Proposed Re-evaluation Decision PRVD2022-06

Zoxamide and Its Associated End-use Products

Consultation Document

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Proposed Re-evaluation Decision for Zoxamide and Associated End-use Products

Under the authority of the *Pest Control Products Act,* all registered pesticides must be re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Zoxamide is a fungicide registered for the control of fungal diseases on potatoes, grapes and onions (bulb). Currently registered products containing zoxamide can be found in the Pesticide Label Search and in Appendix I.

This document presents the proposed re-evaluation decision for zoxamide, including the proposed amendments (risk mitigation measures) to protect human health and the environment, as well as the science evaluation on which the proposed decision is based. All products containing zoxamide that are registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period,[1] during which the public (including the pesticide manufacturers and stakeholders) may submit written comments and additional information to PMRA Publications. The final re-evaluation decision will be published after taking into consideration the comments and information received during the consultation period.

Proposed Re-evaluation Decision for Zoxamide

Under the authority of the *Pest Control Products Act* and based on an evaluation of available scientific information, Health Canada is proposing continued registration of zoxamide and associated end-use products registered for sale and use in Canada.

Zoxamide is a valuable disease management tool for vegetable and grape growers due its rainfastness, residual properties and low to medium risk for resistance development.

With respect to human health, dietary as well as occupational and non-occupational risks from all uses were shown to be acceptable under the current conditions of use. Therefore, no additional mitigation measures are proposed.

Zoxamide risk to non-target terrestrial organisms (earthworms, beneficial arthropods, honeybees, birds, wild small mammals and terrestrial plants) are considered to be acceptable for all registered uses with no additional mitigation measures. No terrestrial buffer zones are required.

Risks from spray drift and runoff of zoxamide, at the currently registered rates, were identified for certain aquatic organisms. To protect aquatic organisms, the risk mitigation measures proposed include additional precautionary label statements and spray buffer zones.

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

Risk mitigation measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law. The proposed label amendments including any revised/updated label statements and/or mitigation measures, as a result of the re-evaluation of zoxamide, are summarized below. Refer to Appendix IX for details.

Risk mitigation:

To protect the environment, the following risk-reduction measures are proposed:

- Precautionary label statements to inform users of the potential toxicity of zoxamide to aquatic organisms.
- Spray buffer zones for the protection of freshwater aquatic habitats such as:
    - 1–10 m for field sprayer; 5–45 m for airblast; 5–350 m for aerial
- To reduce the potential for runoff of zoxamide to adjacent aquatic habitats, precautionary label statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecast.

Other label updates:

- An update to the standard statement to minimize human exposure from spray drift.
- Clarify the application method for bulb onion (specify ground application).

International context

Zoxamide is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States, the European Union and Switzerland. Internationally and within the available information, no evidence of a ban as of 27 August 2021 to prohibit all uses of zoxamide for health or environmental reasons has been identified.

Next steps

Upon publication of this proposed re-evaluation decision, the public, including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses. Refer to Appendix I for details on specific products impacted by this proposed decision.

Other information

The relevant confidential test data on which the proposed decision is based (in the References section of this document) are available for public inspection, upon application, in Health Canada's Reading Room. For more information, please contact Health Canada's Pest Management Information Service.

Additional scientific information

Additional scientific data are not required at this time.

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

Science Evaluation

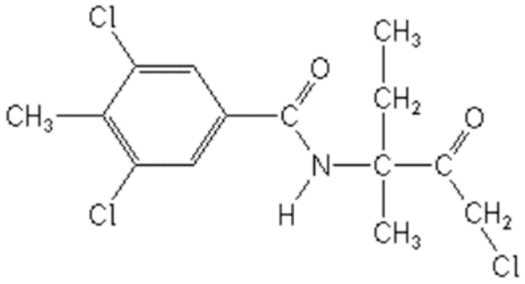
1.0 Introduction

Zoxamide is a benzamide fungicide registered for use on potatoes, grapes and onions (bulb) for control of various oomycete diseases (for example, late blight and downy mildew). It is registered for application using ground (boom and airblast) and aerial equipment (potato only).

Appendix I lists all zoxamide products that are registered under the authority of the *Pest Control Products Act*. Appendix II lists all the uses for which zoxamide is presently registered.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name		Zoxamide
Function		Fungicide
Chemical Family		Benzamide
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	3,5-dichloro-*N*-[(1*RS*)-3-chloro-1-ethyl-1-methyl-2-oxopropyl]-4-methylbenzamide
2	**Chemical Abstracts Service (CAS)**	3,5-dichloro-*N*-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide
CAS Registry Number		156052-68-5
Molecular Formula		$C_{14}H_{16}Cl_3NO_2$
Structural Formula		
Molecular Weight		336.65
Purity of the Technical Grade Active Ingredient		98%
Registration Number		26841

2.2 Physical and Chemical Properties

Property	Result
Vapour pressure at 25°C	$<1.3 \times 10^{-2}$ mPa
Ultraviolet (UV) / visible spectrum	The active ingredient did not show significant absorbance at $\lambda > 300$ nm.
Solubility in water at 20°C	0.681 mg/L
n–Octanol/water partition coefficient	log K_{ow} = 3.76
Dissociation constant	No measurable dissociation

3.0 Human health assessment

3.1 Toxicology summary

Zoxamide is a benzamide fungicide which binds fungal β-tubulin to inhibit microtubule polymerization. A detailed review of the toxicology database for zoxamide, and its metabolites, was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The toxicology assessment also considered information found in the published scientific literature. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with zoxamide and its metabolites.

Phenyl-radiolabelled zoxamide was rapidly absorbed in rats following an oral gavage exposure. The peak plasma concentration was reached within 8 hours in both sexes following a single low- or high-dose, indicating similar rates of absorption. Tissue retention was minimal after 7 days, with the liver, stomach, and intestines showing the highest tissue concentration of radiolabel in rats. A supplemental study in mice indicated the potential for retention in the bone marrow. In rats, the fecal route was the predominant route of excretion following either a single low- or high-dose. Urinary excretion was higher in females than males. Oral administration of a single low-dose resulted in similar elimination via the bile and urine in both sexes. Biliary excretion was not measured in the high dose group, so the extent of absorption cannot be compared. The half-life of elimination was similar between low- and high-dose groups and in both sexes. Although the extent of oral absorption following a high-dose was not measured, the low dose is more representative of the critical studies used in the human health risk assessment.

Zoxamide was extensively metabolized in the rat to 36 metabolites following a single low- or high-dose, as well as a repeated low-dose. Metabolism occurred predominantly by hydrolysis, glutathione conjugation, reductive dehalogenation, secondary oxidation of aromatic methyl and aliphatic side chains, and terminal glucurionic acid/amino acid conjugation. With the exception of zoxamide, no metabolite accounted for more than 10% of the administered dose (AD). There was no apparent difference in biliary metabolites between male and females. Levels of individual fecal and urinary metabolites were largely similar between sexes and dose levels.

However, a larger proportion of unchanged zoxamide was present in the feces after high-dose administration, suggesting incomplete absorption. Excretion of unchanged zoxamide was slightly reduced in the repeated low-dose group suggesting enzyme induction.

Toxicokinetic studies of two major potato/minor rat metabolites of zoxamide were considered. A single oral high-dose of either RH-141,452 or RH-141,455 were administered to male rats. RH-141,452 was excreted primarily unchanged in the urine, accounting for 94% of the AD. RH-141,455 was excreted unchanged primarily in the feces and urine, accounting for 73% and 11% of the AD, respectively. Tissue distribution and biliary metabolism were not measured.

Zoxamide was of low acute oral toxicity in mice and rats, and of low acute dermal and inhalation toxicity in rats. In rabbits, zoxamide was mildly irritating to the eye and non-irritating to the skin. The metabolites RH-141,452 and RH-141,455 were of low acute oral toxicity in mice. In guinea pigs, zoxamide was a strong skin sensitizer when assessed by the Buehler and Maximization test methods. A local lymph node assay (LLNA) was requested due to the strong skin sensitization effects observed. A LLNA waiver request was accepted because a second Maximization Test that used a higher purity of Zoxamide (99%) showed decreased severity and frequency of sensitization effects.

A repeat-dose dermal toxicity study in rats showed increased skin irritation and dermal scabbing following treatment. Changes to the dermis included hyperplasia, hyperkeratosis, and inflammation with associated cell infiltration. There was no evidence of systemic toxicity after dermal exposure. A 90-day inhalation toxicity/pulmonary sensitization study waiver request was accepted based on the finding that the spray droplet spectrum would contain less than 0.1% respirable droplets and would not penetrate below the human pharynx.

Administration of zoxamide in repeat-dose dietary toxicity studies revealed body weight as the most sensitive endpoint. There were no treatment-related findings in available short-term and chronic dietary toxicity studies in mice. Dogs were the species most sensitive to the toxicological effects induced by zoxamide. The most sensitive oral endpoint for risk assessment was decreased body weight and body weight gain in females. Male dogs were less sensitive and showed decreased body weight and body weight gain at the next dose level when compared to female dogs. Both sexes demonstrated liver and thyroid toxicity at the highest dose tested. Liver effects included hypertrophy and altered clinical parameters such as increased alkaline phosphatase (ALP) and decreased red blood cell (RBC) counts. In dogs, the thyroid gland was also a target site of toxicity as evidenced by a treatment-related increase in thyroid follicular epithelium hypertrophy and thyroid weight in the 90-day and 1-year dietary toxicity studies, respectively. However, thyroid weight was not measured in the 90-day study, and thyroid hormone levels were not measured in either dog study. Longer duration of dosing indicated an increased severity of treatment-related toxicity in dogs. Repeat-dose studies conducted with mice (3 and 18 months) and rats (2 years) showed no treatment-related adverse effects.

In rat and mouse dietary chronic toxicity and/or oncogenicity studies, there was no evidence of treatment-related oncogenicity at any dose level. Zoxamide was not genotoxic in a standard battery of in vitro and in vivo assays, which included a bacterial gene mutation assay, a chromosomal aberration assay in Chinese hamster ovary (CHO) cells, a mammalian gene mutation assay in CHO cells, and micronucleus assays in mice and rats. An increased frequency of numerical chromosomal aberrations was observed in the in vitro chromosomal aberration assay.

However, two in vivo micronucleus assays, one of which included a kinetochore analysis, showed no increase in the frequency of numerical aberrations or presence of micronuclei. As a result, the chromosomal aberrations seen in the in vitro studies are deemed not to be of toxicological concern.

Metabolites RH-141,452 and RH-141,455 were not genotoxic based on results from a bacterial gene mutation assay. A full battery of genotoxicity tests for these metabolites was not available.

The dietary two-generation reproductive toxicity study in rats showed no treatment-related reproductive effects. In P_1 females, systemic toxicity was evidenced by decreased body weights above the limit dose. In offspring, decreased body weights, spleen weights (only F_{1a}), and reduced extramedullary hematopoiesis in the spleen were observed at all doses in the F_1 and F_2 generations. There was some indication of sensitivity of the young based on body weight and spleen effects in offspring in the absence of maternal toxicity. However, these body weights and spleen effects in offspring were not considered to be serious, there was a lack of a clear dose response, and recovery was demonstrated.

In both rat and rabbit gavage developmental toxicity studies, no treatment-related adverse effects were noted in either dams or fetuses. There was no evidence of developmental toxicity or sensitivity of the young in either rats or rabbits at doses up to and including the limit dose.

The neurotoxic potential of zoxamide was examined in rats following acute and short-term exposures. In both acute and short-term neurotoxicity studies, there were no treatment-related deaths, no effects on motor activity or functional observational battery (FOB) parameters and no associated neuropathology at doses above the limit dose. Overall, both studies showed no evidence of selective neurotoxicity.

Studies elucidating the mechanism of action of zoxamide were assessed. Zoxamide readily bound fungal β-tubulin. Zoxamide also inhibited polymerization of mammalian β-tubulin in vitro; however, inhibition required a longer incubation time, demonstrating a relatively weak interaction. Environmental metabolites that lack the haloketone toxophore (RH-24549, RH-127450, and RH-163353) only weakly inhibited fungal tubulin polymerization, and did not bind mammalian tubulin. Pre-incubation of zoxamide with S9-fraction or whole rat liver slices prior to exposure mitigated toxicity in CHO cells. It is likely that removal of the haloketone toxophore during mammalian metabolism is responsible for reduced tubulin binding and decreased toxicity.

