**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
	All infants < 1 year	18.5	19.0
	Children 1–2 years	32.3	32.5
	Children 3 to 5 years	26.8	26.9
	Children 6–12 years	18.1	18.2
	Youth 13–19 years	11.0	11.1
	Adults 20–49 years	8.6	8.7
	Adults 50+ years	6.6	6.8
	Females 13-49 years	8.0	8.2
	Total population	10.7	10.8
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.8 mg/kg bw** **Estimated acute drinking water concentration = 2.7 µg/L**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Water**
	All infants < 1 year	12.9	13.2
	Children 1–2 years	14.4	14.4
	Children 3 to 5 years	12.0	12.1

	Children 6–12 years	8.9	9.0
	Youth 13–19 years	5.9	6.0
	Adults 20–49 years	4.6	4.7
	Adults 50+ years	3.3	3.4
	Females 13-49 years	4.4	4.4
	Total population	7.3	7.4

Table 7 Transformation Products of the Active Substance Bixafen Relevant to the Environment

Code and Chemical name	Chemical structure	Study	Findings
M42 Bixafen-pyrazole-4-carboxylic acid		Anaerobic soil (PMRA No. 2642687)	• Day 0 to Day 146 not detected; max 9.0% M42 (single detection) on Day 210 (Day 181 of anaerobic incubation)
M44 & M45 Bixafen-desmethyl-pyrazole-4-carboxylic acid (2 tautomers)		Aerobic soil (PMRA No. 2642684)	• <0.1 – 2.9% extracted M44/45, gradual increasing trend starting Day 14 for all soils
M43 Bixafen-pyrazole-4-carboxamide		Metabolism of [pyrazole-5-14C]bixafen in confined rotational crops (PMRA No. 2642763)	• M43 was described by the applicant as a potential soil metabolite that was taken up by the plants and found at concentrations in plants >10%
M21 bixafen-desmethyl		Degradation in Soil Under Rotational Crops (PMRA No. 2642685)	• Max 2.7% extracted M21 at the end of the study (Day 418; dichlorophenyl label); gradual increasing trend throughout study
		BCF in Fish (PMRA No. 2642712)	• 14.9% and 22.5% of the ^{14}C-residues on Day 14 in viscera and edible extracts, respectively

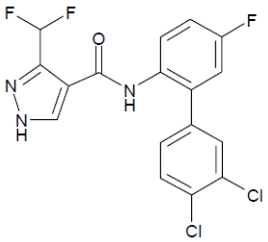
Code and Chemical name	Chemical structure	Study	Findings
Glucuronidated Bixafen-desmethyl	 + glucuronic acid, - H_2O	BCF in Fish (PMRA No. 264271)	• 15.1% and 14.9% of the ^{14}C-residues on Days 7 and 14, respectively, in viscera; none found in edibles
Anaerobic unknown		Anaerobic soil (PMRA No. 2642687)	• Single detection of 2.3% on Day-119 (Day-90 of anaerobic incubation; pyrazole label)
Non-extracted residues		Aerobic soil (PMRA No. 2642684)	• 7.5 – 12.0% non-extracted ^{14}C-residues after 120 days • Increasing trends in most cases. NERs were consistently higher for the dichlorophenyl label.
		Anaerobic soil (PMRA No. 2642687)	• 1.4 – 10.5% non-extracted ^{14}C-residues after 210 days (118 days of anaerobic incubation) • Increasing trend
		Degradation in Soil Under Rotational Crops (PMRA No. 2642685)	• Mean non-extracted ^{14}C-residues increased from 5.1% at Day-30 to 16.2% at the end of the study (Day 418)
		Total sediment system (water + sediment) (PMRA No. 2642813)	• Max 5% non-extracted ^{14}C-residues in sediment after 90 days (dichlorophenyl label in River Roding system) • Increasing trends

Table 8 Fate and Behaviour of Bixafen in the Terrestrial Environment

Property	Test substance	Value	Transformation products	Comments	PMRA No.
Abiotic transformation					
Hydrolysis	Stable to hydrolysis at environmentally relevant pH values.				
Phototransformation on soil	Bixafen parent 2 labels: [pyrazole-5-^{14}C]-bixafen [dichlorophenyl-UL-^{14}C]-bixafen	DT_{50} = 109 days (SFO; continuous irradiation)	No major transformation products. Multiple unknown minor transformation products, with the largest individual peak accounting for 1.4% AR (day 8 sample). The maximum	Direct phototransformation on soil surfaces is not a major route of transformation for bixafen in the environment.	2642683

Property	Test substance	Value	Transformation products	Comments	PMRA No.
			sum of unidentified extracted radioactivity was 4.4% AR.		
Phototransformation in air	Bixafen is not expected to be volatile under field conditions based on vapour pressure and Henry's law constant. A phototransformation study in air is not required.				
Biotransformation					
Biotransformation in aerobic soil	Bixafen parent 2 labels: [pyrazole-5-^{14}C]-bixafen & [dichlorophenyl-UL-^{14}C]-bixafen 4 European soils Study duration: 120 days	DT_{50} = 963 - 1773 days (SFO)	<0.1 – 2.9% extracted M44/45, gradual increasing trend starting Day 14 for all soils	Parent bixafen is persistent in aerobic soil. Biotransformation in aerobic soil is not an important route of dissipation for bixafen.	2642684
Biotransformation in anaerobic soil	Bixafen parent 2 labels: [pyrazole-5-^{14}C]-bixafen & [dichlorophenyl-UL-^{14}C]-bixafen 1 European soil Study duration: 29 days (aerobic conditions) + 181 days (anaerobic conditions)	DT_{50} = 819 days (SFO)	Maximum 9.0% M42 (single detection) on Day 210 (Day 181 of anaerobic incubation). Day 0 to Day 146 not detected.	Parent bixafen is persistent in anaerobic soil. Biotransformation in anaerobic soil is not an important route of dissipation for bixafen.	2642687
Mobility					
Adsorption / desorption in soil	Bixafen parent 1 label: [dichlorophenyl-UL-14C]-bixafen	K_{OC} = 3858 to 5812 mL/g K_d = 50.16 to 128.15 mL/g	N/A	Bixafen is classified as having a slight potential for mobility in soil.	2642679
Soil leaching	No soil leaching study with bixafen was submitted and none is required.				
Volatilization	A volatilization study was not submitted nor required for the review of bixafen. The vapour pressure of bixafen is 1.1×10^{-7} Pa at 25°C and the calculated Henry´s constant is 9.177×10^{-10} atm·m3/mol in water at 25°C. Bixafen not expected to volatilize from water, moist soil, or vegetation.				
Field studies					
Field dissipation (Alberta)	Bixafen parent Bare ground site	DT_{50} = 550 days (SFO; Plot T-1)	Not tracked.	Bixafen is likely to accumulate in soil. Carryover into next	2642692

