Proposed Registration Decision PRD2018-01

Quinoxyfen

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Overview

Proposed Registration Decision for Quinoxyfen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing cancellation of the registration of Quinoxyfen Technical Fungicide and Quintec Fungicide, containing the technical grade active ingredient quinoxyfen, to control or suppress powdery mildew on several fruit and vegetable crops.

Quinoxyfen Technical Fungicide (Registration Number 29754) and Quintec Fungicide (Registration Number 29755) are conditionally registered in Canada. The detailed review for Quinoxyfen Technical Fungicide and Quintec Fungicide can be found in Evaluation Report ERC2013-02, *Quinoxyfen*.

At the time of the original registration, the evaluation of the scientific information demonstrated that Quintec Fungicide had value and that human health and environmental risk was acceptable. However, additional information was required to address uncertainties with regard to the chronic risk to aquatic organisms and the bioaccumulation potential of the major transformation product of quinoxyfen: 2-oxo-quinoxyfen. As such, a conditional registration was granted. The current applications were submitted to address the required information and to convert Quinoxyfen Technical Fungicide and Quintec Fungicide from conditional registration to full registration.

The evaluation of the additional environmental information found that quinoxyfen meets the criteria for Track 1 substances under the Toxic Substances Management Policy (TSMP). The PMRA's implementation of the TSMP is outlined in Regulatory Directive DIR99-03, T*he Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. This directive describes how Track 1 substances are managed by the PMRA, and calls for the virtual elimination of Track 1 substances. For use of Quintec Fungicide to control or suppress powdery mildew on several fruits and vegetables, as well as use on hops, specific risk mitigation measures are required, which include buffer zones to minimize risk related to spray drift. Therefore, registration of the use of Quintec Fungicide is granted for a phase-out period of three years beginning 1 July 2018 until 30 June 2021.

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 Quinoxyfen Technical Fungicide and Quintec 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

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

generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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

Before making a final registration decision on quinoxyfen, the PMRA will consider any comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[44] on quinoxyfen, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA'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 Quinoxyfen?

Quinoxyfen is a fungicide that controls or suppresses powdery mildew on stone fruits, grapes, strawberry, melon, squash, lettuce and hops.

Health Considerations

Can Approved Uses of Quinoxyfen Affect Human Health?

Quintec Fungicide, containing quinoxyfen, is unlikely to affect your health when used according to label directions.

Potential exposure to quinoxyfen 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

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

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

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

used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

In laboratory animals, the technical active ingredient, quinoxyfen, was of low acute toxicity via the oral, dermal and inhalation routes of exposure, and non-irritating to the skin. Quinoxyfen was mildly irritating to the eyes; therefore, the signal word and hazard statement "CAUTION – EYE IRRITANT" are required on the label. Quinoxyfen caused an allergic skin reaction; consequently, the signal words "POTENTIAL SKIN SENSITIZER" are required on the label.

The end use product, Quintec Fungicide, was of low toxicity via oral, dermal or inhalation routes of exposure, and was minimally irritating to the eyes and slightly irritating to the skin. It did not cause an allergic skin reaction. Consequently, no hazard signal words are required on the label.

Registrant-supplied short-term and long-term (lifetime) animal toxicity tests were assessed for the potential of quinoxyfen to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment included abortions, anemia and effects on body weight and the liver in adult animals. There was no indication that the young animal was more sensitive than the adult animal. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and children one to two years old, the subpopulation which would ingest the most quinoxyfen relative to body weight, are expected to be exposed to less than 9% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from quinoxyfen is not of health concern for all segments of the population. Quinoxyfen is not carcinogenic; therefore, a chronic cancer dietary exposure assessment is not required.

Animal studies revealed no acute health effects. A single dose of quinoxyfen is not likely to cause acute health effects in the general population (including infants and children). An acute reference dose was not established, therefore, an acute dietary intake estimate is not required.

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 Canada and the United States using quinoxyfen on cantaloupes, cherries, grapes, hops, lettuce, peaches, plums, strawberries and winter squash were acceptable. The MRLs for this active ingredient can be found using the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage.

Occupational Risks From Handling Quintec Fungicide

Occupational risks are not of concern when Quintec Fungicide is used according to the label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Quintec Fungicide, as well as field workers re-entering freshly treated fields can come in direct contact with Quintec Fungicide residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Quintec Fungicide must wear a long sleeved shirt, long pants, shoes plus socks and chemical resistant gloves. As an extra precaution, workers that handle the concentrated product are advised to wear coveralls, chemical resistant gloves, goggles and rubber boots. The label also requires that workers do not enter treated fields 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 risk to these individuals is not a concern. For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Quinoxyfen Is Introduced into the Environment?

Quinoxyfen meets the Government of Canada's criteria for a Track 1 substance under the TSMP, which means that quinoxyfen is toxic, takes a long time to break down and accumulates in living organisms. Because of these environmental concerns, it is proposed that the registered use of quinoxyfen on field crops be cancelled by 30 June 2021. Interim risk reduction measures are proposed to further minimize environmental exposure during the phase-out period.

Quinoxyfen can enter into the environment when applied as a fungicide to field crops.

In the environment, quinoxyfen can be broken down slowly by bacteria. It binds strongly to soil particles, making it unlikely to move downward in the soil and reach groundwater. Quinoxyfen is expected to build-up in the environment and accumulate in the tissues of organisms. Quinoxyfen is not expected to be found in air and is not expected to move long distances in the atmosphere.

In the terrestrial environment, quinoxyfen does not pose a risk to birds, small mammals, plants, earthworms, bees and beneficial arthropods. Precautionary label statements pertaining to terrestrial organisms can be removed from the current product label.

In the aquatic environment, quinoxyfen may pose a risk to aquatic invertebrates, fish, plants, algae and amphibians. Spray buffer zones are required to protect aquatic biota from spray drift.

The information considered in ERC2013-02 showed that the persistence characteristics of quinoxyfen were both above and below the cut-off values for Track 1 substances under the TSMP. PMRA considered additional environmental information to examine the accumulation of quinoxyfen by fish and to further characterize the behaviour of quinoxyfen and risks to the environment. PMRA also considered other environmental information reviewed by the European Commission (2016). New information collected when considered with the older information, shows that quinoxyfen persists in the environment and has the potential to accumulate in the tissues of organisms through various routes of exposures. Characteristics such as persistence, accumulation in animal tissues and effects indicate that quinoxyfen may be of concern from exposure to the environment over a long period of time.

Based on the available environmental information, PMRA concluded that quinoxyfen meets the Government of Canada's criteria for a Track 1 substance under the TSMP. These criteria are also outlined in the *Persistence and Bioaccumulation Regulations* (SOR/2000-107) which are used to define persistent or bioaccumulative under sections of the *Canadian Environmental Protection Act* (CEPA, 1999). Under TSMP, substances meeting these criteria (Track 1) are persistent, bioaccumulative, toxic and primarily the result of human activity. Track 1 substances are targeted for virtual elimination from the environment, but may be registered for a limited time in exceptional circumstances. Quinoxyfen meets all four criteria of a Track 1 substance as per the *Toxic Substances Management Policy* of the Government of Canada.

Value Considerations

What Is the Value of Quintec Fungicide?

The active ingredient in Quintec Fungicide, quinoxyfen, is the only active ingredient from its mode of action group that is registered to control or suppress powdery mildew on stone fruits, grapes, strawberry, melon, squash, lettuce and hops.

Quintec Fungicide is an effective tool for the control or suppression of an important disease, powdery mildew, on several fruits and vegetables. Quintec Fungicide has a unique and highly specific mode of action to control or suppress powdery mildew species that may have become resistant to other types of fungicides.

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 Quintec Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Quinoxyfen Fungicide was mildly irritating to the eyes; therefore, the signal word and hazard statement "CAUTION – EYE IRRITANT" are required on the label. Quinoxyfen caused an allergic skin reaction; consequently, the signal words "POTENTIAL SKIN SENSITIZER" are required on the label.

No hazard signal words are required on the Quintec Fungicide label.

Environment

Spray buffer zones are required to protect aquatic biota.

Precautionary label statements pertaining to terrestrial organisms can be removed from the current product labels.

Next Steps

Before making a final registration decision on quinoxyfen, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on quinoxyfen (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

Quinoxyfen

The detailed review for Quinoxyfen Technical Fungicide and Quintec Fungicide can be found in Evaluation Report ERC2013-02, *Quinoxyfen*.