A quantitative structure-activity relationship (QSAR) analysis of select impurities and metabolites showed no alerts of toxicological concern compared to zoxamide.

The identification of zoxamide and select metabolites is presented in Appendix III, Table 3.1. Results of the toxicology studies conducted on laboratory animals with zoxamide and select metabolites are summarized in Appendix III, Table 3.2. The toxicological reference values for use in the human health risk assessment are summarized in Appendix III, Table 3.3.

3.1.1 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or drinking water, 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 standard complement of required studies including oral 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 some evidence of sensitivity of the young in the rat two-generation reproductive toxicity study. Parental animals had decreased body weight at the highest dose, whereas both filial generations had decreased body weight, spleen weight, and reduced extramedullary hematopoiesis of the spleen at all doses. However, the decreased body weight in the offspring did not show a clear dose response and body weight recovered over time. As there was a low level of concern for these effects, an additional uncertainty factor for the use of a LOAEL was not warranted. There were no treatment-related adverse effects identified in the rat and rabbit developmental toxicity studies.

Overall, the effects are well characterized and the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young. The body weight and spleen effects in offspring are not considered to be serious effects and, as noted previously, there was non clear dose response and recovery was demonstrated. Furthermore, the reference values selected for risk assessment are protective of these effects. On the basis of this information, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold.

3.2 Dietary exposure and risk assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference value. PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Sufficient information was available to adequately assess the dietary exposure and risk from zoxamide. Chronic dietary (food and drinking water) exposure and risk assessments for zoxamide was conducted using Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005–2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS).

Further details on the consumption data are available in PMRA's Science Policy Note SPN 2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. For more information on the dietary risk estimates or the residue chemistry information used in the dietary assessment, see Appendix IV.

3.2.1 Determination of acute reference dose (ARfD)

No endpoint of concern attributable to an acute exposure was identified in the toxicology database. Therefore, an acute reference dose was not established.

3.2.2 Acute dietary exposure and risk assessment

Since an acute reference dose was not established, an acute risk assessment was not required.

3.2.3 Determination of acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 48 mg/kg bw/day from the 12-month dietary toxicity study in the dog was selected. At the LOAEL of 255 mg/kg bw/day, reductions in body weights and body weight gain were observed in females. This study provides 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 composite assessment factor (CAF) is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{48 \text{ mg/kg bw/day}}{100} = 0.5 \text{ mg/kg bw/day of zoxamide.}$$

The ADI provides a margin of 164 to the dose level at which reduced body and spleen weights in offspring, as well as reduced extramedullary haematopoiesis in the spleen were observed in the rat 2-generation reproductive toxicity study.

3.2.4 Chronic dietary exposure and risk assessment

The chronic dietary risk was calculated using average consumption of different foods and drinking water, and potential residues of zoxamide in food and drinking water. The estimated exposure was then compared to the ADI, which is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is shown to be acceptable.

The assessment was conducted using Canadian Maximum Residue Limit (MRL)/American Tolerance/Codex MRL levels, whichever is highest, and assuming all crops were 100% treated. Theoretical and experimental factors were used, where available. Drinking water contribution to the exposure was accounted for by direct incorporation of the chronic estimated environmental concentrations (EECs) value obtained from modelling (see Section 3.3) into DEEM.

The chronic dietary exposure estimates (from food and drinking water) were below 16% of the ADI for the general population and all other subpopulations and thus, the chronic risk was shown to be acceptable.

3.2.5 Cancer assessment

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

3.3 Exposure from drinking water

Residues of zoxamide in potential drinking water sources were estimated from water modelling.

3.3.1 Concentrations in drinking water

The estimated environmental concentrations (EECs) of zoxamide were calculated using the Pesticides in Water Calculator model (PWC, version 1.52). The use pattern modelled was eight applications of 224 g active ingredient (a.i.)/ha with a 7-day interval between applications. Modelling for surface water used a standard Level 1 scenario, a small reservoir adjacent to an agricultural field. EECs in groundwater were calculated by selecting the highest EEC from a set of standard scenarios representing different regions of Canada. All scenarios were run for 50 years.

The highest groundwater yearly EEC value of 295 µg/L was used in the chronic exposure assessments.

3.3.2 Drinking water exposure and risk assessment

Drinking water exposure estimates were combined with food exposure estimates, with EEC point estimates incorporated directly in the dietary (food and drinking water) assessments. Chronic risks were shown to be acceptable. Please refer to Section 3.2.4 for details.

3.4 Occupational and non-occupational exposure and risk assessment

Occupational and non-occupational (for example, residential) risk is estimated by comparing potential exposures with the most relevant reference value from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce potential risk would be required.

3.4.1 Toxicological reference values

3.4.1.1 Short-, intermediate- dermal and inhalation

For short-, and intermediate-term occupational exposures via the dermal and inhalation routes, the offspring LOAEL of 82 mg/kg bw/day from the two-generation reproductive toxicity study in rats was selected for the risk assessment. At all doses, reductions in body weight, decreased spleen weight, and extramedullary hematopoiesis of the spleen were observed in both filial generations during the periods of lactation and weaning. However, these effects were not

considered to be serious effects, there was no clear dose response, and recovery was demonstrated. Therefore, no additional factors for use of a LOAEL were applied. The target margin of exposure (MOE) for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Although a 28-day dermal toxicity in rats was available, it was not chosen for endpoint selection. In the 2-generation reproductive study in rats, there was a decrease in extramedullary hematopoiesis in offspring, which was not seen in the parental generation. The 28-day dermal study showed one incidence of minimal extramedullary hematopoiesis at the high-dose; however, histopathology was only performed on control and high-dose animals, precluding a dose-response assessment. In turn, based on a dermal absorption value of 8.8%, the equivalent systemic dose in the dermal study would be approximately 90 mg/kg bw/day, which is comparable to the dose level where decreased extramedullary hematopoiesis was seen in the 2-generation reproductive toxicity study. The incidence of decreased extramedullary hematopoiesis was more pronounced in pups in the 2-generation reproductive toxicity study as compared to the spleen effects noted in the 28-day dermal toxicity study. Taken together, the 2-generation reproductive toxicity study was deemed more appropriate for endpoint selection to ensure protection of potentially sensitive populations.

A short-term inhalation toxicity study was not available as a waiver request was accepted based on the finding that the spray droplet spectrum would contain less than 0.1% respirable droplets and therefore would not penetrate below the human pharynx.

3.4.1.2 Dermal absorption factor

A dermal absorption value of 9% was determined for zoxamide based on the dermal absorption study conducted in male rats. The derived absorption value after 10 h exposure was 8.8%.

3.4.1.3 Cancer assessment

See Section 3.2.5.

3.4.2 Non-occupational exposure and risk assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

There are no domestic-class products containing zoxamide registered in Canada; therefore, residential handler exposure is not anticipated.

Commercial-class products containing this active ingredient are not expected to be used in residential settings. There is, however, a potential for non-occupational exposure to zoxamide residues during agricultural applications (bystanders exposed to spray drift).

To minimize potential exposures from drift, all current end-use product labels include a standard best practice spray drift labels statement, and this label statement is proposed to be updated to meet the current labelling standard.

3.4.3 Occupational exposure and risk assessment

There is potential for exposure to zoxamide through mixing, loading, or applying the pesticide, and when entering a treated site to conduct postapplication activities such as scouting and hand harvesting crops.

3.4.3.1 Mixer, loader, and applicator exposure and risk assessment

Based on the current use pattern, potential exposure of mixers/loaders and applicators is expected from short-/intermediate duration and to occur via both dermal and inhalation routes of exposure.

The following exposure scenarios were assessed based on the currently registered use pattern:

1) mixing/loading of liquid formulation and applying as a spray using groundboom
2) mixing/loading of liquid formulation and applying as a spray by aerial equipment
3) mixing/loading of dry flowable formulation and applying as a spray by airblast
4) mixing/loading of dry flowable formulation and applying as a spray using groundboom
5) mixing/loading of dry flowable formulation and applying as a spray by aerial equipment
6) mixing/loading of wettable granule formulation and applying as a spray by airblast
7) mixing/loading of wettable granule formulation and applying by aerial equipment
8) mixing/loading of wettable granule formulation and applying using groundboom

Chemical-specific handler exposure data were not available for zoxamide; therefore, dermal and inhalation exposures were estimated using exposure data from the Agricultural Handlers Exposure Task Force (AHETF). Exposure of mixers/loaders and applicators was estimated using unit exposure (UE) values from AHETF for workers wearing a long-sleeved shirt, long pants, and chemical-resistant gloves. Additional inputs in the exposure assessment included default area treated per day (ATPD) values, the maximum registered application rates, and average worker body weight of 80 kg.

Toxicological reference values used in the assessment are summarized in Appendix III. Short/intermediate-term dermal and inhalation risks can be combined based on the same reference value derived from the same toxicity study for the dermal and inhalation routes.

The risk assessment for mixers/loaders and applicators using various application equipment is presented in Appendix VI (Table 6.1 to 6.3). Since the short/intermediate-term dermal reference value is based on an oral study, short/intermediate-term dermal exposure is adjusted for 9% dermal absorption.

For all assessed scenarios, the estimated MOEs are greater than the target MOEs for workers wearing a single layer of clothing and chemical-resistant gloves. On this basis, risks are considered to be acceptable for workers mixing/loading, and applying zoxamide. No additional mitigation measures are proposed.

3.4.3.2 Postapplication worker exposure and risk assessment

For workers entering treated fields to conduct postapplication activities, dermal exposure is considered to be the primary route of exposure. Considering the low volatility of this active ingredient and assuming at least 12 hours have passed before entry, inhalation exposure to zoxamide is not expected for postapplication workers entering treated sites.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before workers can enter after application. The REI is the duration of time that must elapse in order to allow residues to decline to a level where risks are considered to be acceptable for postapplication worker activities (that is, performance of a specific activity that results in exposures at or above the target MOE). Based on the current use pattern, there is potential for short/intermediate term postapplication exposure to zoxamide for workers in treated fields.

Exposure of workers entering treated sites was estimated using activity-specific transfer coefficients (TCs) and default dislodgeable residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant, which is a measurement of pesticide residue on foliage that can be transferred to human skin and clothing. No chemical-specific DFR data were available for zoxamide; therefore, a standard peak DFR value of 25% of the application rate and 10% of dissipation per day was used. Health Canada's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Postapplication Assessments* presents further details on the derivation and use of these standards for pesticide assessments. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination and reflect standard agricultural work clothing worn by adult workers. The activity-specific TC from the Agricultural Re-Entry Task Force (ARTF) was used for this risk assessment. For more information about estimating worker postapplication exposure, refer to Health Canada's Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Exposure to Pesticides*. Additional inputs in the exposure assessment included an 8-hour workday for all activities, and an average worker body weight of 80 kg. Exposure estimates for workers conducting postapplication activities were adjusted for a 9% dermal absorption.

The short-/intermediate-term risk assessment for workers conducting postapplication activities is summarized in Appendix VII, Table 7.1. The calculated short-intermediate-term MOEs for postapplication workers are above the target MOE. On this basis, postapplication risks for workers entering treated sites are shown to be acceptable under current conditions of use. No additional mitigation measures are proposed.

3.5 Aggregate exposure and risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). For zoxamide, the aggregate assessment consisted of combining food and water exposure only (see Section 3.2), and was shown to be acceptable.

3.6 Cumulative assessment

The *Pest Control Products Act* requires that the agency consider cumulative exposure to pesticides with a common mechanism of toxicity.

A preliminary grouping was made with other Canadian registered benzamide products fluopicolide and fluopyram based on structural similarity. Zoxamide binds fungal β-tubulin while fluopicolide interacts with spectrins and fluopyram inhibits succinate dehydrogenase. As a result, there is no common mode of action for which to base a cumulative health risk assessment on for this grouping.