Property	Test substance	Value	Transformation products	Comments	PMRA No.
	(Ecoregion 9.2) Plot T-1: 3 applications (75 g a.i./ha each) within a 21-day period, at 10- and 11-day intervals. Plot T-2: same amount of bixafen parent as Plot T-1, but as 1 application of the full amount.	DT_{50} = 748 days (SFO; Plot T-2)		growing season was 62% (Plot T-1; April, or day- 266) and 82% (Plot T-2; day-274). Bixafen does not appear to be inherently susceptible to leaching.	
Field dissipation (New Jersey)	Bixafen parent Bare ground site (Ecoregion 8.3) Plot T-1: 3 applications (75 g a.i./ha each) within a 21-day period, at 10-day intervals. Plot T-2: same amount of bixafen parent as Plot T-1, but as 1 application of the full amount.	Slow $t_{1/2}$ = 300 days (DFOP; Plot T-1) t_R = 110 days (IORE; Plot T-2)	Not tracked.	Bixafen is likely to accumulate in soil. Carryover into next growing season was 14.5% (Plot T-1; April, day-251) and 19.4% (Plot T-2; day-259). Bixafen does not appear to be inherently susceptible to leaching.	2642691
Field leaching	No field leaching study with bixafen was submitted and none is required.				

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

Table 9 Fate and Behaviour in the Aquatic Environment

Study type	Test material	Value	Transformation products	Comments	PMRA No.
Abiotic transformation					
Hydrolysis	Bixafen parent One label: [pyrazole-5-^{14}C]-bixafen	pH 4, 7, and 9: stable to hydrolysis	No transformation products.	Hydrolysis is not expected to be an important route of dissipation for bixafen in the environment.	2642680
Phototransformation in water	Bixafen parent 1 label: [dichlorophenyl-UL-14C]-bixafen	DT_{50} = 81 days (SFO)	No major transformation products. No major transformation products (> 10% AR) were formed. Multiple unknown minor degradates were observed, with the largest individual peak accounting for 1.5% AR (polar radioactivity detected by HPLC at day 8). The maximum of total unidentified radioactivity was 4.6% AR and was reached at day 8.	Direct phototransformation in water is not a major route of transformation for bixafen in the environment.	2642681
Biotransformation					
Biotransformation in aerobic water systems	Bixafen parent 2 labels: [pyrazole-5-^{14}C]-bixafen & [dichlorophenyl-UL-^{14}C]-bixafen 2 water-sediment systems (Clayton, US and River Roding, UK) Study duration: 118 days	Total system only: DT_{50} = 4198 to 6793 days (Clayton, US; SFO) DT_{50} = 1144 to 2357 days (River Roding, UK; SFO)	One minor component was observed at a maximum level of 1.4% in the water of system River Roding at day 14, pyrazole label, and to ca 1.2% in the corresponding sediment extracts at day 59.	Bixafen dissipated steadily from the water phase to the sediment phase. Total applied radioactivity declined from ca. 93-98% in the water phase at time zero to ca.7-8% at day 118 for the system Clayton, and from 93-95% to 10-17% for the system River Roding. Conversely, the radioactivity detected in the sediment increased from zero at time zero to 74-89% at the end of the study. In all cases the radioactivity consisted largely of the parent bixafen.	2642813

				Parent bixafen is persistent in aerobic water systems. Biotransformation aerobic water systems is not an important route of dissipation for bixafen.	
Biotransformation in anaerobic water systems	The applicant requested a data waiver for conducting an anaerobic aquatic metabolism study with bixafen based on slow degradation of bixafen in anaerobic soil and aerobic aquatic environments. Half-lives calculated from these studies indicate the parent bixafen is persistent in the environment and will rapidly dissipate to the sediment in the aquatic environment. No major transformation products (>10% AR) were measured in these studies. This waiver request was considered acceptable to the PMRA.				
Partitioning					
Adsorption / desorption in sediment	Not required as an acceptable adsorption/desorption study in soil was submitted.				
Field studies					
Field dissipation	No aquatic field dissipation study with bixafen was submitted and none is required.				
Bioconcentration / bioaccumulation					
Bioconcentration in fish	Bixafen parent 1 label at 2 concentrations : 0.1 and 1 µg [Dichlorophenyl-UL-14C]-bixafen / L Bluegill sunfish (*Lepomis macrochirus*) Study duration: 28 days (exposure) + 14 days (depuration)	$BCF_{k,g,l}$ = 381 (high concentration) $BCF_{k,g,l}$ = 454 (low concentration)	Characterization of transformation products in fish and water was performed during a 14-day parallel study. The main metabolic reactions of Bixafen in fish were: • Demethylation of the pyrazole moiety leading to M21 (Bixafen-desmethyl) (14.9% and 22.5% of the TRR on Day 14 in viscera and edible extracts, respectively) • Glucuronidation of Bixafen-desmethyl (15.1% and 14.9% of the TRR on Days 7 and 14 in viscera, respectively; none found in edibles) • An unknown compound was also observed accounting for 1.7% and 1.6% of the TRR in extracts from viscera on Days 7 and 14, respectively.	Bixafen residues were depurated with a half-life of 1.84 and 1.95 days for the high and low concentrations, respectively. Bixafen is not expected to bioaccumulate in fish.	2642712

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

Table 10 Toxicity of Bixafen to Non-target Terrestrial Organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
Invertebrates					
Earthworm (*Eisenia fetida*)	8wk-Chronic	Bixafen	Reproduction: NOEL: 100 mg a.i./kg soil dw LOEL: 200 µg a.i./L Survival: NOEL: ≥400 mg a.i./kg soil dw LOEL: >400 µg a.i./L	N/A	2642728
Pollinator (honey bee; *Apis mellifera*)	48hr-Acute oral	Bixafen	Survival: Oral LC_{50}: >121.4 µg a.i./bee No mortality observed.	Practically nontoxic	2642727
	48hr-Acute contact	Bixafen	Survival: Contact LC_{50}: >100 µg a.i./bee No mortality observed.	Practically nontoxic	2642727
	72hr-Brood / hive	Bixafen	72 hr LD_{50}: >100 µg a.i./larva 72 hr NOED: 4 µg a.i./larva	N/A	2642701
	10d-Dietary	Bixafen	Mortality: LD_{50}: >17.3 µg a.i./bee NOAEL: 8.26 µg a.i./bee LOAEL: 17.3 µg a.i./bee LC_{50}: >948 mg a.i./kg diet NOAEC: 470 mg a.i./kg diet LOAEC: 948 mg a.i./kg diet Daily Food Consumption: NOAEL: 17.3 µg a.i./bee LOAEL: >17.3 µg a.i./bee NOAEC: 948 mg a.i./kg diet LOAEC: >948 mg a.i./kg diet	N/A	2642702
Predatory arthropod (Green lacewing; *Chrysoperla carnea*)	6wk-Chronic (extended lab)	Bixafen EC (125 G)	Survival: LR_{50}: >246 g a.i./ha LR_{50}: >2 L product/ha	N/A	2642694
Predatory arthropod (*Typhlodromus pyri*)	2wk-Contact (lab)	Bixafen EC (125 G)	Reproduction: Not acceptable Survival: LR_{50}: 116 g a.i./ha	N/A	2642698