1.0 The Active Ingredient, Its Properties and Uses

The identity of quinoxyfen, and the physical and chemical properties of quinoxyfen and its associated end-use product, Quintec Fungicide, as well as the directions for use and mode of action were reviewed in ERC2013-02.

2.0 Methods of Analysis

The methods for analysis of the active ingredient and impurities, alone and in formulation, as well as the residues of quinoxyfen in/on plants, and in soil/sediment and water were reviewed in ERC2013-02.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

As noted above, the detailed review of the toxicology database for quinoxyfen, as well as the toxicology endpoints for use in the human health risk assessment, can be found in ERC2013-02.

As discussed in ERC2013-02, 5,7-dichloro-4-(4-flurophenoxy)-2-(1H)-quinolone, designated as "2-oxo-quinoxyfen" or 3-OH quinoxyfen, is a major environmental transformation product identified in the environmental fate studies and in the prospective groundwater monitoring studies. In a toxicokinetic study, 2-oxo-quinoxyfen was identified only at very low levels (0.012% of the administered dose) in rat feces. Consequently, it was not considered to be a major metabolite in mammals and, therefore, its toxicology profile has not been adequately addressed by the database for the parent compound. Additional information was requested from the applicant to address the toxicity of 2-oxo-quinoxyfen. An acute oral toxicity study in rats was submitted, which indicated that 2-oxo-quinoxyfen was of low acute oral toxicity. The results suggest that 2-oxo-quinoxyfen is not likely to be more toxic than the parent, quinoxyfen. The results of the acute toxicity study with 2-oxo-quinoxyfen can be found in Appendix I, Table 1.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA with a set time frame. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. As of September 20, 2017, no human or domestic animal incidents have been received by the PMRA.

3.2 Occupational and Bystander Risk Assessment

For a complete review of the occupational and bystander risk assessment, please refer to ERC2013-02.

3.3 Food Residues Exposure Assessment

For a complete review of the food residue data, please refer to ERC2013-02.

Since the publication of ERC2013-02, the dietary risk assessment has been updated and is reported below.

3.3.1 Dietary Risk Assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.3.1.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic analysis for quinoxyfen: 100% crop treated, default processing factors, Canadian maximum residue limits and American tolerances. The basic chronic dietary exposure from all supported quinoxyfen uses (food alone) for the total population, including infants and children, and all representative population subgroups is less than 9% of the acceptable daily intake (ADI), and therefore not of concern. Chronic dietary exposure to quinoxyfen from food and drinking water is 3.3% (0.006513 mg/kg bw/day) of the ADI for the total population. Therefore, aggregate exposure from food and drinking water is also not of concern. The highest exposure and risk estimate is for children 1-2 years old at 8.7% (0.017363 mg/kg bw/day) of the ADI. (Appendix I, Table 2)

3.3.1.2 Acute Dietary Exposure Results and Characterization

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

3.3.2 Aggregate Exposure and Risk

The aggregate risk for quinoxyfen consists of exposure from food and drinking water sources only, for which there are no concerns; there are no residential uses. (Refer to section 3.3.1.1)

4.0 Impact on the Environment

For a complete review of the impact of quinoxyfen on the environment, please refer to ERC2013-02. The updated information is provided below and the results are summarised in Tables 3 to 7.

4.1 Fate and Behaviour in the Environment

Environmental fate in soil

Additional data from two laboratory biotransformation studies of quinoxyfen in soil were examined. The first study was conducted with four soils from Germany and the United Kingdom (UK, loamy sand, sandy clay loam, clay loam and sandy loam) over 200 days at 20˚C. A DT_{50} was not reached prior to study termination; half-lives were therefore reported as >200 days. An unidentified major compound was detected and continued to increase in concentration until study termination. A minor transformation product, DCHQ, was also identified. A second part of the study examined the effect of the variation of temperature (in addition to the 20˚C, tests were done at 10˚C and 30˚C), soil moisture content [40 and 60% water holding capacity (WHC)] and initial concentrations on the biotransformation in two of the four soils over 100 days. Temperature had significant effect on transformation rate, as estimated half-lives in the loamy sand were well above 200 days at 10˚C, 210 days at 20˚C and 119 days at 30˚C. Initial concentration did not have any effect on the transformation rate in the loamy sand. Estimated half-lives were 220, 210 and 220 days at 1/4, one and four times the application rate, respectively. Soil moisture content also did not have significant effect on the transformation rate in the sandy clay loam (half-lives were 442 and 495 days at 60 and 40 % WHC, respectively).

Another study recently reviewed by the European Commission (2016) examined the aerobic biotransformation in four German soils (loamy sand, sandy clay loam, sandy loam and clay) at 20˚C. The reported DT_{50} values ranged from 268 to 537 days. Since the DT_{50s} were estimated well beyond study termination at 124 days, there are some uncertainties with these estimates. 2-Oxo-quinoxyfen and DCHQ were both observed as major transformation products, both of which declined after 161 days, when samples were analysed in one of the soils.

Both studies support the information reported previously: that quinoxyfen and potentially the major transformation product, 2-oxo quinoxyfen are persistent under laboratory conditions. In addition, the biotransformation rate is temperature dependent.

During the current review, new deficiencies were noted for 2-oxo-quinoxyfen in the previously submitted mobility study. The overall mobility conclusion and classification have been updated to consider the newly identified uncertainties: laboratory studies do not allow the classification for mobility of the transformation product 2-oxo-quinoxyfen.

The terrestrial field dissipation study conducted in Canada was revised. The original DT_{50} of 83.6 days was recalculated, as the dissipation was characteristic of an initial rapid degradation, followed by a slower phase, that is, a biphasic dissipation curve, rather than by a constant degradation rate. The revised calculation resulted in a DT_{50} of 72 days, a DT_{90} of 287 days and a representative half-life of 92.4 days. This did not change the original persistence classification of quinoxyfen, which is moderately persistent for this study from Southern Ontario. The rationale for the recalculation was to better consider the pattern of decline.

Terrestrial field dissipation studies conducted in Europe were reported in the UK review for the initial registration of quinoxyfen in Europe. As the studies were performed in Canadian equivalent ecoregions, they were added to complement the current environmental fate assessment of quinoxyfen. A wide range of DT_{50} values between 13 and > 226 days was reported for eight studies performed in UK, South Germany, Northern and Southern France. It was concluded from these studies that quinoxyfen is persistent in soil under field conditions due to the wide range of DT_{50} values. A biphasic pattern of dissipation was noted, as shown by a significantly slower rate after the DT_{50} was reached. When detected, 2-oxo-quinoxyfen concentrations remained close to the LOQ level.

Further to the above European terrestrial field dissipation studies, data were monitored during five consecutive years of quinoxyfen use under operational field conditions in France, UK and Germany, where quinoxyfen was applied once or twice annually, in the spring or early summer. When cumulating quinoxyfen and 2-oxo-quinoxyfen residues measured in entire soil profiles over five years, overall, between the second and last year, they both carried over residues, with 2-oxo-quinoxyfen consistently accumulating over time.

All European field monitoring studies generally indicated that quinoxyfen carried over to the next season and may accumulate in soil over time depending on the application rate and timing. Although half-life criteria could not be estimated with data from the field monitoring studies, these studies did demonstrate that quinoxyfen can be persistent under actual use conditions. This is also consistent with laboratory data.

Quinoxyfen is persistent in soil under laboratory conditions, which is supported by the long-lasting residues observed in field dissipation and monitoring studies. The range of half-lives below and above the persistence criterion in field dissipation studies is partly due to the biphasic dissipation pattern of quinoxyfen and/or the half-life calculation procedure and do not adequately characterize the long-term fate of quinoxyfen under field conditions. The biphasic pattern is not observed in laboratory aerobic biotransformation studies, where quinoxyfen exceeded the persistence criterion.

As quinoxyfen biotransforms, 2-oxo-quinoxyfen concentrations generally increase slowly, then remain stable or slowly decrease in laboratory biotransformation studies in soil. There are no laboratory studies available to calculate DT_{50} values for the transformation product, due to the persistence of the parent compound and the length of time for formation of the transformation product. In a terrestrial field dissipation study conducted over a period of a year, 2-oxo-quinoxyfen concentrations were low and stable. In terrestrial field monitoring studies, concentrations of 2-oxo-quinoxyfen slowly increased over five years in three soils. Thus, despite the absence of DT_{50} estimations, there is evidence that 2-oxo-quinoxyfen may be persistent under field conditions.