A preliminary grouping was also made with the other Canadian registered β-tubulin inhibitors carbendazim and thiophanate-methyl based on a similar fungal mode of action. However, zoxamide had much less affinity for mammalian tubulin in vitro and required a much longer incubation time than carbendazim. In addition, zoxamide was extensively metabolized in rats, and selected metabolites of zoxamide had negligible affinity for mammalian tubulin in vitro. Therefore, currently, there is no molecular or mechanistic data to show that zoxamide binds mammalian β-tubulin in vivo to any significant extent. In turn, for the current re-evaluation, the PMRA did not identify a common mammalian mode of action with carbendazim or thiophanate-methyl.

For the current re-evaluation, the PMRA did not identify information indicating that zoxamide shares a common mechanism of toxicity with other pest control products and it does not appear to produce a toxic metabolite common to other pest control products. Therefore, a cumulative risk assessment is not required at this time.

3.7 Health incident reports

As of 21 October 2021, no human or domestic animal incident reports involving zoxamide have been submitted to the PMRA.

4.0 Environmental assessment

4.1 Fate and behaviour in the environment

Summaries of physico-chemical properties relevant to the environment and environmental fate of zoxamide and its major transformation products (where available) are presented in Appendix VIII, Tables 8.1 and 8.2.

Zoxamide dissipates rapidly in the environment via hydrolysis and biotic transformation (mineralization as well as binding to soil or sediment). In the terrestrial environment, zoxamide is non-persistent to slightly persistent in soil under anaerobic and aerobic conditions, respectively. In laboratory studies mineralization was significant in aerobic soils (up to 57.8% applied radioactivity, AR) but it was limited in anaerobic soil (up to 5.1 AR). The non-extractable residues (NER) in soil accounted for up to 39.2% to 26.4% of AR in aerobic and anaerobic soil studies. The following three major transformation products (TPs; ≥10% applied) were identified in soil with the latter identified only under aerobic conditions: RH-127450, RH-24549 and RH-163353. Laboratory studies showed that RH-127450 and RH-24549 are non-persistent and RH-163353 is non-persistent to moderately persistent in soils under aerobic conditions. Hydrolysis is also expected to contribute to the overall dissipation of zoxamide (half-life 16.3 days at pH 7). Hydrolysis resulted in four major transformation products, RH-129151, RH-150721, RH-141288 and RH-24549. RH-150721 and RH-129151 were transitory intermediates leading to the formation of RH-24549 and RH-141288.

Photolysis is not a route of dissipation of zoxamide in soil. Based on terrestrial field studies conducted in Canada and the United States (equivalent ecoregion), zoxamide is non-persistent in soil with no carry-over of its residues to the next growing season and no detection below the 15-cm soil depth in soil.

Zoxamide can enter aquatic environments through spray drift and run-off from the application sites. In the aquatic environment, zoxamide is non-persistent and dissipates from water by biotic and abiotic transformation. The laboratory studies showed that zoxamide mineralized up to 21.9% and 9.1% AR and the NER was accounted for up to 80.6% and 39.7% AR in aerobic and anaerobic water/sediment systems, respectively. Two major transformation products were detected, RH-127450 and RH-163353. Laboratory studies showed that RH-127450 is moderately persistent to persistent in aquatic systems. The kinetic examination of RH-163353 was not possible because it was still forming at the end of the study. Photolysis may contribute to the dissipation of zoxamide in photic zones of water bodies. RH-139432 was the only major phototransformation product in water and was stable to photolysis.

The leaching assessment for zoxamide considered information from various sources. Zoxamide is sparingly soluble in water (0.68 mg/L) and is expected to be short-lived in the environment, based on laboratory-derived fate studies. The criteria of Cohen et. al. (1984) and the groundwater ubiquity score (GUS) indicates that zoxamide is a non-leacher. Further evidence from studies of adsorption/desorption, aged soil column leaching and terrestrial field dissipation studies (no detection below 15 cm) indicate a low potential for leaching. Detection of zoxamide in surface water and groundwater in Canada and the United States are rare and occur at low levels. Water monitoring data from 2009 to 2019 showed that zoxamide is detected at a frequency of 0.33% across all samples (N = 929 and 1502 for samples relevant to drinking water sources and the environmental assessment, respectively), with the maximum concentration of 493 ng/L in a surface water sample in areas of intense potato production and fungicide use in the United States. Conservative water modelling (using Pesticide in Water Calculator (PWC) version 1.52) for different regions of Canada showed a yearly detection of 295 µg a.i./L of the combined residue (zoxamide and six of its major transformation products: RH-24549, RH-141288, RH-129151, RH-139432, RH-127450 and RH-163353). Based on the weight of evidence it can be concluded that the potential for zoxamide to leach to groundwater is low.

Results from the adsorption/desorption laboratory studies for the major TPs in soil showed that RH-127450 exhibits low to moderate mobility, RH-24549 moderate to high mobility and RH-163353 high mobility. Based on the GUS indices, these TPs are borderline leachers, and results of an aged soil column leaching study showed that RH-127450 was only detected in the 0–10 cm layers. RH-24549 and RH-163353 have slightly greater potential for leaching down to 20 cm. These TPs are non-persistent to moderately persistent in soil. Based on the available information it was concluded that leaching of these TPs to groundwater is unlikely. No monitoring data are available for transformation products and they were not monitored in the field dissipation studies.

Zoxamide has low vapour pressure ($<1.0 \times 10^{-7}$ mm Hg) and the Henry's law constant (6.49×10^{-8} atm.m^3/mole) indicates that it is not volatile from water and moist soil surfaces. Volatilization of zoxamide from the soil or leaf surfaces under the field conditions is low with losses of 3.9% and 5.1%, respectively, after 24 hours. Therefore, concentrations of zoxamide in air after a field application are expected to be low. If zoxamide residues were to reach the troposphere as the result of a spray application, it is likely that they would be degraded in air due

to reactions with a number of reactive radical species. An estimate of the persistence of zoxamide in air showed that it would be short-lived (half-life <12 hours). Zoxamide is not expected to be transported medium- or long-range distances in the atmosphere.

Although the octanol/water partition coefficient for zoxamide (Log K_{ow} = 3.76) suggests a potential for bioaccumulation in aquatic organisms, results obtained from a bioconcentration study conducted on bluegill sunfish indicate that zoxamide does not bioaccumulate in fish due to rapid depuration (whole fish steady-state BCF = 95-136 in whole fish).

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse ecological effects on non-target species. This integration is achieved by comparing exposure concentrations [(in other words, the estimated environmental concentration (EEC)] in various environmental media, such as soil, water, air and food with concentrations at which adverse effects occur (in other words, toxicity endpoints such as LC_{50}, LD_{50}, NOEC or NOEL). The EECs are estimated using models, which take into consideration the application rate(s), chemical properties and environmental fate properties and the dissipation of the pesticide between applications (Appendix VIII, Tables 8.3–8.7).

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 using uncertainty factors to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). Summaries of toxicity data for both terrestrial and aquatic non-target organisms are presented in Appendix II, Tables 8-9. For assessment of risk, toxicity endpoints chosen from the most sensitive species in a taxon were used as surrogates for the wide range of species that can be potentially at risk following exposure to zoxamide (Appendix VIII, Table 8.10).

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 RQ 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*). 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 LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats), and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

EECs were determined based on the following application parameters, using the highest rates for each application method:

- Airblast for grape - On-field: 8 × 224 g a.i./ha with an application interval of 7 days, Off-field: early season, 74% drift;

- Ground boom field sprayer for onion - On-field: 8 × 0.19 g a.i./ha with an application interval of 7 days, Off-field: 6% drift;

- Aerial for potato - On-field: 3 × 0.204 g a.i./ha with an application interval of 7 days, Off-field: 23% drift.

4.2.1 Risks to terrestrial organisms

The screening level risk assessment for terrestrial organisms included zoxamide alone is presented in Appendix VIII, Tables 8.11–8.14. Some toxicity data on the transformation product RH-127450 and formulated product, Zoxium 240 SC were also available. For acute and chronic data, the level of concern (LOC) for the screening level risk assessment was not exceeded for earthworms and beneficial arthropods, honeybees and their broods, and birds and mammals up to the highest seasonal application rate of zoxamide.

For terrestrial plants, the highest rate tested for toxicity from overspray was 500 g a.i./ha, with no adverse effects observed on any of the species tested (NOEC = 500 g a.i./ha). The RQ for direct exposure from overspray marginally exceeded the LOC (RQ = 1.1) and, thus, the potential off-site risks to plants from spray drift were considered negligible. (Appendix VIII, Table 8.14). No spray drift buffer zones are proposed.

Based on the risk assessment for the highest registered seasonal use rate for grape, risks to terrestrial organisms from currently registered uses of zoxamide are considered acceptable and no additional mitigation measures are proposed.

4.2.2 Risks to aquatic organisms

The screening level EECs in water are intended to be a conservative estimate of pesticide concentrations in water. The two major transformation products in aerobic aquatic systems, RH-127450 and RH-163353 have been identified as potentially relevant for the aquatic risk assessment. Therefore, in calculating the EECs for the risk assessment of aquatic organisms (screening level and refined), combined residues of zoxamide, RH-127450 and RH-163353, were used. The inclusion of these two TPs in the combined estimate of exposure with zoxamide was based on their persistence in aquatic systems and the lack of sufficient toxicity studies, in particular chronic studies, conducted with the transformation products. A half-life of 144 days in aquatic systems was calculated based on the combined residues of zoxamide, RH-127450 and RH-163353 from water/sediment laboratory studies. EECs for 15 cm and 80 cm depths of water are used to assess the risk to amphibians and other aquatic biota, respectively.

The endpoints used in the risk assessment were based on studies with zoxamide and the effects metrics were derived by dividing the acute EC_{50} or LC_{50} from the appropriate laboratory study by an uncertainty factor of two (2) for aquatic invertebrates, and by a factor of 10 for fish and amphibians. Uncertainty factors are not applied to chronic endpoints. To assess the risk to

amphibians from zoxamide the effects metrics for the most sensitive fish was used as surrogate data. The screening level risk assessment of zoxamide for aquatic organisms for representative use patterns are presented in Appendix VIII, Tables 8.15-8.17.

The screening level risk assessment of aquatic organisms indicated that for the highest seasonal rates used for grape, onion and potato, the risk quotient (RQ) values for zoxamide exceeded the LOC for freshwater and marine invertebrates, freshwater and marine fish, amphibians, aquatic vascular plants and green algae. A refined risk assessment taking into consideration spray drift and runoff into waterbodies was conducted.

Refined risk assessment due to spray drift

The risk to aquatic organisms was further characterized by taking into consideration the concentrations of zoxamide that could be deposited through spray drift in aquatic habitats that are downwind and directly adjacent to the treated field. The assessment of potential risk from drift was assessed for the use patterns of zoxamide on grape using early season airblast applications (74% drift), on onion using field sprayer (groundboom, 6%) and on potato, using aerial application (Appendix VIII, Tables 8.15-8.17). Note that the spray drift risk assessment for marine organisms considers only one application and acute toxicity endpoints.

For acute effects, the LOC was exceeded for the following:

- freshwater fish (airblast and aerial applications); and
- amphibians, aquatic vascular plants and algae (airblast, aerial and groundboom applications).

For chronic effects, the LOC was exceeded for the following:

- freshwater invertebrates (airblast); and
- freshwater fish and amphibians (airblast, aerial and groundboom)

The overall results indicate that zoxamide may pose a risk to aquatic organisms from spray drift. To reduce risk, aquatic spray buffer zones and precautionary label statements informing users of the potential toxicity of zoxamide to aquatic organisms are proposed.