			LR_{50}: 0.948 L product/ha		
	2wk-Contact (extended lab, freshly dried residue)	Bixafen EC (125 G)	Reproduction: NOEL: 1.002 L product/ha LOEL: 2 L product/ha Survival: LR_{50}: >244 g a.i./ha LR_{50}: >2 L product/ha	N/A	2642695
Parasitic arthropod (*Aphidius rhopalosiphi*)	48hr-Contact (lab)	Bixafen EC (125 G)	Survival: LR_{50}: 35.5 g a.i./ha LR_{50}: 0.291 L product/ha	N/A	2642699
	48hr-Contact (extended lab, freshly dried residue)	Bixafen EC (125 G)	Reproduction: Not acceptable Survival: Not acceptable	N/A	2642697
	48hr-Contact (extended lab, aged residue)	Bixafen EC (125 G	Reproduction: NOEL: ≥1 L product/ha LOEL: >1 L product/ha	N/A	2642696
Birds					
Bobwhite quail (*Colinus virginianus*)	Acute oral	Bixafen	LD_{50}: >2000 mg a.i./kg bw	Practically nontoxic	2642717
	5d-Acute dietary	Bixafen	LC_{50}: >4847 mg a.i./kg diet	Slightly toxic	2642720
	22wk - Reproduction	Bixafen	Based on mean-measured concentrations: NOAEC: <95 mg a.i./kg diet LOAEC: 95 mg a.i./kg diet Most sensitive endpoint(s): eggs laid/pen, female weight gain **Reliable with restrictions.**	N/A	2642721
	6wk-Reproduction	Bixafen	NOAEC: 206 mg a.i./kg diet (30.6 mg a.i./kg bw/day) LOAEC: 282 mg a.i./kg diet Most Sensitive Endpoint(s): eggshell thickness, 14-d survivor weight, mean food consumption	N/A	2642722
Mallard duck (*Anas platyrhynchos*)	5d-Acute dietary	Bixafen	LC_{50}: >4990 mg a.i./kg diet	Slightly toxic	2642719
	21wk-Reproduction	Bixafen	Based on mean measured concentrations: NOAEC: 408 mg a.i./kg diet LOAEC: 1030 mg a.i./kg diet Endpoint(s) affected: Hatchling and 14-day old	N/A	2642726

			survivor body weights **Reliable with restrictions.**		
Canary (*Serinus canaria*)	Acute oral	Bixafen	LD_{50}: >2000 mg a.i./kg bw	Practically nontoxic	2642718
Rat	Acute Oral	Bixafen (95.8% purity)	$LD_{50\ female}$: >2000 mg kg/bw ($LD_{50\ male}$ cut-off: 5000 mg/kg bw)	Practically nontoxic	2642766
	Acute Oral	F9650 (13.8% bixafen and 30.4% tebuconazole)	$LD_{50\ female}$: 550 mg/kg bw	Slightly toxic	2643780
	Chronic Toxicity and Carcinogenicity	Bixafen (95.8% purity)	NOAEL $_{male}$: 2.0 mg/kg bw/day LOAEL $_{male}$: 12.1 mg/kg bw/day	N/A	2642790
	Two-generation Reproductive Toxicity	Bixafen (95.8% purity)	NOAEL $_{male}$: 26.4 mg/kg bw/day LOAEL $_{male}$: 169 mg/kg bw/day NOAEL $_{female}$: 30.8 mg/kg bw/day LOAEL $_{female}$: 169 mg/kg bw/day	N/A	2642785
Vascular plants					
Vascular plant	21d-Seedling emergence	Bixafen formulation F9650-1 (12.7% a.i.)	Most sensitive monocot: corn (based on dry weight) EC_{25}/IC_{25}: 75.7 g a.i./ha NOEC: 72 g a.i./ha Most sensitive dicot: cucumber (based on dry weight) EC_{25}/IC_{25}: 1.63 g a.i./ha NOEC: 1.24 g a.i./ha	N/A	2642729
	21d-Vegetative vigour	Bixafen formulation F9650-1 (12.7% a.i.)	Most sensitive monocot: onion (based on dry weight) NOEC: <1.46 g a.i./ha Most sensitive dicot: cucumber (based on dry weight) EC_{25}/IC_{25}: 20.4 g a.i./ha NOEC: 5.57 g a.i./ha	N/A	2642730

Table 11 Screening Level Risk Assessment of Bixafen for Non-target Terrestrial Species Other Than Birds and Mammals

Organism	Exposure	Endpoint value	EEC	RQ	Level of Concern[1]
Invertebrates					
Earthworm (*Eisenia fetida*)	8wk-Chronic (Reproduction)	NOEL: 100 mg a.i./kg soil dw	0.057 mg a.i./kg soil	0.00057	Not exceeded
	8wk-Chronic (Survival)	NOEL: ≥400 mg a.i./kg soil dw	0.057 mg a.i./kg soil	0.00014	Not exceeded
Pollinator (honey bee; *Apis mellifera*)	48hr-Acute oral	LC_{50}: >121.4 ug a.i./bee	3.66 µg a.i./bee	0.030	Not exceeded
	48hr-Acute contact	LC_{50}: >100 ug a.i./bee	0.307 µg a.i./bee	0.0031	Not exceeded
	72hr-Brood / hive	72 hr LD_{50}: >100 ug a.i./larva 72 hr NOED: 4 µg a.i./larva	1.56 µg a.i./larva 1.56 µg a.i./larva	0.016 0.39	Not exceeded Not exceeded
	10d-Dietary	Mortality: LD_{50}: >17.3 µg a.i./bee NOED: 8.26 µg a.i./bee	3.66 µg a.i./bee	0.44	Not exceeded
Predatory mite (*Typhlodromus pyri*)	2wk-Contact (glass plates)	LR_{50}: 116 g a.i./ha (survival)	In-field[2]: 96 g a.i./ha	0.83	Not exceeded
	2wk-Contact (extended lab, freshly dried residue)	LR_{50}: >244 g a.i./ha (survival)	In-field[2]: 96 g a.i./ha	0.39	Not exceeded
Parasitoid wasp (*Aphidius rhopalosiphi*)	48hr-Contact (glass plates)	LR_{50}: 35.5 g a.i./ha (survival)	In-field[2]: 96 g a.i./ha	**2.7**	**Exceeded**
			Off-field[3]: 13.4 g a.i./ha	0.38	Not exceeded
Predatory arthropod (Green lacewing; *Chrysoperla carnea*)	6wk-Chronic (extended lab, freshly dried residue)	LR_{50}: >246 g a.i./ha	In-field[2]: 96 g a.i./ha	0.39	Not exceeded
Vascular plants					
Vascular plant	21d-Seedling emergence	ER_{25}: 1.63 g a.i./ha	In-field: 128 g a.i./ha	**79**	**Exceeded**
			Off-field[3]: 13.4 g a.i./ha	**8.2**	**Exceeded**
	21d-Vegetative vigour	ER_{25}: 20.4 g a.i./ha	In-field[2]: 96 g a.i./ha	**4.7**	**Exceeded**
			Off-field[3]: 13.4 g a.i./ha	0.66	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) x (2.4 µg a.i./bee); adult oral exposure= application rate (kg a.i./ha) x (98 µg a.i./g) x (0.292 g/day); brood exposure= application rate (kg a.i./ha) x (98 µg a.i./g) x (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 maximum cumulative application rate based on seasonal use rate for soybeans (2 ground applications at 64 g a.i./ha) and a foliar half-life of 10 days
[3] Off-field EEC based on single application to cereals at 58.2 g a.i./ha and 23% drift from aerial application, medium spray quality (ASAE)