Quinoxyfen is considered persistent in soil when taking into consideration the Canadian and Canadian-equivalent European field dissipation studies, field monitoring studies and laboratory studies. There is evidence that 2-oxo-quinoxyfen may be persistent in soil.

Environmental fate in the aquatic environment

Additional information on the biotransformation of quinoxyfen in water-sediment systems was reviewed. Data from two laboratory studies on two soils each (sandy loam and clay loam and, sand and clay loam water-sediment systems) were examined. As in the previous assessment, quinoxyfen rapidly partitioned to sediment where it was transformed into the major transformation product 2-oxo-quinoxyfen. Maximum concentrations of 2-oxo-quinoxyfen of up to approximately 40% applied radioactivity (AR) were reached at 21 and 74 days and slowly declining thereafter or, maximum concentration were reached at the end of the study, at 100 days. Quinoxyfen half-life values reported for these water-sediment systems ranged from 16 to 136 days, indicating that quinoxyfen was slightly to moderately persistent.

A third laboratory study on the biotransformation of quinoxyfen in surface water from a pond indicated little degradation at two different concentrations over the 60-day period of the study.

Environmental fate in air

The estimated half-life of quinoxyfen in air is 23.97 hours of continuous light, or two days based on a 12-h photoperiod (AOPWIN v1.92). However, modelling estimates predict that a significant portion of quinoxyfen in air may be sorbed to particulates, which may increase its residence time and potential for long-range transport. An air monitoring study to assess the potential long-range atmospheric transport of quinoxyfen to cold-climate regions was also submitted. Rainwater samples were collected at two monitoring sites in Sweden in 2005 and 2006 and analysed for their pesticide content, including quinoxyfen. Quinoxyfen was not detected in any sample, while there were frequent findings of other pesticides, including some subjected to long-range transport. However, a number of uncertainties were noted, such as the actual use of quinoxyfen in European countries during these two years, the movement of quinoxyfen between rain events, and the analytical method to recover quinoxyfen. It is unclear whether quinoxyfen would be in dissolved form in rainwater, or whether it would be bound to fine particulates. The method has been used previously for the measurement of pesticides with higher water solubilities compared with quinoxyfen. Overall, the study did not provide evidence of long-range transport. The major transformation product 2-oxo-quinoxyfen was not monitored in this study.

Monitoring results showed regional transport of quinoxyfen: in a study from Spain, quinoxyfen was detected in air samples monitored in a rural area of intense use of pesticides. It was also detected in seawater, sediment and bivalves in the Baltic Sea, off the coast of Lithuania close to regions where quinoxyfen is used.

Collectively, at this time, the limited information available does not provide evidence that would support quinoxyfen as capable of long-range transport. The estimated half-life is equivalent to the 2-day threshold and monitoring studies show some regional transport. No information is available for remote Canadian locations.

Model estimations of 2-oxo-quinoxyfen sorbed to airborne particles range from 0.78 to one. Because the sorbed fraction may be resistant to atmospheric oxidation, current models (for example, AOPWIN) assuming gas phase transport, are not suited for predicting the atmospheric half-life of this substance. Air monitoring data on 2-oxo-quinoxyfen are not available. Therefore, due to limited information, its persistence in air cannot be determined.

Potential for Bioaccumulation

A study on the octanol/water partition coefficient of 2-oxo-quinoxyfen was reviewed. The resulting log K_{ow} of the octanol/water partition coefficient for 2-oxo-quinoxyfen was 4.9 at pH 5 and 4.8 at pH 7 and pH 8. These values indicate a potential for bioaccumulation.

A new laboratory bioconcentration study with quinoxyfen on rainbow trout, algae and daphnia was reviewed, using current guidelines. Bioaccumulation was observed in algae and daphnids exposed to quinoxyfen for 25 and 50 hours, respectively. In rainbow trout, the bioconcentration factor (BCF) was 11,141 (BCF_{kGL}), which is a standardised kinetic value reflecting theoretical bioconcentration at steady-state, corrected for the growth rate of fish over the experiment and, lipid content normalised at 5%.

The BCF study originally submitted was revisited to estimate BCF values according to the current OECD Guidelines, Test No. 305: *Bioaccumulation in Fish: Aqueous and Dietary Exposure* (2012), which considers the standard kinetic value corrected for growth and lipid content. The recalculated BCF_{kGL} were 9656 and 7379 for low and high quinoxyfen exposure, respectively, which are approximately double or 50% greater than the BCF for rainbow trout reported in ERC2013-02, which was 5040. The small fish size likely had a significant impact on the original BCF calculation and rapid fish depuration observed. OECD Guideline 305 corrects for fish growth, which was not part of the guidance methodology at the time of the original assessment by PMRA. This correction resulted in a significant exceedance of the calculated BCF values from those published in ERC2013-02.

Both studies indicate that quinoxyfen bioconcentrates significantly in fish.

In addition, biomonitoring studies from Europe performed in Canadian-equivalent ecoregions were further examined. Although quinoxyfen was detected and quantified in some invertebrates and in fish in regions where quinoxyfen was used, as quinoxyfen concentrations in water were not reported / measured and quinoxyfen concentrations in sediment were generally low, bioaccumulation could not be quantified [BCF or bioaccumulation factor (BAF) values]. 2-oxo-quinoxyfen was not monitored in these studies.

Numerical laboratory criteria clearly indicate substantial bioconcentration above the TSMP BCF criterion of 5000. The submitted field studies were of limited utility to assess the bioaccumulation potential. With regards to the potential for bioaccumulation of 2-oxo-quinoxyfen, based on a laboratory octanol/water partition coefficient study, there is a potential for bioaccumulation, however, it does not meet this TSMP Track 1 criterion.

4.2 Environmental Risk Characterization

The environmental risk assessment of quinoxyfen was described in ERC2013-02. Please refer to this document for more information and previous results.

4.2.1 Risks to Terrestrial Organisms

Additional ecotoxicology data were reviewed and are reported in Appendix I, Table 4. The following are updates to the risk assessment based on the review of the new information that was received.

Honeybees: Quinoxyfen was relatively non-toxic to honeybees when exposed in diet on an acute basis. The screening level of concern (LOC) was not exceeded (Appendix I, Table 5).

Beneficial Arthropods: Studies were conducted with two indicator species (predatory mite and parasitic wasp), whereby insects were exposed to freshly dried residues of a formulation of quinoxyfen (EF-1295) on glass plates for seven days (mite - *Typhlodromus pyri*) and two days (wasp - *Aphidius rhopalosiphi*). The acute exposure scenarios resulted in mortality for both species, however, there were no significant impacts on reproduction for both species at the tested rates. The screening LOC was not exceeded (Appendix I, Table 5).

4.2.2 Risks to Aquatic Organisms

Additional ecotoxicology data were reviewed and are reported in Appendix I, Table 4. The updates for the current risk assessment are also presented below.

Chironomus midge: The risk of the chronic exposure of 2-oxo-quinoxyfen to the freshwater invertebrate, *Chironomus riparius*, was assessed previously in ERC2013-02. A chronic exposure of 2-oxo-quinoxyfen had no effect on the emergence and development rate of *Chironomus riparius.* The highest tested initial water concentration of 116 µg 2-oxo-quinoxyfen/L was chosen as the no observed effect concentration (NOEC). However, in Table 11 of ERC2013-02, the NOEC is described as based on the mean water column concentration of 2-oxo-quinoxyfen when it should have read based on the initial water column concentration. This correction does not affect the risk quotient (RQ) as the numerical value of 116 µg TP/L for the endpoint was correct. Therefore, the risk assessment reported previously in ERC2013-02 remains valid.

Sheepshead Minnow: The toxicity of 2-oxo-quinoxyfen was studied on marine sheepshead minnow embryos (*Cyprinodon variegatus*) for 33 days at five mean measured concentrations at up to 27 µg TP/L. At the end of the study, no effects were noted on embryo hatching success, percentage of embryos that produce live, normal larvae at hatch, larval survival and larval growth (total length and dry weight) at any of the tested concentrations. The NOEC was determined to be 27 µg TP/L, the highest tested concentration.