Refined risk assessment due to runoff

Regardless of the attributes of the active ingredient, conditions may exist that could promote the runoff of any chemical into a body of water (for example, steep slope, heavy rain). Runoff can occur both with compounds that are soluble in water (runoff with flow of water) or adsorbed to soil (soil-particle movement in runoff water) and pose a risk to either free-swimming or sediment-dwelling organisms, respectively. For runoff, a series of representative eco-scenarios are used to characterize the exposure on a Canada-wide basis (modelled EEC values using the Pesticide in Water Calculator (PWC) version 1.52). This assessment considers a 10 ha field draining into a one ha water body with a depth of 80 cm to represent a permanent water body, or 15 cm to represent a seasonal water body used by aquatic-phase amphibians. To assess the risk from runoff, the highest ecological EECs (for potato use pattern) presented in Table 5 for the appropriate water depth and timeframe were compared to the ecotoxicity of zoxamide for the organisms of interest. For example, if a 96-hour LC_{50} was selected as the most sensitive

endpoint, than the 96-hour time averaged EEC was selected to assess risk to the corresponding taxon. Chronic endpoints would use a 21-day EEC value. The RQ values refined for runoff are presented in Table 19. The runoff LOC is exceeded on an acute basis for fish, amphibians, aquatic vascular plants and algae. The runoff LOC is exceeded on a chronic basis for aquatic invertebrates, fish and amphibians. For the most cases, RQ values are <12 but are higher for chronic amphibians (RQ = 28.5). However, the following information was also considered:

a) For the aquatic risk assessment, due to a lack of toxicity information on the two major transformation products (TPs): RH-127450 and RH-163353, their residues have been included in the calculation of EEC as a precautionary approach, along with the highest yearly application rate (6 × 190 g a.i./ha at 7 days interval on potatoes).

b) In soil, these TPs are not very persistent. RH-127450 was a major in 3 of 6 soils and was only detected to a maximum of 15% between days 3 and 14 of a 120 day study. At all other times it was <10%. Similarly, RH-163353, was detected in 3 of 6 soils, up to 15% from day 3 to 7 of 120 day study. Therefore, these TPs are relatively transient and short-lived in soil, which lessens their likelihood of reaching to water bodies through runoff.

c) The endpoints used in the risk assessment was from a 95-days chronic exposure study. Based on the transient nature of TPs in soil, it is unlikely that aquatic organisms being exposed to the highest yearly concentration of these products for 95 days,

d) Zoxamide itself is sparingly soluble in water (0.68 mg/L), therefore it is unlikely run-off in water beyond its solubility,

e) Water monitoring data from 2009 to 2019 showed that zoxamide is rarely detected in surface water (frequency of 0.33%) and when detected, it was present at a maximum concentration of 493 ng/L,

Therefore, it can be concluded that the run-off risk to aquatic organisms, including amphibians is considered acceptable from the currently registered uses of zoxamide.

To reduce the potential for runoff of zoxamide from treated areas to adjacent aquatic habitats, precautionary label statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are proposed.

4.2.3 Spray buffer zones and other mitigation measures for co-formulated products

For co-formulated end-use products, spray buffer zones are first calculated for each active ingredient individually and account for spray droplet size and application rate. Spray buffer zones based on the application rates for zoxamide are presented in Appendix VIII.

Based on the buffer zones previously determined for each active ingredient (from the most recent assessment), end-use product labels are required to be updated so that the labelled buffer zones reflect the largest distances required when comparing each of the co-formulated active ingredients. Similarly for other mitigation measures, the most protective label statements of the co-formulants are proposed for the product label. Zoxamide is co-formulated with two other active ingredients (mancozeb and chlorothalonil) in two commercial products.

4.2.4 Environmental incident reports

As of 7 June 2021 no environmental incidents involving zoxamide had been reported to Health Canada. The USEPA Ecological Incident Information System (EIIS), which was last updated 5 October 2015, was also queried and no environmental incidents related to zoxamide were found.

4.3 Toxic Substances Management Policy considerations

In accordance with the PMRA Regulatory Directive DIR99-03,[1] the assessment of zoxamide against Track 1 criteria of Toxic Substances Management Policy (TSMP) under Canadian Environmental Protection Act was conducted. Health Canada has reached the conclusions that:

- Zoxamide does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to Appendix VIII, Table 8.19).
- Zoxamide does not form any transformation products that meet all Track 1 criteria.

4.3.1 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[2] The list is used as described in the Health Canada's Science Policy Note SPN2020-01[3] and is based on existing policies and regulations including the Toxic Substances Management Policy and Formulants Policy, and taking into consideration the Ozone-depleting Substances and Halocarbon Alternatives Regulations under the *Canadian Environmental Protection Act*, 1999 (substances designated under the Montreal Protocol).

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

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

5.0 Value assessment

Zoxamide is a fungicide important for the control of early blight, late blight, and Botrytis vine rot on potatoes; downy mildew on grapes; and neck rot and downy mildew on onions.

Zoxamide is a valuable disease and resistance management tool for vegetable and grape growers due its rainfastness, residual properties and low to medium risk for resistance development.

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

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

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

Zoxamide, an oomycete fungicide, belongs to the Fungicides Resistance Action Committee (FRAC) group 22 fungicides and is not cross-resistant to other current oomycete fungicides, such as phenylamides, QoI, or cymoxanil. A number of alternative active ingredients to zoxamide are registered for all site-pest combinations, which can be rotated in a disease management program.

List of abbreviations

↑	increased
↓	decreased
µg	microgram(s)
µm	micrometre(s)
♀	female
♂	male
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
ALP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
cm	centimeter
CO_2	Carbon dioxide
d	day
DEEM-FCID™	Dietary Exposure Evaluation Model-Food Commodity Intake Database™
DER	Data Evaluation Record
DIR	Regulatory Directive
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
dw	dry weight
EC	Emulsifiable concentrate
EC_{50}	effective concentration to 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
EER	Estimated Exposure Rate
EFSA	European Food Safety Authority
EIIS	Ecological Incident Information System
ELS	early life stage
EPPO	European Plant Protection Organisation
EU	European Union
F_{1a}	first generation, first litter
F_{1b}	first generation, second litter
F_{2a}	second generation, first litter
F_{2b}	second generation, second litter
fc	food consumption
FIR	Food Ingestion Rate

FLS	full life cycle
FOB	functional observational battery
g	gram(s)
GLP	Good Laboratory Practice
GUS	Groundwater Ubiquity Score
ha	hectare(s)
HC	historical control
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HPLC	High Performance Liquid Chromatography
hr(s)	hour(s)
IC_{50}	Inhibitory concentration 50%
i.d.	internal diameter
IOBC	International Organization for Biological and Integrated Control
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_d	soil-water partition coefficient
K_f	Freundlich coefficients
K_{foc}	Freundlich organic carbon-water partition coefficient
K_{oc}	organic carbon-water partition coefficient
$K_{oc\text{-}ads}$	adsorption organic carbon-water partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre(s)
LC_{50}	concentration estimated to be lethal to 50% of the test population
LD_{50}	dose estimated to be lethal to 50% of the test population
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	Lowest observed effect concentration
LOQ	Limit Of Quantification
LR_{50}	lethal rate 50%
LSC	Liquid scintillation chromatography
MAS	maximum average score for 24, 48 and 72 hours
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
meq	milli equivalent
Met	Metabolite
mg	milligram(s)
MIS	maximum irritation score
µL	microlitre
mL	millilitre(s)
MOE	margin of exposure
MRL	Maximum Residue Limit
N/A	not applicable
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
ng	nano gram
nm	nano meter

no.	number
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon
OECD	Organization for economic cooperation and development
P1	parental generation
PCP	Pest control registration number
PES	Post Extraction Solids
PH	Potential hydrogen
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppm	parts per million
PWC	Pesticide in Water Calculator
QSAR	quantitative structure-activity relationship
RAM	Restricted Access Media
RBC	red blood cells
Reg.	Registration
rel	relative
RQ	risk quotient
RVD	Re-evaluation Decision
S9	mammalian metabolic activation system
SMILES	Simplified molecular-input line-entry system
SPN	Science Policy Note
$t_{1/2}$	half-life
TLC	Thin layer chromatography
TP	transformation product
TSMP	Toxic Substances Management Policy
UF	Uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WBC	white blood cells
WHC	Water Holding Capacity
W/m^2	Watt per square meter
wt	weight
w/v	weight per volume
WWEIA	what we eat in America
w/w	weight per weight
≥	equal to or greater than
>	greater than
ºC	degree(s) Celsius
%	percent
♂	male
♀	female
#	number

Appendix I Registered products containing zoxamide in Canada

Table 1 Products containing zoxamide subject to proposed label amendments[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active Ingredient (%, g/L)
26841	Technical	Gowan Company, L.L.C	Zoxamide Technical Fungicide	Solid	zoxamide: 98%
26840	Commercial		Zoxium 80W	Wettable Powder	zoxamide: 80%
26842			Gavel DF Fungicide	Dry Flowable	zoxamide: 8.3 %; mancozeb 66.7 %
32363			Zing Fungicide	Suspension	zoxamide: 85 g/L; chlorothalonil 500 g/L

[1] as of 10 October 2021, excluding discontinued products or products with a submission for discontinuation

Appendix II Registered uses of zoxamide in Canada

Table 2 Registered uses commercial uses of zoxamide in Canada[1]

Site(s)	Pest(s)	Formulation Type	Application Method	Application Rate (g a.i./ ha)		Maximum Number of Application per year	Minimum Interval Between Applications (days)
				Maximum Single	Maximum Cumulative		
Potatoes	Early blight, late blight Botrytis vine rot	Suspension	Ground and aerial	204	612	3	7
	Early blight, late blight	Dry flowable, Wettable powder		190	1140	6	7
Grape	Downy mildew	Dry flowable	Ground - airblast	190	1140	6	7
	Downy mildew	Wettable powder	Ground - airblast	224	1792	8	7
Onion, bulb	Downy mildew, neck rot	Dry flowable	Ground	190	1500	8	7

[1] as of 10 October 2021, excluding discontinued products or products with a submission for discontinuation

Appendix III Toxicology information for health risk assessment

Table 3.1 Identification of select metabolites of zoxamide

Common Name (Other names)	Chemical Name (IUPAC)
RH-117,281 (Zoxamide)	3,5-dichloro-N-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)- 4-methylbenzamide
	Rat metabolites
RH-127,450	3,5-dichloro-N-(1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide
RH-141,288	3,5-dichloro-N-(3-hydroxy-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide
RH-141,452	3,5-dichloro-4-hydroxymethylbenzoic acid
RH-141,455	3,5-dichloroterephthalic acid
RH-141,643	*N*-(3,5-dichloro-4-methylbenzoyl)isovaline
RH-163,353	3,5-dichloro-N-(2-carboxy-1-ethyl-1-methyl-2- oxoethyl)-4-methylbenzamide
	Environmental metabolites
RH-24,549	3,5-dichloro-4-methylbenzoic acid
RH-127,450	3,5-dichloro-N-(1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide
RH-129,151	2-(3,5-dichloro-4-methylphenyl)-4-ethyl-4-methyl-4H-1,3-oxazin-5(6H)-one
RH-139,432	3,5-dichloro-4-methylbenzamide
RH-150,721	3-amino-3-methyl-2-oxopentyl 3,5-dichloro-4-methylbenzoate
RH-163,353	3,5-dichloro-N-(2-carboxy-1-ethyl-1-methyl-2-oxoethyl)-4-methylbenzamide

Table 3.2 Toxicity profile of technical zoxamide and metabolites

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted

Study Type/Animal/ PMRA#	Study results
Toxicokinetic Studies – Zoxamide	
Absorption, Distribution, Metabolism and Excretion (ADME) Sprague Dawley rat PMRA# 1193584 1193794	^{14}C-Zoxamide was labelled uniformly on the phenyl ring and was suspended in corn oil. **Absorption / Elimination**: Following a single low- and high-dose, zoxamide was rapidly absorbed (~61%) with plasma concentrations reaching a maximum peak within 8 hrs. Elimination from plasma was biphasic ($t_{1/2}$=12-14 hrs), with >85% excreted within 24-48 hrs. The fecal route was the predominant route of excretion, accounting for up to 88% and 79% following a single low- and high-dose, respectively. Urinary excretion was 10–16% in males, and 27–29% in females, following a single low- and high-dose, respectively. Urinary excretion was 4-8% in males, and 8–20% in females, following a pulsed low- and repeated- low dose, respectively. Biliary excretion was similar between sexes, and accounted for 46–48% of the AD following a single-low dose. Biliary excretion was not measured in the high-, pulse-, or repeated-dose group. **Distribution**: The highest tissue residues were found in the liver, stomach, and intestines. Tissue retention was minimal. Very little radioactivity (<4%) remained in tissues 5 days following a single low- or high-, and repeated (5 days)- low dose. Concentration in thyroid was higher after a repeated-dose as compared to single low-dose. Repeat-dose was similar to a single low-dose, however residue concentration in liver and carcass was higher. Zoxamide also distributed to the bone marrow in a dose-dependent manner, however the level was relatively minor compared to the other tissues. Zoxamide was also shown to distribute to bone marrow in mice, proportional to dose.