Table 12 Screening Level Risk Assessment of Bixafen 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]**
Small Bird (0.02 kg)					
Acute	200	Insectivore	7.81	0.04	Not exceeded
Reproduction	13.49	Insectivore	7.81	0.26	Not exceeded
Medium Sized Bird (0.1 kg)					
Acute	200	Insectivore	6.10	0.03	Not exceeded
Reproduction	13.49	Insectivore	6.10	0.20	Not exceeded
Large Sized Bird (1 kg)					
Acute	200	Herbivore (short grass)	3.94	0.02	Not exceeded
Reproduction	13.49	Herbivore (short grass)	3.94	0.13	Not exceeded
Small Mammal (0.015 kg)					
Acute	55	Insectivore	4.49	0.08	Not exceeded
Reproduction	26.4	Insectivore	4.49	0.17	Not exceeded
Medium Sized Mammal (0.035 kg)					
Acute	55	Herbivore (short grass)	8.72	0.16	Not exceeded
Reproduction	26.4	Herbivore (short grass)	8.72	0.33	Not exceeded
Large Sized Mammal (1 kg)					
Acute	55	Herbivore (short grass)	4.66	0.08	Not exceeded
Reproduction	26.4	Herbivore (short grass)	4.66	0.18	Not exceeded

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate.
For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g) $^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item. 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 13 Toxicity of Bixafen to Non-target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
Freshwater invertebrates					
Daphnia magna	48hr-Acute	Bixafen	48-hour EC_{50}: 1100 µg a.i./L No sublethal effects were observed.	Moderately toxic	2642703
	21d-Chronic	Bixafen	NOAEC: 53.5 µg a.i./L LOAEC: 134 µg a.i./L (number of offspring per surviving adult) No sublethal effects noted for offspring.	N/A	2642709
Chironomus riparius	28d-Chronic (spiked sediment)	Bixafen	Based on TWA sediment concentrations: NOAEC: 16.7 mg a.i./kg LOAEC: >16.7 mg a.i./kg Based on TWA sediment concentrations, OC-normalized: NOAEC: 877 mg a.i./kg OC LOAEC: >877 mg a.i./kg OC Based on TWA pore water concentrations: NOAEC: 0.12 mg a.i./L LOAEC: >0.12 mg a.i./L Based on TWA overlying water concentrations: NOAEC: 0.16 mg a.i./L LOAEC: >0.16 mg a.i./L	N/A	2642714
	28d-Chronic (spiked water)	Bixafen	Based on emergence rate (pooled sex) using nominal overlying water concentrations: NOAEC: 0.0156 mg a.i./L LOAEC: 0.0313 mg a.i./L **Reliable with restrictions.**	N/A	2642716
Chironomus dilutus	36d-Chronic (spiked sediment)	Bixafen	Based on TWA sediment concentrations: NOAEC: 18.6 mg a.i./kg dw LOAEC: 38.6 mg a.i./kg dw Based on TWA Pore water concentrations: NOAEC: 0.0582 mg a.i./L LOAEC: 0.114 mg a.i./L	N/A	2642715
Freshwater fish					
Rainbow trout *(Oncorhynchus mykiss)*	96hr-Acute	Bixafen	LD_{50}: 74.0 µg a.i./L Sublethal effects were observed.	Very highly toxic	2642707

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
Fathead minnow (*Pimephales promelas*)	96hr-Acute	Bixafen	96-hour LD_{50}: 108 µg a.i./L Sublethal effects were observed.	Highly toxic	2642706
	33d-Chronic	Bixafen	NOAEC: 4.60 µg a.i./L LOAEC: 8.93 µg a.i./L (total length) **Reliable with restrictions.**	N/A	2642711
Freshwater algae					
Anabeana flos-aquae	96hr-Acute	Bixafen	Using mean measured concentrations: Yield, growth rate, area under the curve (biomass): IC_{50}: >737 µg a.i./L NOAEC: 737 µg a.i./L	N/A	2642733
Pseudokirchneriella subcapitata	72hr-Acute	Bixafen	Using mean measured concentrations: Yield: IC_{50}: 68.47 µg a.i./L NOAEC: <15.6 µg a.i./L Growth rate: IC_{50}: 101.4 µg a.i./L NOAEC: <15.6 µg a.i./L Area under the curve: IC_{50}: 72.99 µg a.i./L NOAEC: 32.5 µg a.i./L	N/A	2642734
Navicula pelliculosa	96hr-Acute	Bixafen	Using mean measured concentrations: Yield: IC_{50}: 15.94 µg a.i./L NOAEC: <0.743 µg a.i./L Growth rate: IC_{50}: 25.63 µg a.i./L NOAEC: 7.31 µg a.i./L Area under the curve (biomass): IC_{50}: 16.04 µg a.i./L NOAEC: <0.743 µg a.i./L	N/A	2642736
Freshwater vascular plants					
Duckweed *(Lemna gibba G3)*	7d Acute-Dissolved	Bixafen	Frond number yield, growth rate: IC_{50}: >410 µg a.i./L NOAEC: 55.7 µg a.i./L Final biomass, biomass growth rate: IC_{50}: >410 µg a.i./L NOAEC: 110 µg a.i./L	N/A	2642731