A RQ of 2.1 was calculated at the screening level, using the estimated environmental concentration (EEC) of 57 µg TP/L, assuming 100% transformation of quinoxyfen to 2-oxo-quinoxyfen (Appendix I, Table 5). Although this value slightly exceeds the LOC (≥ 1), as it is a conservative estimate, it is expected that any scenario to estimate more specific EECs would

bring the RQ < 1. In addition, no effects were seen at the highest concentration tested, which implies that the actual NOEC is potentially higher. In this specific case, an increase of 30 µg TP/L in the NOEC would be needed to bring the RQ < 1, while maintaining a conservative exposure scenario. Therefore, the risk from the exposure of 2-oxo-quinoxyfen to sheepshead minnow is not considered to be of concern.

4.2.3 Incident Reports

An update of incident reports from 2010 was performed. As of September 20, 2017, one environmental and one scientific study incident report have been submitted to the PMRA.

In the environmental incident, honey bee mortality occurred in the summer of 2013. Analysis of the dead bees identified seventeen different active ingredients. Quinoxyfen was detected in bees at a lower concentration than the highest tested concentration for which no acute toxic effects were observed and it was unlikely that quinoxyfen would have significantly contributed to these mortalities. The causality assessment concluded that it was probable that another active ingredient, which is highly toxic to bees, contributed to the bee mortality of this affected bee yard.

The registrant also submitted a new study on the bioconcentration of the parent quinoxyfen in rainbow trout, algae and daphnia, which is reported in Section 4.1.

5.0 Value

Powdery mildew is a very detrimental disease as it reduces the quality and yield of agricultural crops. Quintec Fungicide was requested by growers in need of an effective tool for the control of powdery mildew on several fruits and vegetables. Quinoxyfen offers a new mode of action to manage powdery mildew, which is of particular importance given reports of field resistance to currently registered alternative active ingredients against some powdery mildew species.

Since the original review was conducted, additional alternatives are available to manage powdery mildew on the listed crops (refer to the list of alternatives available in Appendix I, Tables 8 and 9).

Refer to ERC2013-02 for the initial evaluation report on value and non-safety adverse effects information for Quintec Fungicide.

5.1 Supported Uses

The list of supported and unsupported claims can be found in ERC2013-02, Appendix I, Table 21. The following corrections from Table 21 in ERC2013-02 should be noted: On head and leaf lettuce, the maximum number of application is four (not five) and, on hops, the disease claim *Sphaerotheca macularis* was supported for suppression (not control).

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

During the original review process, quinoxyfen and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria of the TSMP. From a preliminary review, it was concluded that quinoxyfen did not meet all Track 1 criteria as quinoxyfen was not persistent in water, the depuration half-life in fish was rapid and, significant bioaccumulation under field conditions was not observed. Please refer to ERC2013-02 for further details on this assessment.

Based on the review of additional information, combined with reviewing key studies according to current standards, the PMRA has reached the following conclusions:

The PMRA considers quinoxyfen to be persistent, bioaccumulative and toxic (PBT) and it meets all criteria for a Track 1 substance under Canada's TSMP policy:

- Quinoxyfen is considered CEPA-toxic equivalent to aquatic organisms, as it is toxic to most aquatic organisms on an acute or chronic basis and is expected to elicit toxic effects under environmentally relevant conditions (ERC2013-02).
- As quinoxyfen meets persistence criterion in at least one media (soil), then the criterion for persistence is considered to be met.
    - Soil laboratory data clearly meet the TSMP Track 1 criterion for persistence. These studies also showed that the quinoxyfen degradation rate is strongly influenced by temperature.
    - In field dissipation studies, there is a wide range of half-lives below and above the criterion. It was concluded that the DT_{50}s from the field studies did not properly characterise the degradation behaviour of quinoxyfen and did not provide sufficient evidence that quinoxyfen was not persistent.
    - To assess the persistence criteria, field studies are traditionally preferred over laboratory studies, as they reflect more realistic conditions of use of a pesticide and consider all potential routes of transformation. Because it was determined that the DT_{50} values derived from the field studies did not adequately characterise the persistence of quinoxyfen in the current assessment, DT_{50} values derived from laboratory data were preferred. In addition, the biphasic dissipation pattern noted in a number of field studies suggests that although quinoxyfen initially degrades relatively quickly, the degradation rate slows down over time resulting in quinoxyfen residues remaining in the soil for long periods of time. The degradation is better described when also considering the second half of the degradation curve (DT_{90}s).

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

    - In monitoring studies conducted over two to five years, yearly applications of quinoxyfen resulted in no observable decline over the study period. Although DT_{50}s cannot be calculated for the field monitoring studies, the persistent behaviour was more consistent with the DT_{90}s obtained from the field dissipation studies and the DT_{50} values from the soil laboratory studies.
    - In water and air, quinoxyfen does not meet TSMP criterion for persistence.
- Data related to bioaccumulation were calculated to meet current standards and compared against the TSMP. The laboratory BCF values substantially exceeded the TSMP criteria of greater than 5000 in two studies with rainbow trout.

Quinoxyfen exceeds TSMP criterion for bioaccumulation, based on laboratory data from two studies with BCF > 5000. No reliable field data allowing the quantification of bioaccumulation are available.

The PMRA cannot confirm 2-oxo-quinoxyfen to be persistent; however, 2-oxo-quinoxyfen is not bioaccumulative, nor toxic. Therefore, 2-oxo-quinoxyfen does not meet all the criteria for a Track 1 substance under Canada's TSMP policy:

- 2-Oxo-quinoxyfen may meet at least one persistence criterion (soil).
    - 2-Oxo-quinoxyfen is formed in soil under laboratory and field conditions. Rates of dissipation were not calculable; however, available data indicate that 2-oxo-quinoxyfen may be persistent and the criterion may be met.
    - In water, 2-oxo-quinoxyfen is formed under laboratory conditions. Rates of dissipation were not calculable. Based on available data, it cannot be determined if the criterion for persistence in water is met.
    - In air, 2-oxo-quinoxyfen persistence could not be determined due to limited information.
- 2-Oxo-quinoxyfen does not meet TSMP criteria for bioaccumulation, based on log K_{ow}. No laboratory or field data on bioaccumulation are available.
- No toxicity has been shown in available toxicity data of 2-oxo-quinoxyfen to aquatic organisms.

Comparison of available data for quinoxyfen and 2-oxo-quinoxyfen against TSMP Track 1 criteria are shown in Tables 5 and 6. Quinoxyfen meets the Government of Canada's criteria for a Track 1 substance under the *Toxic Substances Management Policy*. These criteria are also outlined in the *Persistence and Bioaccumulation Regulations* (SOR/2000-107) which are used to define persistent or bioaccumulative under sections of the *Canadian Environmental Protection Act* (CEPA, 1999). When Track 1 criteria are met, PMRA's implementation of the TSMP (DIR99-03) calls for strict risk management, therefore, PMRA is proposing to phase-out the use of quinoxyfen.

6.2 Formulants and Contaminants of Health or Environmental Concern

For information on the formulants and contaminants of health or environmental concern, please refer to ERC2013-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for quinoxyfen is adequate to define the majority of toxic effects that may result from exposure to quinoxyfen. In repeated dose toxicity studies on laboratory animals, the primary target of toxicity was the liver in all tested species and the hemolytic system in dogs. There was no evidence of cancer in mice or rats. Sensitivity of the young was not observed in the developmental toxicity studies. There was an increase in abortions in the rabbit developmental toxicity study at a maternally toxic dose, which was also the highest dose tested. In the reproductive toxicity study, a marginal decrease in pup body weights was observed during lactation in the absence of adverse effects in the parents, and was considered to be of low toxicological concern. There was no evidence of reproductive toxicity, and quinoxyfen was not considered to be genotoxic or neurotoxic.

7.2 Environmental Risk

Due to the toxicity of quinoxyfen to aquatic organisms, its persistence in the environment and its potential for bioaccumulation, quinoxyfen meets the Government of Canada's criteria for a Track 1 substance under the *Toxic Substances Management Policy*. These criteria are also outlined in the *Persistence and Bioaccumulation Regulations* (SOR/2000-107) which are used to define persistent or bioaccumulative under sections of the *Canadian Environmental Protection Act, 1999* (CEPA, 1999). Under TSMP, substances meeting these criteria (Track 1) are persistent, bioaccumulative, toxic and primarily the result of human activity. Track 1 substances that cannot be managed successfully throughout their life cycle are targeted for virtual elimination from the environment, that is, phase-out of generation and uses.