Study Type/Animal/ PMRA#	Study results
	Metabolism: There were a total of 36 metabolites, including zoxamide following a single low- or high-dose as well as a pulsed low-dose. Metabolism occurred predominantly by hydrolysis, glutathione conjugation, reductive dehalogenation, secondary oxidation of aromatic methyl and aliphatic side chains, and terminal glucurionic acid/amino acid conjugation. With exception of parent, no metabolite accounted for more than 10% of the AD. Levels of fecal and urinary metabolites were largely similar between sexes and dose levels. However, a larger proportion of unchanged parent was present in the feces after high-dose administration, suggesting incomplete absorption. Excretion of unchanged parent was slightly reduced in the pulsed low-dose group suggesting enzyme induction. There was no apparent difference in biliary metabolism between male and females.
Bone Marrow Distribution CD-1 mouse PMRA# 1193804	**Supplemental** ^{14}C-Zoxamide was labelled uniformly on the phenyl ring. A single high-dose of zoxamide (2000 mg/kg bw/day) distributed to mouse bone marrow, and reached concentrations of 5-55 ppm (µg/g bone marrow). However, only bone marrow and whole blood were measured so comparison to other tissues cannot be made.
Toxicokinetic Studies – Metabolites	
ADME **RH-141,452 (Metabolite)** Sprague Dawley rat PMRA# N/A	**Distribution** >95% of radioactivity was in the urine and feces; tissue distribution was not measured. **Metabolism** Glucuronide and glycine conjugates were present in urine at ~3%. **Excretion** 97% excreted within 24 hrs. Most eliminated in urine (~98%), with a small amount in feces (~2%). Very little found in expired air (~0.01%).
ADME **RH-141,455 (Metabolite)** Sprague Dawley rat PMRA# 1193808	**Distribution** >95% of radioactivity was in the urine and feces; tissue distribution was not measured. **Metabolism** There was no metabolism detected. >96% was identified as unchanged RH-141,455. **Excretion** 47% excreted within 24 hrs. Most (>90%) was eliminated by 4 days. Mostly eliminated in feces (73%), and urine/cage wash (20%).
Acute Toxicity Studies – Zoxamide	
Acute Oral Toxicity (gavage) Sprague Dawley rat PMRA# 1193566	LD_{50} > 5000 mg/kg bw (♂/♀) No deaths occurred. Diarrhea and/or feces containing white material in a few rats by day 2. Red stained fur on eye/muzzle on a few rats. **Low acute toxicity**
Acute Oral Toxicity (gavage) CD-1 mouse PMRA# 1193567	LD_{50} > 5000 mg/kg bw (♂/♀) No mortality, clinical signs, or gross pathology. **Low acute toxicity**

Study Type/Animal/ PMRA#	Study results
Acute Dermal Toxicity Sprague Dawley rat PMRA# 1193549	LD_{50} > 2000 mg/kg bw (♂/♀) No treatment related deaths. Red stained fur on eyes/muzzle on a few rats. 1 ♂, 1 ♀ had scant feces on day 2. Desiccation and/or reddened skin on several rats on day 2 and days 6–8 was observed. No gross pathology. **Low acute toxicity**
Acute Inhalation Toxicity (nose-only) Sprague Dawley rat PMRA# 1193550	LC_{50} > 5.3 mg/L (♂/♀) No mortality. Red stained muzzle or eyes in 3 controls and 5 high-dose rats with recovery by day 1. No gross pathology. **Low acute toxicity**
Skin Irritation NZW rabbit PMRA# 1193552	MAS (at 24, 48, 72 hrs) = 0 MIS = 0 **Non-irritating**
Eye Irritation ♂ NZW rabbit PMRA# 1193551	MAS (at 24, 48, 72 hrs) = 15.2 MIS = 19.5 at 24 hrs All scores 0 on day 7. Corneal opacity observed; resolution by 72 hrs. **Mildly irritating**
Skin Sensitization (Buehler method) 93.83% pure ♀ Hartley guinea pig PMRA# 1288707	Positive **Potential skin sensitizer**
Skin Sensitization (Maximization Test) 92.9% pure ♂ Hartley guinea pig PMRA# 1288702	Positive **Potential skin sensitizer**
Skin Sensitization (Maximization Test) 98.9% pure ♂ Hartley guinea pig PMRA# 1288703	Positive **Potential skin sensitizer**

Study Type/Animal/ PMRA#	Study results
Skin Sensitization (Local lymph node assay) waiver PMRA# 1288701, 1484778	A waiver was submitted to the PMRA to address the concerns for the strong sensitizing effects of zoxamide. The waiver was accepted based on the following information: • The sensitization database is adequate to classify sensitization • A second Maximization Test (PMRA# 1288703) was not submitted in the original 1999 submission. This study used a higher purity of zoxamide (98.9%) than the previous studies (93.83% and 92.9%) and had less severe skin sensitization effects and decreased frequency of sensitization.
Acute Toxicity Studies - Metabolites	
Acute Oral Toxicity (gavage) **RH-141,452 (Metabolite)** CD-1 mouse PMRA# 1424763	LD_{50} > 5000 mg/kg bw No treatment-related deaths. 1 ♂ had scant feces at day 1 only. 1 ♂ had brown/yellow anogenital staining at day 1 only. No gross pathology. **Low acute toxicity**
Acute Oral Toxicity (gavage) **RH-141,455 (Metabolite)** CD-1 mouse PMRA# 1193806	LD_{50} > 5000 mg/kg bw No mortality, clinical signs, or gross pathology **Low acute toxicity**
Short-Term Toxicity Studies – Zoxamide	
28-day Dermal Toxicity Sprague Dawley rat PMRA# 1193569	NOAEL (systemic) = 1000 mg/kg bw/day (♂/♀) LOAEL (dermal) = 150 mg/kg bw/day (♂/♀) **≥ 150 mg/kg bw/day:** ↑ scabbing, skin hyperplasia, hyperkeratosis, and inflammation, hyperplastic sebaceous glands, mixed inflammatory cell infiltrations (mononuclear and polymorphonuclear leukocytes) and vasculitis / peri-vasculitis in deeper dermis (♂/♀) **≥ 400 mg/kg bw/day:** ↓ albumin, ↓ globulin (♀) **1000 mg/kg bw/day:** ↓ lymphocytes, ↑ neutrophils (♂); ↑ WBC count (♀)
90-day inhalation/ pulmonary sensitization study waiver PMRA# 712919, 656307	A 90-day inhalation/ pulmonary sensitization study waiver request was accepted based on: • The fact that the spray droplet spectrum would contain less than 0.1% respirable droplets and therefore would not penetrate below the human pharynx.
90-day Oral Toxicity (diet) CD-1 mouse PMRA# 1193556	NOAEL = 1212/1666 mg/kg bw/day (♂/♀) No treatment-related deaths or clinical signs of toxicity were observed.
90-day Oral Toxicity (diet)	NOAEL = 281/322 mg/kg bw/day (♂/♀) **≥ 322 mg/kg bw/day:** ↑ abs/rel liver wt., ↓ bwg (♀) (non-adverse)

Study Type/Animal/ PMRA#	Study results
Beagle dog PMRA# 1193558	**≥ 1055/1139 mg/kg bw/day:** ↓ bw, ↓ bwg, ↓ total feed consumption, ↓ albumin, albumin/globulin ratio, ↑ abs/rel liver weight accompanied by diffuse hepatocellular hypertrophy, ↑ thyroid follicular epithelium hypertrophy (♂/♀); ↓ lymphocytes, ↑ neutrophils (♂); ↓ RBC, ↑ MCH ↑ MCHC (♀)
12-month dietary Beagle dog PMRA# 1193568	NOAEL = 255/48 mg/kg bw/day (♂/♀) **≥ 255/278 mg/kg bw/day:** ↑ abs/rel. liver wt., ↑ abs/rel thyroid wt., ↑ ALP (♂/♀) (non-adverse); ↓ bw, ↓ bwg, ↑ incidence and duration of soft feces (♀). **994/1016 mg/kg bw/day**: ↑ abs/rel liver wt, ↑ abs/rel thyroid wt, ↑ diffuse hepatocyte hypertrophy, ↑ ALP, ↓ fc (♂/♀); ↓ bw, ↓ bwg, ↑ incidence and duration of soft feces (♂); 1 raised liver focus, 1 multi-focal necrosis of liver (♀).
Chronic Toxicity / Oncogenicity Studies – Zoxamide	
18-Month Chronic Toxicity/Oncogenicity (diet) CD-1 mouse PMRA# 1193570	NOAEL = 1021/1289 mg/kg bw/day (♂/♀) ↑ non-significant trend for bronchioalveolar adenomas (♀). The maximal incidence was within historical control range (HC). When combined with bronchioalveolar carcinomas, there was no statistical significance. **No evidence of treatment-related oncogenicity**
2-year Chronic Toxicity/Oncogenicity (diet) Sprague Dawley rat PMRA# 1193572 1193573 1193574 1193575	NOAEL = 1058/1331 mg/kg bw/day (♂/♀) **≥ 260/328 mg/kg bw/day:** ↑ rel liver wt. at interim sacrifice (♀) (equivocal and non-adverse) **No evidence of treatment-related oncogenicity**
Reproduction / Developmental Toxicity Studies – Zoxamide	
2-Generation Reproductive Toxicity (dietary/gavage) Sprague Dawley rat PMRA# 1193576 1193577	**Parental Toxicity** NOAEL = 360/409 mg/kg bw/day (♂/♀) **≥ 1474/1624 mg/kg bw/day:** ↑ rel. kidney wt, ↑ abs/rel liver wt (♂/♀) (non-adverse); ↓ bw (P_1 and F_1) during pre-mating, ↓ food efficiency during pre-mating in (P_1 and F_1) (♀) **Offspring Toxicity** LOAEL = 82 mg/kg bw/day **≥ 82 mg/kg bw/day**: ↓ bw (F1a: PND14, 21; F1b: PND21; F2a: PND4,7, 21; F2b: PND0, 4, 7), ↓ bwg (F1), ↓ extramedullary hematopoiesis, ↓ spleen weights (F1a) (♂/♀) **≥ 489/534 mg/kg bw/day:** ↓ spleen weights (F1b and F2a) (non-adverse) **Reproductive Toxicity** NOAEL = 1474/1624 mg/kg bw/day (♂/♀)

Study Type/Animal/ PMRA#	Study results
	No adverse treatment-related effects on reproductive parameters. **Evidence of sensitivity of the young**
Developmental Toxicity (gavage) Sprague Dawley rat PMRA# 1193578	**Parental Toxicity** NOAEL = 1000 mg/kg bw/day **Developmental Toxicity** NOAEL = 1000 mg/kg bw/day No adverse effects No evidence of sensitivity of the young **No evidence of treatment-related malformations**
Developmental Toxicity (gavage) NZW rabbit PMRA# 1193579	**Parental Toxicity** NOAEL = 1000 mg/kg bw/day **Developmental Toxicity** NOAEL = 1000 mg/kg bw/day No adverse effects No evidence of sensitivity of the young **No evidence of treatment-related malformations**
Genotoxicity Studies – Zoxamide	
Bacterial Reverse Mutation Assay S. typhimurium (TA98, TA100, TA1535, TA1537, TA102) PMRA# 1193580	**Negative ± metabolic activation** Tested up to a limit concentration Precipitates formed at higher concentrations
In vitro mammalian gene mutation at HGPRT locus Chinese hamster ovary cells PMRA# 1193581	**Negative ± metabolic activation** Non-mutagenic at the HGPRT locus in CHO cells
In vitro mammalian cytogenetics (chromosomal aberration) Chinese hamster ovary cells PMRA# 1193582	**Negative for structural chromosome aberrations ± metabolic activation** **Positive for numerical chromosome aberrations ± metabolic activation**
In vivo mammalian cytogenetics (Micronucleus Assay)	**Negative**