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
Duckweed *(Lemna minor)*	7d Acute-Dissolved	Bixafen	Frond number yield, frond number growth rate, final biomass, biomass growth rate: IC_{50}: >0.747 mg a.i./L NOAEC: 0.747 mg a.i./L **Reliable with restrictions.**	N/A	2642732
Marine invertebrates					
Eastern oysters (*Crassostrea virginica*)	96hr-Acute	Bixafen	Based on mean measured concentrations: 96-hr IC_{50}: >0.360 mg a.i./L	Highly toxic	2642704
Mysid shrimp *(Americamysis bahia)*	96hr-Acute	Bixafen	LC_{50}: >0.243 mg a.i./L **Reliable with restrictions.**	Highly toxic	2642705
Mysid shrimp *(Americamysis bahia)*	28d-Chronic	Bixafen	Based on TWA concentrations: NOAEC: 0.0886 mg a.i./L LOAEC: 0.164 mg a.i./L Most sensitive endpoint: F0 male length, F0 female length Affected endpoints: F0 Male Total Length (Day 28), F0 Female Total Length (Day 28), F0 Female Dry weight (Day 28), and F1 11-day Survival	N/A	2642710
Estuarine amphipod *(Leptocheirus plumulosus)*	10d-Acute (spiked sediment)	Bixafen	Survival: Mean-measured bulk sediment: LC_{50}: >92.18 mg a.i./kg NOAEC: 92.18 mg a.i./kg LOAEC: >92.18 mg a.i./kg Mean-measured pore water: LC_{50}: >29.6 µg a.i./L NOAEC: 29.6 µg a.i./L LOAEC: >29.6 µg a.i./L Mean-measured overlying water: LC_{50}: >21.6 µg a.i./L NOAEC: 21.6 µg a.i./L LOAEC: >21.6 µg a.i./L **Reliable with restrictions.**	N/A	2642713
Marine algae					
Marine alga (*Skeletonema costatum;* strain SKEL,	96hr-Acute	Bixafen	Using mean measured concentrations: Yield:	N/A	2642735

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA No.
CCAP1077/5)			IC_{50}: 151.1 µg a.i./L NOAEC: 64.6 µg a.i./L Growth rate: IC_{50}: >241µg a.i./L NOAEC: 64.6 µg a.i./L Area under the curve (biomass): IC_{50}: 198.9 µg a.i./L NOAEC: 64.6 µg a.i./L		
Marine fish					
Sheepshead minnow *(Cyprinodon variegatus)*	96hr-Acute	Bixafen	96 hr LC_{50}: 0.151 mg a.i./L Sublethal effects were observed. **Reliable with restrictions.**	Highly toxic	2642708

Table 14 Screening Level Risk Assessment of Bixafen for Aquatic Organisms

Organism	Exposure: Endpoint descriptor	Endpoint value (mg a.i./L)	Converted value[1] (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC[2] = 1 exceeded
FRESHWATER SPECIES						
Pelagic invertebrate (*Daphnia magna*)	Acute (48hr): immobilization (EC_{50})	1.1	0.55	0.0160	0.030	No
	Chronic (21d): reproduction (NOAEC)	0.0535	0.0535	0.0160	0.30	No
Freshwater alga (*Navicula pelliculosa*)	Acute (96hr): yield (IC_{50})	0.0159	0.0080	0.0160	**2.0**	**Yes**
Benthic invertebrate (*Chironomus riparius*)	Chronic (28d spiked water): emergence rate (NOAEC)	0.0156	0.0156	0.0160	**1.0**	**Yes**
Freshwater Fish (Rainbow trout; *Oncorhynchus mykiss*)	Acute (96hr): LC_{50}	0.074	0.0074	0.0160	**2.2**	**Yes**
Freshwater Fish (Fathead minnow; *Pimephales promelas*)	Acute (96hr): LC_{50}	0.108	0.0108	0.0160	**1.5**	**Yes**
	Chronic (33d): body length (NOAEC)	0.0046	0.0046	0.0160	**3.5**	**Yes**
Amphibians	Acute (96hr): LC_{50}	0.074	0.0074	0.0853	**12**	**Yes**
	Chronic (33d): body length (NOAEC)	0.0046	0.0046	0.0853	**19**	**Yes**
Freshwater alga (bluegreen; *Anabeana flos-aquae*)	Acute (96hr): yield (IC_{50})	> 0.737	> 0.3685	0.0160	< 0.04	No
Freshwater alga (green; *Pseudokirchneriella subcapitata*)	Acute (72hr): yield (IC_{50})	0.0685	0.0343	0.0160	0.47	No

Organism	Exposure: Endpoint descriptor	Endpoint value (mg a.i./L)	Converted value[1] (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC[2] = 1 exceeded
Vascular plant (duckweed; *Lemna gibba G3*)	Acute (7d): frond number yield (IC_{50})	> 0.410	> 0.205	0.0160	< 0.08	No
Vascular plant (duckweed; *Lemna minor*)	Acute (7d): frond number yield (IC_{50})	> 0.747	> 0.374	0.0160	< 0.04	No
MARINE SPECIES[3]						
Marine invertebrate (Eastern oyster; *Crassostrea virginica*)	Acute (96hr): shell deposition (IC_{50})	> 0.360	> 0.180	0.0160	< 0.09	No
Marine invertebrate (mysid shrimp; *Americamysis bahia*)	Acute (96hr): IC_{50}	> 0.243	> 0.122	0.0160	< 0.13	No
	Chronic (28d): body length (NOAEC)	0.0886	0.0886	0.0160	0.18	No
Marine alga (diatom; *Skeletonema costatum*)	Acute (96hr): yield (IC_{50})	0.151	0.0755	0.0160	0.21	No
Estuarine amphipod (*Leptocheirus plumulosus*)	Acute (10d spiked sediment): survival (LC_{50}, overlying water)	> 0.0216	> 0.0108	0.0160	**< 1.5**	**Yes**
Sheepshead minnow (*Cyprinodon variegatus)*	Acute (96hr): LC_{50}	0.151	0.0151	0.0160	**1.1**	**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 15 Refined Risk Assessment for Non-target Aquatic Organisms Exposed to Drift of Bixafen

	Rainbow Trout (acute)	Fathead Minnow (acute)	Fathead Minnow (chronic - ELS)	Amphibian (acute)	Amphibian (chronic)	Freshwater Diatom (acute)	Benthic Invertebrate (chronic)	Estuarine Amphipod (acute)	Sheepshead Minnow (acute)
Screening Level Information									
Converted Ecotox Endpoint (mg/L)	0.0074	0.0108	0.0046	0.0074	0.0046	0.0080	0.0156	>0.0108	0.0151
GROUND Screening Level EEC (mg/L)	0.0160	0.0160	0.0160	0.0853	0.0853	0.0160	0.016	0.016	0.016
AERIAL Screening Level EEC (mg/L)	0.00728	0.00728	0.00728	0.0388	0.0388	0.00728	0.00728	0.00728	0.00728
Ground Boom (Field) Sprayer Medium (6% drift)									
EEC Refined for Drift (mg/L)	0.0010	0.0010	0.0010	0.0051	0.0051	0.0010	0.0010	0.0010	0.0010
RQ Refined for Drift	0.13	0.089	0.21	0.69	**1.1**	0.12	0.062	<0.089	0.064
LOC Exceeded	No	No	No	No	**Yes**	No	No	No	No
Aerial - Agricultural Crops - Medium (23% drift)									
EEC Refined for Drift (mg/L)	0.0017	0.0017	0.0017	0.0089	0.0089	0.0017	0.0017	0.0017	0.0017
RQ Refined for Drift	0.23	0.16	0.36	**1.2**	**1.9**	0.21	0.107	<0.155	0.111
LOC Exceeded	No	No	No	**Yes**	**Yes**	No	No	No	No