Quinoxyfen is generally persistent in the terrestrial environment and soil temperature has a strong influence on its rate of transformation. In soil, it transforms to two major transformation products, 2-oxo-quinoxyfen and DCHQ, with the former being likely persistent and accumulating in soil over time.

Quinoxyfen is slightly to moderately persistent in the aquatic environment. It partitions rapidly from the water layer to sediment, where it is transformed to 2-oxo-quinoxyfen, which increases then slowly degrades in water systems.

As 2-oxo-quinoxyfen has not shown any toxic effects to aquatic organisms and its log K_{ow} is below the TSMP Track 1 criterion for bioaccumulation, 2-oxo-quinoxyfen does not meet the Government of Canada's criteria for a Track 1 Substance under the *Toxic Substances Management Policy*.

Quinoxyfen was considered toxic to aquatic organisms in the previous assessment (ERC2013-02). Based on new and revised data, quinoxyfen has been shown to bioconcentrate substantially in fish under laboratory conditions. In the field, quinoxyfen was detected in biota in monitoring studies from Europe but the bioaccumulation information was inadequate to calculate BAFs. Based on unequivocal laboratory data, PMRA considers quinoxyfen to be bioaccumulative in fish.

From the additional and revisited information reviewed, PMRA concludes that there are no short-term concerns with quinoxyfen affecting beneficial arthropods and bees. The previous standard risk assessment of quinoxyfen for aquatic organisms remains valid (see ERC2013-02).

Risk reduction measures are proposed in the interim to minimize environmental exposure during an eventual phase-out period. The risk in the short term is currently mitigated through updated buffer zones on the directions for use on the product label, based on a longer half-life in water system, as well as revisions to label statements:

Label statements for bees and beneficial arthropods were revised, based on the review of new data provided. Label statements for bees and beneficial arthropods can be removed from the current end-use product label Quintec Fungicide.

7.3 Value

The value information provided to support the registration of Quintec Fungicide was primarily in the form of efficacy trials along with scientific rationales to extrapolate the use among similar crops. The level of efficacy observed in the efficacy trials varied from suppression to control (refer to ERC2013-02, section 7.3 Value). Quintec Fungicide is an effective fungicide with a unique mode of action, and has value in integrated pest management programs as it may prevent resistance development in susceptible pathogens in the labelled crops.

8.0 Proposed Regulatory Decision

Health Canada’s PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing cancellation of the registration of Quinoxyfen Technical Fungicide and Quintec Fungicide, containing the technical grade active ingredient quinoxyfen, to control powdery mildew on several fruit and vegetable crops.

The evaluation of the additional environmental information found that quinoxyfen meets the criteria for Track 1 substances under the TSMP. The PMRA's implementation of the TSMP is outlined in Regulatory Directive DIR99-03, T*he Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. This directive describes how Track 1 substances are managed by the PMRA, and calls for the virtual elimination of Track 1 substances. For use of Quintec Fungicide to control powdery mildew on several fruits and vegetables, as well as use on hops, specific risk mitigation measures designed to minimize the risks include buffer zones to minimize spray drift. Therefore, registration of the use of Quintec Fungicide is granted for a phase-out period of three years beginning 1 July 2018 until 30 June 2021.

List of Abbreviations

˚C	degrees Celsius
♀	female
>	greater than
=	equal
<	less than
≥	greater than or equal to
%	percent
µg	micrograms
ADI	acceptable daily intake
a.i.	active ingredient
AOPWIN	model that estimates the gas-phase reaction rate for the reaction between the most prevalent atmospheric oxidant, hydroxyl radicals, and a chemical and calculates atmospheric half-lives for chemicals
AR	applied radioactivity
BAF	bioaccumulation factor
BCF	bioconcentration factor
BCF_K	kinetic BCF
BCF_{kG}	kinetic BCF corrected for growth
BCF_{kGL}	kinetic BCF corrected for growth and lipid content
BCF_{kL}	kinetic BCF corrected for lipid content
BCFss	kinetic BCF at steady state
bw	body weight
CEPA	*Canadian Environmental Protection Act*
d	day(s)
DACO	data code
DAT	day(s) after treatment
DFOP	double first-order in parallel
DIR	directive
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EEC	estimated environmental concentrations or European Economic Community
ELS	early live stage
ERC	evaluation report
g	gram
h	hour(s)
ha	hectare(s)
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
KOWWIN	model that estimates the log octanol-water partition coefficient, log K_{ow}, of chemicals using an atom/fragment contribution method
L	litre
LD_{50}	lethal dose 50%
LOC	level of concern

LOD	limit of detection
log	logarithm
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m^3	cubic metre(s)
Max	maximum
mg	milligram(s)
MRL	maximum residue limit
N/A	not applicable
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
OECD	Organization for Economic Cooperation and Development
PBT	persistent, bioaccumulative, toxic
pg	picogram(s)
pH	measure of the acidity or basicity of an aqueous solution
PMRA	Pest Management Regulatory Agency
RQ	risk quotient
S.	Southern
SFO	single first-order rate model
$T_{1/2\ representative}$	representative half-life
TP	transformation product
TSMP	Toxic Substances Management Policy
UK	United Kingdom
USEPA	United States Environmental Protection Agency
WHC	Water holding capacity

Appendix I Tables and Figures

Table 1 Toxicity Profile of 2-oxo-quinoxyfen

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Fischer 344 rats PMRA 2642066	LD_{50} ♀ > 5000 mg/kg bw **Low acute toxicity**

Table 2 Food Residue Chemistry Overview of Risk Assessment

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
Basic chronic dietary exposure analysis **ADI = 0.2 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.23 Φg/L**	**All infants < 1 year**	2.5	2.5
	Children 1–2 years	8.7	8.7
	Children 3 to 5 years	7.0	7.0
	Children 6–12 years	3.9	3.9
	Youth 13–19 years	2.5	2.5
	Adults 20–49 years	2.9	2.9
	Adults 50+ years	2.9	2.9
	Females 13-49 years	2.9	2.9
	Total population	3.3	3.3

Table 3 Fate and Behaviour in the Environment

Study	Compound	Value	Remarks	Reference
Biotransformation				
Aerobic soil	Quinoxyfen	Four European soils, 20°C, SFO DT_{50} > 200 d (beyond the length of the study for 4 soils: loamy sand, sandy clay loam, clay loam and sandy loam)	Persistent. Degradation rate varies inversely with temperature.	1771844 1771845
	Unidentified	Rates of dissipation not calculable. %AR up to 27.4 at 200 DAT		

Study	Compound	Value	Remarks	Reference
Aerobic soil	Quinoxyfen	Four German soils, 2 radiolabels each, 20°C, SFO: Loamy sand: 434 and 527 d Sandy clay loam: 453 and 268 d Sandy loam: 379 and 281 d Clay: 537 and 280 d	Persistent.	2805818
	2-oxo-quinoxyfen	Rates of dissipation not calculable. Max AR: 6.2 – 16.8% at 124 – 83 DAT		
Aerobic water/ sediment (dark system)	Quinoxyfen	Two water-sediment systems, 20°C, SFO Total system: DT_{50} 25 and 136 d	Slightly to moderately persistent.	1642962 Updated data reported in 2805818
	2-oxo-quinoxyfen	Rates of dissipation not calculable 42.8% AR in sediment at 100 DAT		
	Unidentified	Rates of dissipation not calculable 12.8% AR in sediment at 100 DAT.		
Aerobic water/ sediment (dark system)	Quinoxyfen	Two water-sediment systems, 20°C, SFO Total system: DT_{50} 16 and 48 d	Slightly to moderately persistent.	2805818
	2-oxo-quinoxyfen	Rates of dissipation not calculable Max AR: 39.2 – 43.3% at 100 – 21 DAT		
Aerobic pond filtered water (dark)	Quinoxyfen	Low and high doses, 21°C, SFO DT_{50} 115.0 and 128.6 d	Moderately persistent.	2805818
Adsorption/ desorption	2-oxo-quinoxyfen	Study revised: adsorption results for 2-oxo-quinoxyfen were preliminary and were not reliable. *Revised from ERC2013-02*		1642964
Field dissipation	Quinoxyfen	Ontario (Ecoregion 8.1, Ontario) DT_{50} 72 d DFOP, DT_{90} 287 d DFOP $T_{1/2\ representative}$: 92.4 d DFOP *Calculation updated after the ERC2013-02 was published.*	Moderately persistent	1667658
Field dissipation	Quinoxyfen	***Applications to bare soil*** Southern Germany DT_{50}: 50 and > 214 d DT_{90}: > 540 d ***Applications to cropped soil*** UK DT_{50}: 190 and > 226 d DT_{90}: > 573 d France DT_{50}: 13 to 82 d DT_{90}: > 217 to 750d	Non-persistent to persistent.	2806711 2806709 2806714 2806708 2806713 2806710 2806707