Study Type/Animal/ PMRA#	Study results
CD-1 mice PMRA# 1193583	
In vivo mammalian cytogenics (mammalian erythrocyte test with kinetochore analyses) Sprague Dawley rat PMRA# 2929340	**Negative**
Genotoxicity Studies – Metabolites	
Bacterial Reverse Mutation Assay **RH-141,452 (Metabolite)** S. typhimurium (TA98, TA100, TA1535, TA1537, TA102) PMRA# 1424764	**Negative ± metabolic activation**
Bacterial Reverse Mutation Assay **RH-141,455 (Metabolite)** S. typhimurium (TA98, TA100, TA1535, TA1537, TA102) PMRA# 1193807	**Negative ± metabolic activation**
Neurotoxicity Studies – Zoxamide	
Acute Neurotoxicity Sprague-Dawley rats PMRA# 1193805	NOAEL = 1976 mg/kg bw/day No treatment related deaths, neuropathology, or effects on FOB **No evidence of selective neurotoxicity**
90-day dietary toxicity / neurotoxicity Sprague Dawley rats PMRA# 1193557	NOAEL = 1509 mg/kg bw/day No treatment related deaths or effects on FOB. One high dose female had multi-centric lymphosarcoma (non-treatment related). **No evidence of selective neurotoxicity**
Other Studies	
Mechanism of action PMRA# 1424762	**Supplemental** RH-117281 (Zoxamide) inhibited nuclear division in the fungus Phytophthora capsici by binding to the β-subunit of tubulin to promote microtubule disruption. Zoxamide was comparable in potency to carbendazim in inhibiting microtubule assembly and growth of mouse lymphoma cells, however required a longer incubation time. It is likely that zoxamide binds at or near the colchicine binding site of tubulin.

Study Type/Animal/ PMRA#	Study results
Mechanism of action PMRA# 2836506	Zoxamide environmental metabolites RH-24549, RH-127450 and 163353 showed low to no fungitoxicity towards Phytophthora capsici and low to no cytotoxicity towards a human tumour cell line (HCT-116). These metabolites did not readily bind tubulin in P. capsici or mammalian (bovine) cells in vitro.
In vitro mammalian metabolism PMRA# 3056415	V79 cells were treated with zoxamide that was incubated with either rat liver microsomes, S9 fraction, or whole liver slices. Incubation with either S9-fraction or whole liver slices caused mainly glutathione- and glucuronic acid-conjugation and eliminated V79 toxicity. Incubation with microsomes caused mainly hydroxylation, and this did not eliminate toxicity. Therefore, conjugation reactions are potentially important for detoxification of zoxamide, and provides a potential mechanism for the absence of mammalian toxicity in vivo.
Comparative QSAR Analysis PMRA# 2785842	In a QSAR modeling study, the predictive software application "OECD QSAR Toolbox 3.4.0.17" was used to determine the toxic potential of three impurities and metabolites of zoxamide as compared to the parent compound zoxamide. The knowledge base includes many endpoints such as skin sensitization, genotoxicity, and skin irritation/corrosion. The program found that the impurities and metabolites were largely equivalent to zoxamide with respect to the number of alerts activated and that there are no new areas of toxicological concern.
Comparative QSAR Analysis PMRA# 2785844	In a QSAR modeling study, the predictive software application "OECD QSAR Toolbox 3.2.0.103" was used to determine the toxic potential of six impurities and metabolites of zoxamide as compared to the parent compound zoxamide. The knowledge base includes many endpoints such as skin sensitization, genotoxicity, and skin irritation/corrosion. The program found that these impurities and metabolites were largely equivalent to zoxamide with respect to the number of alerts activated and that there are no new areas of toxicological concern.

Table 3.3 Toxicology reference values for use in health risk assessment for zoxamide

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	No endpoint of concern attributable to an acute exposure was identified in the toxicology database; therefore, an ARfD was not established.		
	ARfD = not applicable		
Repeated dietary general population	1-year chronic dietary study in dogs	NOAEL = 48 mg/kg bw/day based on decreased body weight and body weight gain	100
	ADI = 0.5 mg/kg bw/day		
Short- and intermediate-term dermal[2]	2-generation reproduction study in rats	LOAEL = 82 mg/kg bw/day based on decreased spleen weights, decreased extramedullary hematopoiesis and decreased body weight in the F1 and F2 generations.	100
Short- and intermediate-term inhalation[3]	2-generation reproduction study in rats	LOAEL = 82 mg/kg bw/day based on decreased spleen weights, decreased extramedullary hematopoiesis and decreased body weight in the F1 and F2 generations.	100
Cancer	A cancer risk assessment was not required.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.
[2] Since an oral - LOAEL was selected, a dermal absorption factor of 9% was used in a route-to-route extrapolation.
[3] Since an oral - LOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Appendix IV Dietary exposure and risk assessments

Table 4.1 Dietary chronic exposure and risk assessments

Population Subgroup	Food only		Food and Drinking Water	
	Exposure (mg/kg bw/day)	%ADI[1]	Exposure (mg/kg bw/day)	%ADI[1]
General Population	0.011876	2.4	0.017837	3.6
All Infants (< 1 year old)	0.021023	4.2	0.043288	8.7
Children 1–2 years old	0.071311	14.3	0.079508	15.9
Children 3–5 years old	0.043237	8.6	0.049907	10.0
Children 6–12 years old	0.017961	3.6	0.022921	4.6
Youth 13–19 years old	0.007439	1.5	0.011640	2.3
Adults 20–49 years old	0.007037	1.4	0.012959	2.6
Adults 50–99 years old	0.007959	1.6	0.013718	2.7
Females 13–49 years old	0.007569	1.5	0.013391	2.7

[1]Acceptable Daily Intake (ADI) of 0.5 mg/kg bw/day

Appendix V Food residue chemistry summary

Zoxamide is a fungicide currently registered for use on grapes, potatoes and bulb onions.

Since zoxamide is not registered on animal feed items in Canada, a residue definition in animal commodities is not required at this time.

The nature of the residue in plant commodities is adequately understood based on metabolism studies in grapes, potatoes, tomatoes and cucumbers. The residue definition **in fruits** for both enforcement and risk assessment is zoxamide: 3,5-dichloro-N-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide. The residue definition in root crops for both enforcement and risk assessment is zoxamide: 3,5-dichloro-*N*-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide, including the metabolites 2,6-dichloro-1,4-benzene-dicarboxylic acid and 3,5-dichloro-4-hydroxymethyl benzoic acid (expressed in parent equivalent).

Available enforcement analytical methods are deemed adequate.

Available confined crop rotation data are adequate to support the plant back intervals specified on product labels. That is, 30 days for leafy, root and tuber vegetables and 140 days for all other unlabelled crops.

The available crop field trial data are adequate to support the registered domestic uses and established Maximum Residue Limits (MRLs).

Available processing studies are adequate to support MRLs established for zoxamide in raisins, potato chips, potato granules and potato flakes.

Overall, sufficient information was available to adequately assess the dietary exposure and risk from zoxamide.

Appendix VI Mixer/loader and applicator exposure and risk assessment

Table 6.1 Short-/intermediate-term risks to workers mixing/loading and applying zoxamide using groundboom equipment

Crop	Maximum AR[a] (kg a.i./ha)	ATPD (ha)[b]	Unit Exposure M/L (µg/kg a.i.)		Unit Exposure Applicator (µg/kg a.i)		Dermal exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation exposure[e] (mg/kg bw/day)	Inhalation MOE[f]	Combined MOE[g]
			Dermal	Inhalation	Dermal	Inhalation					
Liquid formulation Open mix/load liquids (AHETF) and application using groundboom (AHETF); PPE: long sleeved-shirt, long pants and chemical-resistant gloves											
Potato	0.20	360	58.5	0.63	25.4	1.680	0.0068	12,059	0.0021	39,048	9213
Wettable granules and dry flowable formulation Open mix/load liquids (AHETF) and application using groundboom (AHETF); PPE: long sleeved-shirt, long pants and chemical-resistant gloves											
Potato	0.19	360	84.14	21.8	25.4	1.680	0.0089	9213	0.0211	3868	2724
Bulb onion	0.19	26	84.14	21.8	25.4	1.680	0.0006	> 100,000	0.0014	54,667	37,273

AR = application rate; ATPD (ha) – area treated per day; MOE = margin of exposure; M/L = mixer/loader

[a] Maximum AR (kg a.i./ha) as per current product labels

[b] ATPD (ha) = default PMRA values

[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure (µg/kg a.i.) / 1000) × Maximum AR (kg a.i./ha) × ATPD (ha) × dermal absorption factor (9%)/ average worker bw of 80 kg

[d] Dermal MOE based on a NOAEL of 82 mg/kg/bw/day; target MOE=100 (Appendix III)

[e] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure (µg/kg a.i.) / 1000) × ATPD (ha) × Maximum AR (kg a.i./ha) / average worker bw of 80 kg

[f] Inhalation MOE based on a NOAEL of 82 mg/kg/bw/day; target MOE=100 (Appendix III)

[g] Combined MOE = $1/(1/MOE_{dermal}) + (1/MOE_{inhalation})$

Table 6.2 Short-/intermediate-term risks to workers mixing/loading and applying zoxamide using airblast equipment

Crop	Maximum AR[a] (kg a.i./ha)	ATPD (ha)[b]	Unit Exposure M/L (µg/kg a.i.)		Unit Exposure Applicator (µg/kg a.i)		Dermal exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation exposure[e] (mg/kg bw/day)	Inhalation MOE[f]	Combined MOE[g]
			Dermal	Inhalation	Dermal	Inhalation					
Wettable granules and dry flowable formulation Open mix/load dry flowable (AHETF) and application using airblast (AHETF); PPE: long sleeved-shirt, long pants and chemical-resistant gloves; applicator without chemical-resistant hat											
Grapes	0.22	20	84.14	21.8	3769.3	9.080	0.0165	4970	0.0015	54,667	4556

AR = application rate; ATPD (ha) – area treated per day; MOE = margin of exposure; M/L –mixer/loader

[a] Maximum AR (kg a.i./ha) as per current product labels

[b] ATPD (ha) = default PMRA values

[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure (µg/kg a.i.) / 1000) × Maximum AR (kg a.i./ha) × ATPD (ha) × dermal absorption factor (9%)/ average worker bw of 80 kg

[d] Dermal MOE based on a NOAEL of 82 mg/kg/bw/day; target MOE=100 (Appendix III)

[e] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure (µg/kg a.i.) / 1000) × ATPD (ha) × Maximum AR (kg a.i./ha) / average worker bw of 80 kg

[f] Inhalation MOE based on a NOAEL of 82 mg/kg/bw/day; target MOE=100 (Appendix III)

[g] Combined MOE = $1/(1/MOE_{dermal}) + (1/MOE_{inhalation})$

Table 6.3 Short-/intermediate-term risks to workers mixing/loading and applying zoxamide using aerial equipment

Crop	Activity	Max AR[a] (kg a.i./ha)	ATPD (ha)[b]	Unit Exposure M/L (ug/kg a.i.)		Unit Exposure App (ug/kg a.i)		Dermal exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation exposure[e] (mg/kg bw/day)	Inhalation MOE[f]	Combined MOE[g]
				Dermal	Inhalation	Dermal	Inhalation					
Liquid formulation Open mix/load liquids (AHETF) and application using groundboom (AHETF); PPE: long sleeved-shirt, long pants and chemical-resistant gloves												
Potato	M/L	0.20	400	58.5	0.63	-	-	0.0053	15472	0.00063	> 100,000	13828
	A			-	-	2.67	0.00969	0.003	> 100,000	0.00001	> 100,000	> 100,000
Wettable granules and dry flowable formulatiosn Open mix/load liquids (AHETF) and application using groundboom (AHETF); PPE: long sleeved-shirt, long pants and chemical-resistant gloves												
Potato	M/L	0.19	400	84.14	21.8	-	-	0.0072	11389	0.02071	3959	2938
	A			-	-	2.67	0.00969	0.003	> 100,000	0.00001	> 100,000	> 100,000