Table 16 Refined Risk Assessment for Non-target Aquatic Organisms Exposed to Run-off of Bixafen

	Rainbow Trout (acute)	Fathead Minnow (acute)	Fathead Minnow (chronic - ELS)	Amphibian (acute)	Amphibian (chronic)	Freshwater Diatom (acute)	Benthic invertebrate (chronic)	Estuarine amphipod (acute)	Sheepshead Minnow (acute)
Screening Level Information									
Converted Ecotox Endpoint (mg/L)	0.0074	0.0108	0.0046	0.0074	0.0046	0.0080	0.0156	>0.0108	0.0151
GROUND Screening Level EEC (mg/L)	0.0160	0.0160	0.0160	0.0853	0.0853	0.0160	0.0160	0.0160	0.0160
Refined Assessment for Run-off									
EEC Refined for Run-off (mg/L)	0.014	0.014	0.014	0.016	0.015	0.014	0.014	0.014	0.014
RQ Refined for Run-off	**1.9**	**1.3**	**3.0**	**2.2**	**3.3**	**1.8**	0.90	**<1.3**	0.93
LOC Exceeded	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	No	**Yes**	No

Table 17 Toxic Substances Management Policy Considerations for Bixafen: Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Bixafen endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	*Laboratory studies*
			Yes: DT_{50} = 963 - 1773 days (aerobic) DT_{50} = 819 days (anaerobic)
			Field dissipation studies
			Yes: DT_{50} = 550 and 748 days (Alberta; SFO) Slow $t_{1/2}$ = 300 days (DFOP) and t_R = 110 days (IORE)
	Water	Half-life ≥ 182 days	Yes: Total system representative half-lives range from 1144 to 6793 days in aerobic water sediment systems.
	Sediment	Half-life ≥ 365 days	Yes: Total system representative half-lives range from 1144 to 6793 days in aerobic water sediment systems.
	Air	Half-life ≥ 2 days or evidence of long range transport	No: AOPWIN (v1.92) predicted half-life < 1 day based on a 12 hour day Long range transport in air unlikely based on properties of parent.
Bioaccumulation[4]	Log K_{OW} ≥ 5		No: 3.3
	BCF ≥ 5000		No: BCFk,g,l = 381 (high concentration) BCFk,g,l = 454 (low concentration)
	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.

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

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

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

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

Table 18 List of Supported Uses

Crops	Supported disease claim	Rates and application interval
Wheat	Control of tan spot (*Pyrenophora tritici-repentis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of stagonospora glume blotch (*Stagonospora nodorum*)	Rate: 364 ml/ha No. seasonal applications: 1
	Control of septoria leaf blotch (*Septoria tritici*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of leaf rust (*Puccinia*	Rate: 279 – 364 ml/ha

Crops	Supported disease claim	Rates and application interval
	triticina = Puccinia recondita)	No. seasonal applications: 1
	Control of stripe rust (*Puccinia striiformis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of stem rust (*Puccinia graminis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of powdery mildew (*Blumeria graminis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
Barley	Control of septoria leaf blotch (*Septoria passerinii*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of leaf rust (*Puccinia hordei*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of stripe rust (*Puccinia striiformis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of stem rust (*Puccinia graminis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of powdery mildew (*Blumeria graminis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
Oats	Control of stem rust (*Puccinia graminis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
	Control of crown rust (*Puccinia coronata*)	Rate: 279 ml/ha No. seasonal applications: 1
	Control of powdery mildew (*Blumeria graminis*)	Rate: 279 – 364 ml/ha No. seasonal applications: 1
Aerial application to cereal crops		45 L water/ha
Soybean	Suppression of brown spot (*Septoria glycines*)	Rate: 370 ml/ha No. seasonal applications: 2 Application interval: 10 – 14 days
	Control of frogeye leaf spot (*Cercospora sojina*)	Rate: 279 – 400 ml/ha No. seasonal applications: 2 Application interval: 10 – 14 days
	Control of Asian soybean rust (*Phakopsora pachyrhizi*)	Rate: 279 – 400 ml/ha No. seasonal applications: 2 Application interval: 10 – 14 days

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

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

American tolerances for bixafen are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

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

Table 1 compares the MRLs proposed for bixafen in Canada with corresponding American tolerances.

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

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)
Milk	0.05	0.04
Fat, meat and meat byproducts of cattle, goat, horse and sheep	0.2	0.08 (Meat and fat of cattle, goats, sheep, horses) 0.4 (Meat byproducts of cattle, goats, sheep, horses)
Eggs; fat, meat and meat byproducts of hog and poultry	0.01	Not established

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

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

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

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2642829	2016, Tier 2 Summary of the Physical and Chemical Properties of the Active Substance F9650 (Bixafen/BYF 00587) and End-Use Products F9651-2 500, F9652-1 500, F9653-1 500, and F9654-1 500, DACO: 12.7
2642835	2016, Tier III DOCUMENT N Overall Summary and Assessment of Conclusions, DACO: 12.7
2642807	2007, Bixafen (BYF 00587), pure substance Melting Point A.1. (OECD 102) Boiling Point A.2. (OECD 103) Thermal Stability (OECD 113), DACO: 2.14.4, 2.14.5, 830.7200, 830.7220
2642808	2007, Bixafen, BYF 00587, technical substance Melting Point A.1. (OECD102) Boiling Point A.2. (OECD103) Thermal Stability (OECD113), DACO: 2.14.4, 2.14.5, 830.7200, 830.7220
2642671	2007, Relative density of bixafen (BYF 00587) pure and technical substance, DACO: 2.14.6, 3.5.6, 830.7300
2642677	2005, Vapour Pressure A.4 (OECD 104), DACO: 2.14.9, 830.7950
2642805	2007, Physical characteristics color, physical state and odor of bixafen (BYF 00587), pure substance and technical substance, DACO: 2.14.1, 2.14.2, 2.14.3, 3.5.1, 3.5.2, 3.5.3, 830.6302, 830.6303, 830.6304
2642664	2007, Spectral Data Set of BYF 00587, DACO: 2.16
2642676	2005, Determination of the Water Solubility (Column elution method) of BYF 00587, DACO: 2.14.7, 2.14.8, 830.7840
2642674	2007, Solubility of bixafen (BYF 00587) in organic solvents, DACO: 2.14.7, 2.14.8, 830.7840
2642673	2005, Partition Coefficient 1 - Octanol/Water (HPLC-Method), DACO: 2.14.11, 830.7550
2642672	2007, Dissociation contant of bixafen (BYF 00587) in water (screening method), DACO: 2.14.10, 8.2.3.2, 830.7370
2642669	2005, Determination of the pH-Value, DACO: 2.16
2642668	2006, Storage Stability of BYF 00587, DACO: 2.14.14, 3.5.10, 830.6317
2642806	2014, Stability to elevated temperature, metals and metal ions and corrosion characteristics to plastic containers of Bixafen according to OCSPP 830.6313 and OCSPP 830.6320, DACO: 2.14.13, 3.5.10, 3.5.14, 830.6313, 830.6320
2727260	2007, Determination of Bixafen (BYF 00587) Active Substance HPLC - external standard, DACO: 2.13.1 CBI
2645160	2007, Validation of HPLC-method AM004606MP2 BYF 00587 - Assay of technical grade active substance, DACO: 2.13.1
2642764	2007, Validation of HPLC-method AM004606MP2 BYF 00587 Assay of Technical Grade Active Substance, DACO: 2.16