Study	Compound	Value	Remarks	Reference
	2-oxo-quinoxyfen	Rates of dissipation not calculable. Concentrations remained close to LOQ/LOD values.		2806712
Field monitoring over 5 years	Quinoxyfen	Evidence of yearly quinoxyfen residue carryover of over 5 years.	No persistence classification	1771851 1771852 1771853
	2-oxo-quinoxyfen	Evidence of yearly 2-oxo-quinoxyfen residue carryover and accumulation of over 5 years.	No persistence classification	
Field monitoring over 2 years	Quinoxyfen	Soil residues from cereal fields in Germany and vineyards in Italy were variable but overall there was little dissipation of quinoxyfen over winter.		1894307 1894309
AOPWIN v1.92	Quinoxyfen	Half-life in air: 1.998 days (based on a 12-h photoperiod) 23.97 h under continuous light	Below the 2-day threshold for long-range transport potential	
Long-range transport Rainwater monitoring	Quinoxyfen	Not detected in rainwater from 2 sites in Sweden, while other pesticides were detected.	No evidence of long-range transport of quinoxyfen	1894313
Regional Air monitoring	Quinoxyfen	Detected among 40 currently used pesticides in air samples collected in an agricultural area of Valencia, Spain. Concentration (mean of 2 samples): 1.64 pg/m^3	Indication of regional transport	2803874
K_{ow} study	2-oxo-quinoxyfen	logK_{ow} of 4.9 at pH 5 logK_{ow} of 4.8 at pH 7 and 9	Potential for bioaccumulation	2270289
Revised BCF values for rainbow trout	Quinoxyfen	Rainbow trout BCF_{kGL}: 9656 (low concentration) BCF_{kGL}: 7379 (high concentration) *Revised from ERC2013-02.*	High bioconcentration in fish	1642993
New BCF study on rainbow trout, algae and daphnid	Quinoxyfen	Rainbow trout BCF_{kGL}: 11 141 Bioaccumulation observed in algae and daphnid	High bioconcentration in fish	2204555 2333181 2333182

Table 4 Additional Toxicity Data on Non-Target Organisms

Test organism	Study type	Substance	Endpoint value	Degree of Toxicity[a]	Reference
Terrestrial Organisms					
Apis mellifera (Honey bee)	48h-Acute oral	Quinoxyfen	48h LD_{50} >100.1 µg a.i./bee 48h NOEL 100.1 µg a.i./bee (no effect at highest dose)	Relatively non-toxic	2270291
Predatory mite *Typhlodromus pyri* (Acari:Phytoseiidae)	7d-Acute	Quinoxyfen	LR_{50} >450.3 g a.i./ha NOER N/A	N/A	2270295

Test organism	Study type	Substance	Endpoint value	Degree of Toxicity[a]	Reference
Parasitic wasp *Aphidius rhopalosiphi* (Hymenoptera, Braconidae)	48h Acute	Quinoxyfen	LR_{50} 278.7 g a.i./ha NOER 93.1 g a.i./ha (based on mortality)	N/A	2270296
Aquatic Organisms					
Marine Species					
Cyprinodon variegatus (sheepshead minnow)	ELS	2-oxo-quinoxyfen	NOEC = 27 µg a.i./L (mortality, length and dry weight of survival larvae) (highest measured concentration tested)	N/A	2270299

[a] USEPA classification, where applicable

Table 5 Screening Level Risk Assessment on Non-target Species

Organism	Substance	Exposure	Endpoint value	EEC	RQ	Level of concern exceeded?
Terrestrial organisms						
Honeybee	Quinoxyfen	Oral	>100.1 µg a.i./bee	3.6 µg a.i./bee	< 0.036	No
Predatory arthropod *T. Pyri*	Quinoxyfen	Contact	>450.3 g a.i./ha	0.242 kg/ha (in-field)	< 0.54	No
Parasitic arthropod *A. Rhopalosiphi*	Quinoxyfen	Contact	278.7 g a.i./ha	0.242 kg/ha (in-field)	0.87	No
Aquatic organisms						
Sheepshead minnow (*Cyprinodon variegatus*)	2-oxo-quinoxyfen	ELS	27 µg TP/L	57 µg TP/L	2.1	Yes

Table 6 Toxic Substances Management Policy Considerations for Quinoxyfen - Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Quinoxyfen Assessment Against Criteria Endpoints	Reference
CEPA toxic or CEPA toxic equivalent[1]		Yes quinoxyfen meets the criteria under praragraph 64(a) of CEPA and should be considered CEPA-toxic equivalent. It is deliberately released to the environment, inherently toxic and bioavailable under field conditions.	
Predominantly anthropogenic[2]	Yes	Yes	
Persistence[3]	Soil Half-life ≥ 182 days	<u>Laboratory Aerobic Soil Biotransformation</u> California sandy loam: 118 days (25°C) Ontario loam: 263 days (25°C)[6] German loamy sand: > 200 days (20˚C)[7]	 1642960 1771844

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Quinoxyfen Assessment Against Criteria Endpoints	Reference
		UK sandy clay loam: > 200 days (20˚C) UK clay loam: > 200 days (20˚C) UK sandy loam soils: > 200 days (20˚C) German Loamy sand: 434 days and 527 days[8] (20˚C) German Sandy clay loam: 453 days and 268 days (20˚C) German Sandy loam: 379 days and 281 days (20˚C) German Clay: 537 days and 280 days (20˚C) <u>Terrestrial Field Dissipation Studies relevant to Canada</u> ***Applications to bare soil*** S. Ontario loam: 72 days (DT_{90} = 287 days) S. Germany Sandy silt loam: 50 days (DT_{90} > 540 days) S. Germany Silt loam: > 214 days ***Applications to cropped soil*** UK Sandy clay loam: 190 days (DT_{90} >573 days) UK Sand: > 226 days France Silty clay loam: 13 days (DT_{90} = 584 days) France Sandy silt loam: 35 days (DT_{90} > 221 days) France Clay loam: 82 days (DT_{90} = 750 days) France Silty clay loam: 30 days (DT_{90} > 217 days) <u>Additional information:</u> Monitoring studies show that quinoxyfen persist under field conditions. No DT_{50} values could be obtained, due to study design. Little or no dissipation of quinoxyfen was observed in these studies. Thus, they do not support the lower DT_{50} values obtained or reported from field dissipation studies.	2805818 1667658 2806711 2806709 2806714 2806708 2806713 2806707 2806712 2806710 1771851 1771852 1771853 1894307 1894309
	Water and sediment Half-life ≥ 182 days in water and ≥ 365 days in sediment	<u>Laboratory Aerobic biotransformation in Water Sediment (whole system)</u> Sandy loam system: 33.7 days (25°C) Sandy loam: 25 days (20°C) Clay loam: 136 days (20°C) Sand: 48 days (20°C) Clay loam: 16 days (20°C) Natural water: 128.6 and 115.0 days (DT_{90}s: 427.1 and 382.1 days)	1771846 2805818 2805818 2805818
	Air Half-life ≥ 2 days or evidence of long-range transport	The estimated half-life in air is 23.97 hours of continuous light, or 2 days based on a 12-h photoperiod. Estimations of quinoxyfen sorbed to airborne particles range from 46 to 70%. Because the sorbed fraction may be resistant to atmospheric oxidation, the estimated half-life in air may be underestimated.	
	<u>Conclusion:</u> Considering information reported in the ERC2013-02 and the current review, the persistence criterion is met in soil, but not in water and air.		