AR = application rate; MOE = margin of exposure; M/L = mixer/loader; A = applicator/pilot

[a] Maximum AR (kg a.i./ha) as per current product labels

[b] ATPD (ha) – area treated per day (default PMRA values)

[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure (µg/kg a.i.) / 1000) × Maximum AR (kg a.i./ha) × ATPD (ha) × dermal absorption factor (9%)/ average worker bw of 80 kg

[d] Dermal MOE based on a NOAEL of 82 mg/kg/bw/day; target MOE=100 (Appendix III)

[e] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure (µg/kg a.i.) / 1000) × ATPD (ha) × Maximum AR (kg a.i./ha) / average worker bw of 80 kg

[f] Inhalation MOE based on a NOAEL of 82 mg/kg/bw/day; target MOE=100 (Appendix III)

[g] Combined MOE = $1/(1/MOE_{dermal}) + (1/MOE_{inhalation})$

Appendix VII Occupational postapplication exposure and risk assessment

Table 7.1 Short-intermediate-term risks to workers conducting postapplication activities

Use	Use directions[a]			Peak DFR[b] (µg/cm^2)	Activity	TC[c] (cm^2/hr)	Dermal exposure[d] (mg/kg bw/day)	Dermal MOE[e]
	Maximum AR (g a.i./ha)	No. of applications	Minimum RTI (days)					
Grape	224	8	7	1.0705	Girdling, turning	19300	0.1859	441
Bulb onion	190	8	7	0.9080	Hand weeding	4400	0.0360	2281
Potato	200	6	7	0.9469	Irrigation (hand set)	1750	0.0149	5498
Potato	200	3	7	0.8535	Irrigation (hand set)	1750	0.0134	6100

AR = application rate; RTI = re-treatement interval; DFR = dislodgeable foliar residue; TC = transferable residues; MOE = margin of exposure

[a] Use directions as per current product labels

[b] Peak DFR (µg/cm^2) –calculated assuming a 25% residue deposition following the application and 10% dissipation per day

[c] TC (cm^2/hr) - highest TC value for a given crop (ARETF, 2015)

[d] Dermal exposure = Peak DFR (µg/cm^2) × 1000 µg/mg × TC (cm^2/hr) × 8 hours × dermal absorption factor (9%)/ average worker body weight of 80 kg

[e] Dermal MOE based on a NOAEL of 82 mg/kg bw/day; target MOE = 100 (Appendix III)

Appendix VIII Environmental assessment

Table 8.1 Physicochemical properties of zoxamide relevant to the environment

Property	Result
Solubility in water (mg/L) at 20°C	0.68
Solubility in organic solvents (g/L) at 20-25 °C	ethyl acetate 20.0 acetone 55.7 xylene 1.56 n-octanol 6.49 n-heptane 0.038 1,2-dichloroethane 12.5
Vapour pressure at 25°C	$<1.0 \times 10^{-7}$ mm Hg $<1.3 \times 10^{-5}$ Pa
Henry's law constant at 25°C[1]	6.49E-08 atm m^3/mole 6.53E-03 Pa m^3/mole 3.7E+05 = 1/H
Ultraviolet (UV) / visible spectrum	Condition λ max (nm) Neutral MeOH 212.0 241.2 Acidic MeOH 212.4 241.4 Alkaline MeOH 218.2 244.8 The samples did not show significant absorbance at λ > 300 nm.
n-Octanol/water partition coefficient (K_{ow})	Log K_{ow} = 3.76
Dissociation constant (p*K*a)	-

Table 8.2 Summary of fate and behaviour of zoxamide in the environment.

Reference/ PMRA#	Study conditions	Value (day)	Mineralization (%CO_2)	Non-extractable residues (% AR)	Major TP (≥10% applied)	Interpretation/Comments
Hydrolysis (^{14}C-Phenyl-U zoxamide)						
1193801 3173306	Sterile aqueous buffer solutions, 25ºC, 30 d	Half-life 16.0 (pH 4) 16.3 (pH 7) 7.7 (pH 9)	Not measured	NA	RH-129151 RH-150721 RH-24549 RH-141288	An important route of dissipation, Up to 12 TPs identified, 4 out of 12 are major TPs (≥ 10% AR), Using the data from Reynolds, and Chong the calculated half-lives for the major TPs as follows: RH-150721 (18.3 days, pH 4), RH-129151 (2.4 to 9.1 days, pHs 7 and 9), RH-150721and RH-129151 were transitory and formed RH-24549 and RH-141288, RH-24549 and RH-141288 were stable to hydrolysis.
Photolysis (^{14}C-phenyl-UL zoxamide)						
Soil – 1193803	American andy loam soil, pH 6.9, 25ºC, 30 d	Not a route of dissipation on soil, Rate of degradation and the pattern of TP formation were very similar in the irradiated samples and the dark controls, suggesting that the degradation is primarily microbial or hydrolytic.				
Water – 1194212	Conducted at pH 4, 12-hour light/12-hour dark cycle using a UV-filtered xenon arc lamp. The intensity and wavelength distribution of the artificial light were similar to natural sunlight in New Jersey, 25ºC, 30 d	Half-life 8 (irradiated) 22 (dark) Corrected half-life = 14.3*	NA	NA	RH-150721 RH-24549 (hydrolysis degradates) RH-139432 (photo-degradate – see comments)	Study conducted at pH 4, Degradation of zoxamide also occurred in the dark controls but the rate of degradation was higher in irradiated samples, Three TPs identified: RH-150721, RH-24549 and 39432, RH-150721and RH-24549 are hydrolysis degradates, RH-139432 is considered photolysis TP,

Reference/ PMRA#	Study conditions	Value (day)	Mineralization (%CO_2)	Non-extractable residues (% AR)	Major TP (≥10% applied)	Interpretation/Comments
						Both hydrolysis and photolysis may occurred at pH 4, Half-life should be used with limitation as the dark control half-life was based on only three datapoints and study was conducted at a pH that is not representative of the most natural wateres.
Air	A study of photolylsis in air was not provided, PMRA calculated half-life in air, using AOPWIN (v 1.92, within EPISuit V.4.11 program) >12 hours EFSA (3173306) calculated half-life in air, using Atkinson (1988) method = 7.5 hours					If residues of zoxamide were to enter the air, it is expected that they would be rapidly degraded and long range transport is unlikely.
Aerobic Soil Biotransformation (^{14}C-Phenyl-U zoxamide)						
1194223	Loamy sand (United States): %OM 2.4, pH 6.9 at 25°C, 122 d	DT_{50} = 23.9	(34.4) DAT 122	(39.2) DAT 90	See comments	Significant mineralization and association with soil particles, Six TPs formed and four identified: RH-129151, RH-139432, RH-127450 and RH-24549, None of TPs individually accounted for >7% AR.
	Silt loam (United States): %OM 1.8, pH 6.8 at 25°C, 122 d	DT_{50} = 20.2	(47.8) DAT 122	(33.0) DAT 122		
3173306	Loam (France) - soil A %OM 2.26, pH 7.4 at 20°C, 122 d	DT_{50} = 2.03	(48.5) DAT 120	(38.3) DAT 28	RH-127450 RH-24549 RH-163353	Treated soil incubated at 20°C and 50% WHC, Sandy loam soil also incubated at10°C, 50% and 100% WHC Major route of dissipation, Significant mineralization and association with soil particles, Total of 23 TPs formed, Only three are major, Their levels are lower at cooler temperatur, DT_{50}s of TPs: RH-127450 DT_{50}s= 3.78–11.69 at 20°C, 50% WHC),***
	Sandy loam (Germany) – soil B %OM 1.20, pH 7.4 at 20°C and at 10°C; 50 and 100% WHC, 122 d	DT_{50}s 2.71 (20°C, 50% WHC) 7.7 (10°C, 50% WHC) 2.27 (20°C, 100% WHC)	(57.8 at 20°C, 50% WHC) DAT 120 (35.5 at 10°C, 50% WHC) DAT 120 (56.2 at 20°C and 100 WHC) DAT 120	(30.2 at 20°C, 50% WHC) DAT 28 (34.1 at 10°C, 50% WHC) DAT 120 (30.9 at 20°C and 100 WHC) DAT 28	RH-127450 RH-24549 RH-163353	
	Clay loam (Italy) – soil C % OM 0.80, pH 8.1 at 20°C,122 d	DT_{50} = 2.38	(55.8) DAT 120	(36.0) DAT 28	RH-24549 RH-163353	

Reference/ PMRA#	Study conditions	Value (day)	Mineralization (%CO_2)	Non-extractable residues (% AR)	Major TP (≥10% applied)	Interpretation/Comments
	Silt loam (England) - soil D % OM 1.8, pH 5.0 at 20°C, 122 d	DT_{50} = 4.16	(42.6) DAT 120	(25.6) DAT 56	RH-127450	RH-24549 DT_{50s} = 5.35–8.44 at 20°C, 50% WHC),[***] RH-163353 DT_{50s} = 5.62–53.65 at 20°C.[***]
Anaerobic Soil Biotransformation (^{14}C-Phenyl-U zoxamide)						
1194228	Loamy sand (United States) %OC 2, pH 7.2 at 25°C, 59 d	DT_{50} = 11.7	(5.1) day 0 to end of study (day 59)	(26.2) DAF 56	RH-127450 RH-24549	Treated soils were incubated first under aerobic conditions for 21 days and then flooded, At the initiation of the anaerobic phase, RH-24549 was present at 7.28% AR and it continously increased until the end of the study to 16.9% AR, RH-127450 was detected at 3.0% at day zero of anaerobic phase and increased to maximum 13.45% AR at the end of the study, No mineralisation occurred at anaerobic phase, 11 TPs identified and only two were major, Not possible to estimate degradation rates of the TPs.
2836499	Sandy loam (EU) %OM 2.07, pH 7.4 at 20°C, 120 d	DT_{50} = 6.1	(<0.1)	(26.4) DAF 120	RH-127450 RH-24549	Soil samples were flooded and after reaching anaerobic conditions, zoxamide was applied, 22 TPs detected and only 2 were major.

Reference/ PMRA#	Study conditions	Value (day)	Mineralization (%CO_2)	Non-extractable residues (% AR)	Major TP (≥10% applied)	Interpretation/Comments
Aerobic Aquatic Biotransformation (^{14}C- Phenyl-U- zoxamide)**						
1194229	Water/sediment (EU – river) Sediment: Loamy sand %OC 0.57; pH 7.4, 106 d	DT_{50} = 6.06–10.4 (total system at 20°C and 10°C, respectively)	21.9–6.3 (at 20°C and 10°C, respectively) DAT 106	Total AR in sediment (day 56–106): 64.4–71.7 at 20°C and 10°C, respectively Bound residue (day 106): 36.6–33.5 at 20°C and 10°C, respectively	Water phase: RH-127450 (12.8%–17.1% AR at 20°C and 10°C respectively) DAT 14- 28 RH-163353 (15.8%–15.3% AR at 20°C and 10° respectively) DAT 20–106 Sediment phase: RH-127450 (19.8%–23.1% AR at 20°C and 10°C respectively) DAT 28–56 RH-163353 (7.4%–12.7% AR at 20°C and 10°C, respectively) DAT 106	Study was conducted at two temperature of 20°C and 10°C in a river and pond water/sediment systems, Levels of the major TPs in sediment were slightly higher in the systems incubated at 10°C than at 20°C, RH-127450 DT_{50}s = 88.9–326.1 days at 20°C and 123 days at 10°C, *** An acceptable fit to the data could not be obtained for RH-163353.***
	(EU-pond) Sediment: Loam %OC 1.83 pH 7.0, 106 d	DT_{50} = 6.09–19.3 (total system at 20°C and 10°C, respectively)	19.7–4.0 (at 20°C and 10°C, respectively) DAT 106	Total AR in sediment (day 56–106): 79.3–80.6 at 20°C and 10°C, respectively Bound residue (day 56–106): (39.9–37.3 at 20°C and 10°C, respectively	Water phase: RH-127450 (7.5%–5.9% AR at 20°C and 10°C respectively) DAT 14- 56 RH-163353 (9.3%–6.0% AR at 20°C and 10° respectively) DAT 20–106 Sediment phase: RH-127450 (22.1%–22.6% AR at 20°C and	