2645154	2015, Amendment no. 1 - Material accountability of technical bixafen (AE 1698406), DACO: 2, 2.13.2, 2.13.3, 2.14 CBI
2645155	2015, Production process and starting materials for bixafen TC, DACO: 2.11.1, 2.11.2, 2.11.3 CBI
2645156	2015, Discussion on the formation of impurities of bixafen TC, DACO: 2.11.4 CBI
2645161	2007, Determination of bixafen (BYF 00587) active substance HPLC - external standard, DACO: 2.13.2
2679242	2016, Spectral data (NMR and MS) for selected specified impurities of bixafen, DACO: 2.13.2 CBI
2645159	2015, Amendment no.1 - Validation of AM004706MP2 bixafen (BYF 00587) impurities in technical grade active substance - HPLC - external standard, DACO: 2.13.1 CBI
2679238	2014, Validation of AM004706MP1 - Bixafen (BYF 00587)- By-products in technical grade active substance HPLC - external standard, DACO: 2.13.1 CBI
2748810	2015, Excerpt from the Bixafen Description of the Manufacturing Process of the Technical Grade Active Substance, DACO: 2.11.3 CBI
2642665	2007, Bixafen, BYF 00587, technical substance Oxidizing Properties A.17, DACO: 2.16
2642817	2015, Method Validation for Determination of Bixafen in Soils, DACO: 8.2.2.1
2642751	2007, Analytical Method 00952/M001 for the Determination of Residues of BYF00587 and BYF00587-(CBI-removed) (BCS-AA-10008) in Soil by HPLC-MS/MS, DACO: 8.2.2.1
2642740	2008, Analytical method 01073 for the determination of bixafen (BYF 00587) in drinking and surface water by HPLC-MS/MS, DACO: 8.2.2.3
2643779	2015, Determination of Physical & Chemical Characteristics of F9651-2, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.5.1, 3.5.11, 3.5.12, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
2643786	2015, Storage Stability and Container Corrosion Evaluation of F9651-2, DACO: 2.14.14, 3.5.10, 3.5.14, 830.6317, 830.6320

2.0 Human and Animal Health

PMRA Document Number	Reference
2642765	2008, BYF 00587 Mechanistic 14-day toxicity study in the rat by oral gavage (hepatotoxicity and thyroid hormone investigations), DACO: 4.3.8
2642766	2005, Acute toxicity in the rat after oral administration, DACO: 4.2.1, 4.6.1, 870.1100
2642767	2005, Acute toxicity in the rat after dermal application, DACO: 4.2.2, 4.6.2, 870.1200
2642768	2006, Acute inhalation toxicity in rats, DACO: 4.2.3, 4.6.3, 870.1300
2642769	2005, Acute Eye Irritation on Rabbits, DACO: 4.2.4, 4.6.4, 870.2400
2642770	2005, Acute Skin Irritation/Corrosion on Rabbits, DACO: 4.2.5, 4.6.5, 870.2500,M4.5.2
2642771	2005, Local lymph node assay in mice (LLNA/IMDS), DACO: 4.2.6, 4.6.6, 870.2600

2642772 2014, F9650 Technical: Local Lymph Node Assay (LLNA) in Mice, DACO: 4.2.6, 4.6.6, 870.2600

2642773 2004, BYF 00587 Exploratory 28-Day Toxicity Study in the Rat by Dietary Administration, DACO: 4.3.3, 870.3050

2642774 2004, BYF00587 Preliminary 28-day toxicity study in the mouse by dietary administration, DACO: 4.3.3, 870.3050

2642775 2006, BYF00587 Preliminary 28-day toxicity study in the rat by dietary administration, DACO: 4.3.3, 870.3050

2642776 2005, BYF 00587 90-Day toxicity study in the rat by dietary administration, DACO: 4.3.1, 4.7.1, 870.3100

2642777 2005, BYF00587 90-Day toxicity study in the mouse by dietary administration, DACO: 4.3.1, 4.7.1, 870.3100

2642778 2009, Position Paper - Bixafen (BYF 00587) Contents: Questions and Response by Bayer CropScience to the Request for a 90 Day Rat Study on Technical Bixafen, DACO: 4.3.1, 4.7.1, 870.3100

2642779 2009, A 90-Day Toxicity Study in the Beagle Dog with Technical Grade BYF 00587 Administered by Oral Gavage (Amended Report), DACO: 4.3.2, 4.7.2, 870.3150

2642780 2016, Waiver request for 21/28-day dermal toxicity rat study with suspension concentrate end-use products of F9650, DACO: 4.3.5, 4.7.4, 870.3200

2642781 2014, Bixafen technical (BYF 00587): 28-Day Dermal Toxicity Study in Wistar Rats, DACO: 4.3.5, 4.7.4, 870.3200

2642782 2016, Waiver request for a rat sub-chronic inhalation toxicity study for F9650, DACO: 4.3.6, 4.7.6, 870.3465

2642783 2007, BYF 00587 Developmental toxicity study in the rabbits by gavage, DACO: 4.5.2, 4.5.3, 870.3700

2642784 2006, BYF 00587 Developmental toxicity study in the rat by gavage, DACO: 4.5.2, 4.5.3, 870.3700

2642785 2007, Technical Grade BYF 00587: A Two Generation Reproductive Toxicity Study in the Wistar Rat, DACO: 4.5.1, 4.8, 870.3800

2642786 2006, Technical Grade BYF 00587: A Dose Range-Finding Reproductive Toxicity Study in the Wistar Rat, DACO: 4.5.1, 4.8, 870.3800