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Quinoxyfen Assessment Against Criteria Endpoints	Reference
Bioaccumulation[4]	Log $K_{ow} \geq 5$	Log K_{ow} (KOWWIN estimate): 5.69 Laboratory study: Log K_{ow} 4.66	
	BCF[5] ≥ 5000	Results of submitted laboratory studies with rainbow trout (*Oncorhynchus mykiss*): Low exposure / High exposure BCF_{SS} 4091 / Not reached BCF_k 4891 / 4533 BCF_{kG} 5874 / 4870 BCF_{kL} 8040 / 6867 **BCF_{kGL} 9656 / 7379** BCF_{SS} 8673 BCF_k 13553 BCF_{kG} 22333 BCF_{kL} 6761 **BCF_{kGL} 11141**	1642993 2204555
	BAF ≥ 5000	The monitoring data submitted were insufficient for determining a BAF. However, quinoxyfen was detected at low levels in biota (fish) and sediment.	1894307, 1894308, 1894309, 1894310
	Conclusion: Based on submitted data, with BCF values greater than 5000, it is concluded that quinoxyfen meets the bioaccumulation criterion.		

[1]A substance is CEPA toxic (or CEPA toxic equivalent) if it is entering or may enter the environment in a quantity or concentration or under conditions that
(a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
(b) constitute or may constitute a danger to the environment on which life depends; or
(c) constitute or may constitute a danger in Canada to human life or health.
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet the persistence criterion identified for one media (soil, water, sediment or air) then 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}).
[5] BCF_{SS} = BCF at steady-state; BCF_K = kinetic BCF; BCF_{KGL} = kinetic BCF corrected for growth and lipid content.
[6] Reported in ERC2013-02 as 80th percentile DT_{50}: 261.2 days
[7] DT_{50} was not reached by study termination.
[8] Both radiolabels are reported.

Table 7 Toxic Substances Management Policy Considerations for 2-Oxo-quinoxyfen - Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		2-oxo-quinoxyfen Assessment Against Criteria Endpoints	Reference
CEPA toxic or CEPA toxic equivalent[1]			No, does not meet the CEPA-toxic equivalence criterion, based on available toxicity data to aquatic organisms.	
Predominantly anthropogenic[1]	Yes		Yes	
Persistence[2]	Soil	Half-life ≥ 182 days	Laboratory Aerobic Soil Biotransformation DT_{50} cannot be calculated because levels still generally increasing at study termination (365 days).	1642960

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		2-oxo-quinoxyfen Assessment Against Criteria Endpoints	Reference
			Major transformation product in 2 of 4 Germany soils (2 radiolabels each): Max AR / AR End of Study (124 days) Loamy sand: 8.2% (124 d) / 8.2% 16.8% (83 d) / 0.0% Sandy clay loam: 6.3% (124 d) / 6.3% 9.9% (83 d) / 5.6% Sandy loam: 6.2% (124 d) / 6.2% 5.9% (124 d) / 5.9% Clay: 1.7% (46 d) / 0.0% 9.2% (83 d) / 5.7%	2805818
			<u>Field studies:</u> DT_{50} cannot be calculated in 9 terrestrial field dissipation studies because levels remained close to LOQ/LOD values.	1667658 2806711 2806709 2806714 2806708 2806713 2806707 2806712 2806710
			Data from three 5-year field monitoring studies with quinoxyfen applied annually indicate persistence with low levels detected at the beginning of the 2nd year and slowly increasing thereafter.	1771851 1771852 1771853
	Aquatic systems	Half-life ≥ 182 days in water or ≥ 365 days in sediment	<u>Laboratory Data</u> Concentrations generally slowly increase (up to > 40% AR at the end of the studies), then remain stable or decrease at minimal rates in the sediment of 3 laboratory water/sediment studies with quinoxyfen. <u>Field Data</u> No field data were available for 2-oxo-quinoxyfen	1771846 1642962 2805818
	Air	Half-life ≥ 2 days or evidence of long-range transport	Not determined. Estimations of 2-oxo-quinoxyfen sorbed to airborne particles range from 0.78 to 1. Because the sorbed fraction may be resistant to atmospheric oxidation, current models (for example, AOPWIN) assuming gas phase transport, are not suited for predicting the atmospheric half-life of this substance.	
	<u>Conclusion</u>: Despite the absence of DT_{50} estimations, there is evidence that the persistence criterion in soil may be met. Persistence criteria in water and air cannot be determined.			
Bioaccumulation[3]	Log K_{ow} ≥ 5		EPISuite estimate: 4.11 Experimental log K_{ow} values: 4.9 (pH 5), 4.8 (pH 7 and pH 9) 2-oxo-quinoxyfen does not meet bioaccumulation criterion.	2270289
	BCF[4] ≥ 5000		No data submitted or available.	
	BAF ≥ 5000		No data available.	
<u>Conclusion</u>:	Because not all criteria are met, 2-oxo-quinoxyfen is not considered to meet TSMP			

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	2-oxo-quinoxyfen Assessment Against Criteria Endpoints	Reference
	Track 1 criteria.		

[1]A substance is CEPA toxic (or CEPA toxic equivalent) if it is entering or may enter the environment in a quantity or concentration or under conditions that
(a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
(b) constitute or may constitute a danger to the environment on which life depends; or
(c) constitute or may constitute a danger in Canada to human life or health.
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment 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 8 List of Conventional Active Ingredients Currently Registered on Grape, Melons, Pumkin, Winter Squash, Head and Leaf Lettuce, Stone fruits, Strawberry and Hops as of October 2017.

Crop	Causal Pathogen	Active Ingredients (FRAC code)
Stone fruit	*Podosphaera clandestina*	fluopyram (7)
		penthiopyrad (7)
		boscalid + pyraclostrobin (7+11)
		metrafenone (U8)
	Sphaerotheca pannosa	myclobutanil(3)
		fluopyram (7)
		boscalid + pyraclostrobin (7+11)
		pyraclostrobin (11)
		sulphur (M)
Grape	*Uncinula necator* (syn. *Erysiphe necator*)	difenoconazole (3)
		flutriafol (3)
		myclobutanil (3)
		tetraconazole (3)
		benzovindiflupyr + difenoconazole (3+7)
		difenoconazole + cyprodinil (3+9)
		spiroxamine (5)
		benzovindiflupyr (7)
		boscalid (7)
		fluxapyroxad (7)
		fluopyram + pyrimethanil (7+9)
		boscalid + pyraclostrobin (7+11)
		kresoxim-methyl (11)
		mandestrobin (11)*
		trifloxystrobin (11)
		polyoxin d zinc salt (19)
		copper (M1)
		folpet (M4)
		sulphur (M2)
		metrafenone (U8)
		pyriofenone (U8)
Strawberry	*Sphaerotheca macularis* (syn. *Podosphaera aphanis*)	flutriafol (3)
		myclobutanil (3)
		tetraconazole (3)

Crop	Causal Pathogen	Active Ingredients (FRAC code)
		fluopyram (7)
		fluxapyroxad (7)
		penthiopyrad (7)
		boscalid + pyraclostrobin (7+11)
		cyprodinil+ fludioxonil (9+12)*
		trifloxystrobin (11)
		calcium polysulphide (M2)
Melons, pumpkin, winter squash	*Sphaerotheca fuliginea*	difenoconazole (3)
		myclobutanil (3)
		prothioconazole (3)
		benzovindiflupyr(7)
		fluxapyroxad (7)
		penthiopyrad (7)
		benzovindiflupyr + difenoconazole (7+3)
		fluopyram + pyrimethanil (7+9)
		boscalid + pyraclostrobin (7+11)
		penthiopyrad + chlorothalonil (7+M5)
		pyraclostrobin (11)
		trifloxystrobin (11)
		azoxystrobin + difenoconazole (11+3)
		benzovindiflupyr + azoxystrobin (11+7)
		polyoxin d zinc salt (19)
		chlorothalonil (M5)
		copper (M1)
		folpet (M4)
		metrafenone (U8)
		pyriofenone (U8)
Head and leaf lettuce	*Erysiphe cichoracearum*	boscalid + pyraclostrobin (7+11)* *greenhouse only*
		cyprodinil+ fludioxonil (9+12)* *greenhouse only*
Hops	*Sphaerotheca macularis*	metrafenone (U8)
		boscalid + pyraclostrobin (7+11)

*suppression claim

Table 9 List of Biological and Other Non-Conventional Active Ingredients Currently Registered on Grape, Melons, Pumkin, Winter Squash, head and Leaf Lettuce, Stone fruits, Strawberry and Hops as of October 2017.

Crop	Causal Pathogen	Active Ingredients (FRAC code)
Grape	*Uncinula necator*	• *Bacillus amyloliquefaciens*, strain D747 (44) • *Bacillus subtilis*, strain QST 713 (44) • extract of *Reynoutria sachalinensis* (P5) • garlic powder • mineral oil • potassium bicarbonate • tea tree oil
Melons, pumpkin, and winter squash	*Sphaerotheca fuliginea*	• mineral oil • potassium bicarbonate • *Bacillus subtilis*, strain QST 713 (44) • *Streptomyces lydicus* strain WYEC 108 • garlic powder • citric acid + lactic acid

Crop	Causal Pathogen	Active Ingredients (FRAC code)
		• extract of *Reynoutria sachalinensis* (P5) • potassium bicarbonate
Head and leaf lettuce	*Erysiphe cichoracearum*	• *Bacillus subtilis*, strain QST 713 (44)
Stone fruits	*Podosphaera clandestina* *Sphaerotheca pannosa*	• potassium bicarbonate • mineral oil
Strawberry	*Sphaerotheca macularis*	• mineral oil • tee tree oil • blad polypeptide • *Bacillus amyloliquefaciens*, strain D747 (44) • *Streptomyces lydicus* strain WYEC 108 • citric acid + lactic acid • extract of *Reynoutria sachalinensis* (P5)
Hops	*Sphaerotheca macularis*	• potassium bicarbonate

References

A. List of Studies/Information Submitted by Registrant

1.0 Human and Animal Health

PMRA Document Number	Reference
2642066	2004, Acute Oral Toxicity Up And Down Procedure In Rats - 3-0H Quinoxyfen Metabolite, DACO: 4.2.1

2.0 Environment

PMRA Document Number	Reference
1642962	1995, The Aerobic Degradation of Radio-Labelled XDE-795 in Natural Water and Associated Sediments, DACO: 8.2.3.5, 8.2.3.5.4.
1771844	1993, The Aerobic Soil Degradation/Metabolism of [^{14}C]-XDE-795 and the Effect of Environmental Conditions on its Degradation Rate, DACO: 8.2.3.4.2.
1771845	1994, Identification of Soil Metabolism Products of XDE-795 by Particle-Beam Liquid Chromatography Mass Spectrometry and Thermospray Liquid Chromatography Mass Spectrometry, DACO: 8.2.3.4.2.
1771850	2001, Field Dissipation of Quinoxyfen Under California Irrigated Conditions, DACO: 8.3.2.
1771851	1999, Residues of Quinoxyfen and its 3-Hydroxy Metabolite in Soil Following Five Annual Applications of EF-1186, Northern France - 1993, DACO: 8.3.2.
1771852	1999, Residues of Quinoxyfen and its 3-Hydroxy Metabolite in Soil Following Five Annual Applications of EF-1186, Germany, DACO: 8.3.2.
1771853	2000, Residues of Quinoxyfen and its 3-Hydroxy Metabolite in Soil Following Five Annual Applications of EF-1186, U.K. - Final Report, DACO: 8.3.2.
2204555	2011, Quinoxyfen Multispecies Bioconcentration Study in Rainbow Trout (*Oncorhynchus mykiss*), Algae (*Pseudokirchneriella subcapitata*) and Daphnid (*Daphnia magna*), DACO: 9.3.2, 9.5.2.1, 9.8.2.
2270289	2013, Determination of Octanol/Water Partition Coefficient for 2-Oxo-Quinoxyfen by Shake Flask Method, DACO: 8.6.
2270291	2011, Laboratory Bioassay to Determine the Acute Oral Toxicity of Technical-Grade Quinoxyfen to the Honeybee, *Apis mellifera*, DACO: 9.2.4.2.
2270295	2011, A Rate-Response Laboratory Test to Determine the Effects of EF-1295 on the Predatory Mite, *Typhlodromus pyri* (Acari: Phytoseiidae), DACO: 9.2.5.
2270296	2011, A Rate-Response Laboratory Test to Determine the Effects of EF-1295 on the Parasitic Wasp, *Aphidius rhopalosiphi* (Hymenoptera, Braconidae), DACO: 9.2.6.
2270299	2012, 2-Oxo-Quinoxyfen: Early Life-Stage Toxicity Test with Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.3.2.

2333181	2011, Quinoxyfen Multispecies Bioconcentration Study in Rainbow Trout (*Oncorhynchus mykiss*), Algae (*Pseudokirchneriella subcapitata*) and Daphnid (*Daphnia magna*). Volume 2, DACO: 9.5.6.
2333182	2011, Quinoxyfen Multispecies Bioconcentration Study in Rainbow Trout (*Oncorhynchus mykiss*), Algae (*Pseudokirchneriella subcapitata*) and Daphnid (*Daphnia magna*). Volume 3, DACO: 9.5.6.
2333183	2011, Quinoxyfen Multispecies Bioconcentration Study in Rainbow Trout (*Oncorhynchus mykiss*), Algae (*Pseudokirchneriella subcapitata*) and Daphnid (*Daphnia magna*). Volume 4, DACO: 9.5.6.
2333184	2011, Quinoxyfen Multispecies Bioconcentration Study in Rainbow Trout (*Oncorhynchus mykiss*), Algae (*Pseudokirchneriella subcapitata*) and Daphnid (*Daphnia magna*). Volume 5, DACO: 9.5.6.
2333185	2011, Quinoxyfen Multispecies Bioconcentration Study in Rainbow Trout (*Oncorhynchus mykiss*), Algae (*Pseudokirchneriella subcapitata*) and Daphnid (*Daphnia magna*). Volume 6, DACO: 9.5.6.
2806707	1999, The Dissipation of Quinoxyfen and its 3-Hydroxy Metabolite in Soil at Intervals Following a Single Application of EF-1186, Northern France - 1994, DACO: 8.2.3.4.
2806708	1999, The Dissipation of Quinoxyfen and its 3-Hydroxy Metabolite in Soil at Intervals Following a Single Application of EF-1186, UK - 1994, DACO: 8.2.3.4.
2806709	1999, The Dissipation of Quinoxyfen and its 3-Hydroxy Metabolite in Soil at Intervals Following a Single Application of EF-1186, Germany - 1994, DACO: 8.2.3.4.
2806710	1999, The Dissipation of Quinoxyfen and its 3-Hydroxy Metabolite in Soil at Intervals Following a Single Application of EF-1186, Southern France - 1994, DACO: 8.2.3.4.
2806711	1996, The Dissipation of XDE-795 and its 3-Hydroxy Metabolite in Soil at Intervals Following Application of EF-1186, Germany - 1993, DACO: 8.2.3.4.
2806712	1996, The Dissipation of XDE-795 and its 3-Hydroxy Metabolite in Soil at Intervals Following a Single Application of EF-1186, Southern France - 1993, DACO: 8.2.3.4.
2806713	1996, The Dissipation of XDE-795 and its 3-Hydroxy Metabolite in Soil at Intervals Following a Single Application of EF-1186, Northern France - 1993, DACO: 8.2.3.4.
2806714	1995, The Dissipation of XDE-795 and its 3-Hydroxy Metabolite in Soil at Intervals Following Application of EF-1186, UK - 1993, DACO: 8.2.3.4.

B. Additional Information Considered

i) Published Information

1.0 Environment

PMRA Document Number	Reference
2036781	European Commission, 2001, Opinion of the Scientific Committee on Plants regarding the evaluation of quinoxyfen in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market. SCP/QUINOX/002-Final, Active: Quinoxyfen, DACO: 12.5.
2803872	European Commission, 2016, Draft (Renewal) Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009, DACO: 12.5.
2803873	European Commission, 2016, Draft (Renewal) Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009, DACO: 12.5.
2803874	Coscollà C., Castillo M., Pastor A. and Yusà V., 2011, Determination of 400 Currently Used Pesticides in Airborne Particulate Matter (PM 10) by Microwave-Assisted Extraction and Gas Chromatography Coupled to Triple Quadrupole Mass Spectrometry, DACO: 8.6.
2805818	European Commission, 2016, Draft (Renewal) Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009, DACO: 12.5.