2642787 2008, A One Year Toxicity Study in the Beagle Dog with Technical Grade BYF 00587 Administered by Oral Gavage, DACO: 4.3.2, 4.4.1, 4.7.2, 870.4100

2642788 2008, BYF 00587: Carcinogenicity study in the C57BL/6J mouse by dietary administration, DACO: 4.4.2, 4.4.3, 870.4200

2642789 2008, BYF00587 Chronic toxicity and carcinogenicity study in the Wistar rat by dietary administration, DACO: 4.4.4, 870.4300

2642790 2008, BYF 00587 Complementary chronic toxicity and carcinogenicity study in the male Wistar rat by dietary administration, DACO: 4.4.4, 870.4300

2642791 2005, BYF 00587 *Salmonella*/microsome test plate incorporation and preincubation method, DACO: 4.5.4, 870.5100

2642792 2006, BYF 00587 V79/HPRT-test in vitro for the detection of induced forward mutations, DACO: 4.5.5, 870.5300

2642793 2006, BYF 00587 In vitro chromosome aberration test with Chinese Hamster V79 cells, DACO: 4.5.6, 870.5375

2642794 2005, BYF 00587 Micronucleus-test on the male mouse, DACO: 4.5.7, 870.5395

2642795 2016, Waiver request for sub-chronic neurotoxicity study with F9650, DACO: 4.5.12, 4.5.13, 870.6200

2642796 2015, An Oral (Gavage) Acute Neurotoxicity Study of F9650 Technical in Rats, DACO: 4.5.12, 4.5.13, 870.6200

2642798 2008, [Dichlorophenyl-UL-14C] BYF 00587: Absorption, Distribution, Excretion and Metabolism in the Rat, DACO: 4.5.9, 870.7485

2642799 2007, [Pyrazole-5-14C] BYF 00587: Absorption, Distribution, Excretion and Metabolism in the Rat, DACO: 4.5.9, 870.7485

2642800 2015, An Escalating Single Dose Oral Pharmacokinetics Study in Male and Female Sprague-Dawley Rats with F9650, DACO: 4.5.9, 870.7485

2642801 2006, [Pyrazole-5-14C] BYF 00587: Distribution of the Total Radioactivity in Male Rats Determined by Quantitative Whole Body Autoradiography, Determination of the Exhaled 14CO2, DACO: 4.5.9, 870.7485

2642802 2007, [Dichlorophenyl-UL-14C]BYF 00587: Distribution of the total radioactivity in male rats determined by quantitative whole body autoradiography, determination of the exhaled 14CO2, DACO: 4.5.9, 870.7485

2642803 2016, Waiver request for an immunotoxicity study in rats for F9650, DACO: 870.78

2115788 Agricultural Reentry Task Force (ARTF). 2008. Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients.

2643810 2015, Amendment No. 2 to Analytical Method 01366 for the determination of BYF00587-pyrazole-4-carboxamide and BYF00587-desmethyl-pyrazole-4-carboxylic acid in/on plant material, DACO: 7.2.1,7.2.2,7.2.3

2643805 2015, Modification M001 of the analytical method 01366 for the determination of BYF 00587-pyrazole-4-carboxamide and BYF 00587-desmethyl-pyrazole-4-carboxylic acid in/on plant material, DACO: 7.2.1,7.2.2,7.2.3

2643807 2006, Analytical Method 01012 for the Determination of Residues of BYF00587 and its Metabolite BYF00587-desmethyl in/on Plant Matrices by HPLC-MS/MS, DACO: 7.2.1,7.2.2,7.2.3

2643808 2008, Amendment No. 1 to Analytical Method 01012 for the Determination of Residues of BYF 00587 and its Metabolite BYF00587-desmethyl in/on Plant Matrices by HPLC-MS/MS, DACO: 7.2.1,7.2.2,7.2.3

2643809 2006, Analytical Method 00983 for the Determination of Residues of BYF00587 in/on Plant Matrices by HPLC-MS/MS, DACO: 7.2.1,7.2.2,7.2.3

2643804 2008, Independent Laboratory Validation of the Analytical Method 00983 for the Determination of Residues of BYF 00587 in/on Plant Matrices by HPLC-MS/MS, DACO: 7.2.1,7.2.2,7.2.3

2642755 2007, Analytical method 01036 for the determination of residues of BYF00587 and its metabolite BYF00587-desmethyl in/on animal tissues by HPLC-MS/MS, DACO: 7.2.1,7.2.2,7.2.3

2642756 2007, Analytical method 01063 for the determination of residues of BYF00587 and its metbolite BYF00587-desmethyl in/on animal tissues, milk and eggs by HPLC-MS/MS, DACO: 7.2.1,7.2.2,7.2.3

2642737 2007, Independent Laboratory Validation of the Analytical method 01063 for the determination of residues of BYF00587 and its metabolite BYF00587-desmethyl in/on animal tissues, milk and eggs by HPLC-MS/MS, DACO: 7.2.1,7.2.2,7.2.3

2642741 2007, Metabolism of [pyrazole-5-14C] BYF 00587 in soybeans after spray application, DACO: 6.3

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2642746 2007, Metabolism of [pyrazole-5-14C] BYF00587 in Wheat after Spray Application, DACO: 6.3

2642747 2007, Metabolism of [dichlorophenyl-UL-14C] BYF00587 in Wheat after Spray Application, DACO: 6.3

2642750 2015, Metabolism of [pyrazole-5-14C] Bixafen in Potatoes, DACO: 6.3

2642749 2015, Metabolism of [dichlorophenyl-UL-14C] Bixafen in Potatoes, DACO: 6.3

2642763 2007, Metabolism of [pyrazole-5-14C]BYF 00587 in confined rotational crops, DACO: 7.4.3

2642762 2006, Metabolism of [dichlorophenyl-UL-14C] BYF 00587 in confined rotational crops, DACO: 7.4.3

2642685 2008, [Pyrazole-5-14C] and [Dichlorophenyl-UL-14C]BYF 00587: Degradation in Soil Under Rotational Crops, DACO: 7.4.3

2642744 2007, Metabolism of [dichlorophenyl-UL-14C] BYF 00587 in the laying hen, DACO: 6.2

2642745 2007, Metabolism of [pyrazole-5-14C]BYF 00587 in the laying hen, DACO: 6.2

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3.0 Environment

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2642730 2015, F9650-1 (12.7 % w/w): A study to determine the effects on the vegetative vigour of higher terrestrial plants according to OECD No. 227 (2006) and OCSPP 850.4150, DACO: 850.4150, 9.8.6

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4.0 Value

PMRA Document Number **Reference**

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B. Additional Information Considered

i) Published Information

1.0 Chemistry

None

2.0 Human and Animal Health

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3.0 Environment

None

4.0 Value

None