Reference/ PMRA#	Study conditions	Value (day)	Mineralization (%CO_2)	Non-extractable residues (% AR)	Major TP (≥10% applied)	Interpretation/Comments
					10°C respectively) DAT 56 RH-163353 (4.4%–13.8% AR at 20°C and 10°C, respectively) DAT 56 -106	
Anaerobic Aquatic Biotransformation – (^{14}C- Phenyl-U- zoxamide)						
2837864	Water/sediment (United States-Taunton river) Sediment: Clay loamy; % OC 4.7; pH 5.5 at 20°C, 365 d	DT_{50} 6.8–8.6 (in water and total system, respectively)	9.05 (day365)	35.9 (day 232)	RH-127450 (46.7% AR DAF 28) RH-163353 (12.8% AR DAF 365)	Two anaerobic river water/sediment system, Test systems were equilibrated to anaerobic conditions for 14 days before dosing.
	Water/sediment (United States - Weweantic river) Sediment: Sandy; % OC 1.1; pH 5.1 at 20°C, 365 d	DT_{50} 7.2–9.6 (in water and total system, respectively)	6.43 (day 365)	39.7 (day 232)	RH-127450 (39.4% AR DAF 56) RH-163353 (13.2% AR DAF 28) RH-150721 (15.3% AR DAF 232)	
Mobility (^{14}C-phenyl-U- zoxamide)						
Adsorption/desorption						
Zoxamide						
1194231	Five American soils: Loam (pH 7.2, OC 1.27) Sandy loam (pH 5.6, OC 0.26) Silty clay loam (pH 4.8, OC 1.77) Sandy loam (pH 6.7, OC 1.1)	K_{oc} (mL/g) 994.1 (loam) 1339 (sandy loam) 1567 (silty clay loam) 1531 (sandy laom) 1056 (silty loam)				Low mobility based on McCall et. al. (1981)

Reference/ PMRA#	Study conditions	Value (day)	Mineralization (%CO_2)	Non-extractable residues (% AR)	Major TP (≥10% applied)	Interpretation/Comments
	Silty loam (pH 6.8, OC 1.04)					
Major soil TPs						
EFSA 3173306	^{14}C RH-24549	K_{foc} (mL/g) 307.4 (sandy loam) 150.2 (silty clay loam) 90.6 (silt loam)				Moderately to highly mobile
	^{14}C RH-127450	K_{foc} (mL/g) 1156 (loam sand) 404 (clay) 447 (silt loam)				Low to moderately mobile
	^{14}C RH-163353	K_{foc} (mL/g) 50 (loam sand) 75 (clay) 79 (silt loam)				Highly mobile
Leaching						
EFSA 3173306	A 3- day aged residues in a sandy loam soil (59% sand content, 1.2 % OC), 30 cm column (5 cm internal diameter)	85.9%–90.8% AR retained by the soil column, 1.8–2.3% AR leached (not characterised) %AR detection in the soil layers Zoxamide: 12.3- 16.5% (0–5 cm layer), not detected in lower layers. RH-127450: 6.9–11.9% (0–5 cm layer), 0.3% (5–10 cm layer) not detected in lower layers. RH-24549: 5.6–8.9% (0–5 cm layer), 1.2% (10–15 cm layer) and 0.6–1.9 (15–20 cm layer). RH-163353: 4.0–6.7% (0–5 cm layer), 1.2% (10–15 cm layer) and 0.5–0.7% (15–20 cm layer)				Majority of residues detected in the 0–5 cm layer (69.6–74.4% AR), Slightly greater potential for leaching of RH-24549 and RH-163353 down to 20 cm, however their levels were <10% AR, Due to short DT_{50}s of the them in soil (Burgener, 3173306), it is unlikely that they would leach to groundwater.
Soil leaching (Cohen criteria and GUS index)	Zoxamide	- Meets two out of eight leaching criteria of the Cohen et al. (1984) - Non-leacher, based on GUS index (<1.8)				
Soil leaching (GUS index)	Major TPs in soil	RH-127450 and RH-24549: Non-leachers to borderline leachers, based on GUS index (<1.8 to <2.8) RH-163353: Borderline leacher, based on GUS index (>1.8 and <2.8)				
Volatilization						
EFSA 3173306	Zoxamide	Based on Henry's law constant (6.49×10^{-8}atm.m^3/mol), volatilization of zoxamide from soil or water in the air is not expected. Volatilization of zoxamide from the soil or leaf surfaces under the field conditions was low with losses of 3.9% and 5.1% from soil and leaf surfaces, respectively, after 24 hours.				

Reference/ PMRA#	Study conditions	Value (day)	Mineralization (%CO_2)	Non-extractable residues (% AR)	Major TP (≥10% applied)	Interpretation/Comments
		Concentrations of zoxamide in air after a field application are expected to be low.				
Terrestrial Field studies (zoxamide)						
1193838 and 1193839	Canadian and American field studies	DT_{50}s: 4.6–15 days				Zoxamide is non-persistent in soil under field conditions, No carry over to the next season, No zoxamide residues below 15 cm soil depth, Transformation products were not monitored.
Bioaccumulation						
1193819 (Robinson, 1998)	Bluegill sunfish (*Lepomis macrochirus*)	Steady-state BCF = 95–136 (whole fish)				Zoxamide has a low potential to bioaccumulate.

AR = Applied radioactivity,
OC = Organic carbon,
OM = Organic matter,
WHC = water holding capacity,
DAT = Day after treatment,
DTF = Day after flooding,
TP = Transformation products,
RH-129151 = 4*H*-1,3-Oxazin-5(6*H*)-one, 2-(3,5-dichloro-4-methylphenyl)-4-ethyl-4-methyl,
RH-24549 = Benzoic acid, 3,5-dichloro-4-methyl,
RH-150721 = Benzoic acid, 3,5-dichloro-4-methyl, 3-amino-3-methyl-2-oxopentyl ester (re-arranged product of 129151),
RH-141288 = Benzamide, 3,5-dichloro-*N*-(1-ethyl-3-hydroxy-1-methyl-2-oxopropyl)-4-methyl,
RH-139432 = amide,
NA = not applicable,
d = day,
*Correct photolysis half life calculated as ln(2)/(k-irr-k-dark). Ln = 0.693 (constant), k values are rates of dissipation,
** In the risk assessment of aquatic organisms, half-life of a combined residues of zoxamide and its major transformation products, RH-127450, and RH-163353 (144 days) was used because both RH-127450, and RH-163353 can be persistent in aquatic system, they have similar chemical structures and due to the lack of chronic toxicity studies with these TPs, concern for chronic effects can not be rule out,
*** Calculated by EFSA (7173306), using FOCUS Kinetic Guidance Document.

Table 8.3 Screening level (on-field) and off-field (drift) EECs in soil and water systems

Representative crop	Test substance	Soil on-field EEC µg a.i,/kg soil[1]	Soil off-field EEC µg a.i./kg soil[1]	Water on-field (80 cm) µg a.i./L[2]	Water on-field (15 cm) µg a.i./L[2]	Water off-field (80 cm) µg a.i./L[2]	Water off-field (15 cm) µg a.i./L[2]	Marine drift µg a.i./L[4]
Grape*: 224 g a.i/ha × 8 applications, 7d interval; applied with airblast equipment (early season, 74% drift)	Zoxamide	409	302	200	1065	148	788	21
	RH-127450[3]	255	189					
	Zoxamide + RH-127450 + RH163353	NA	NA					
Grape: 190 g a.i./ha × 6 applications, 7d interval; applied with airblast equipment (early season , 74% drift)	Zoxamide	308	228	131	700	97	518	18
	RH-127450[3]	205.2	152					
	Zoxamide + RH-127450 + RH-163353	NA	NA					
Onion*: 190 g a.i./ha × 8 applications, 7d -interval; applied by field sprayer (groundboom) with medium spray droplet size (6% drift)	Zoxamide	347	21	169	903	10	54	1
	RH-127450[3]	216	13					
	Zoxamide + RH-127450 + RH-163353	NA	NA					
Potato: 190 g a.i/ha × 6 applications, 7d interval; applied by field sprayer with medium spray droplet size (6% drift)	Zoxamide	308	18.5	131	700	8	42	1
	RH-127450[3]	205.2	12.3					
	Zoxamide + RH-127450 + RH-163353	NA	NA					
Potato*: 204 g a.i/ha × 3 applications, 7d interval; on Potato applied by aerial equipment with medium spray droplet size (23% drift)	Zoxamide	220	51	74	395	17	91	6
	RH-127450[3]	171	39.3					
	Zoxamide + RH-127450 + RH-163353	NA	NA					
Potato: 204 g a.i/ha × 3 applications, 7d interval; applied by field	Zoxamide	220	13					
	RH-127450[3]	171	10.3					

Representative crop	Test substance	Soil on-field EEC µg a.i,/kg soil[1]	Soil off-field EEC µg a.i./kg soil[1]	Water on-field (80 cm) µg a.i./L[2]	Water on-field (15 cm) µg a.i./L[2]	Water off-field (80 cm) µg a.i./L[2]	Water off-field (15 cm) µg a.i./L[2]	Marine drift µg a.i./L[4]
sprayer with medium spray droplet size (6% drift)	Zoxamide + RH-127450 + RH-163353	NA	NA	74	395	4	24	2

[1]The screening level (on-field) EEC of zoxamide on soil is based on direct over spray on soil, using the highest cummulative application rate, the 90% upper confidence bound on the mean for all available representative aerobic soil half-lives ($t_{1/2}$s = 21.2 days at 20°C), assuming soil bulk density of 1.5 g/cm^3 and that product is evenly distributed in the 0-15 cm depth of the soil,

[2]EECs in water are based on combined residues of zoxamide, RH0127450, and RH-163353 in two different depths, using the maximum cumulative rates of zoxamide for different use patterns and the combined residue half-life of 144 days,

[3]Screening EEC for RH-127450 in soil is calculated by multiplying the total applied parent (a.i.) concentration by the TP/a.i. molecular weight ratio, assuming 100% conversion of the parent to the TP and using RH-127450 highest half-life in soil (t1/2 = 11.7 days),

[4]Based on drift for one application to marine systems,

NA = not applicable,

*At the screening level, direct over-spray of these scenarios were considered.

Table 8.4 Major fate inputs for the water modelling

Fate parameter	**Drinking water** Combined residue of zoxamide, RH-24549, RH-141288, RH-129151, RH-139432, RH-127450 and RH-163353	**Ecological water** Combined residue of zoxamide, RH-127450 and RH-163353
K_{oc} (L/kg)	9.2	60
Water half-life (d)*	144	144
Sediment half-life (d)**	1040	1040
Photolysis half-life (d)	107	14.3
Hydrolysis half-life (d)	stable	16.5
Soil half-life (d)	41.78	NA

NA = not applicable for ecological modelling,
*Aerobic aquatic whole system,
**Anaerobic aquatic whole system.

Table 8.5 Calculated EECs (in µg a.i./L) for the ecological risk assessment of the combined residue of zoxamide and its major transformation products of RH-127450, and RH-163353*

Use	Water depth	Water column				Pore water	
		Peak	24 hour	96 hour	21 day	Peak	21 day
6 × 190 g a.i./ha at 7 d on potatoes	80 cm	41	40	37	26	8.6	8.4
	15 cm	211	203	182	114	--	--
8 × 224 g a.i./ha at 7 d on grapes	80 cm	27	26	24	19	6.9	7.3
	15 cm	134	129	118	84	--	--
8 × 187 g a.i./ha at 7 d on onions	80 cm	31	30	28	20	7.5	7.3
	15 cm	160	154	138	88	--	--

*calculated using Pesticide in Water Calculator (PWC) version 1.52

Table 8.6 Maximum and mean estimated environmental concentrations (EEC)[a] of zoxamide in vegetation and insects (grapes: 8 × 224 g a.i./ha, 7 day interval, foliar half-life 10 days), Direct over-spray – early season airblast (on-field and off-field)

Environmental compartment	Fresh/dry weight ratios	Maximum residue concentration				Mean residue concentration			
		Fresh weight (mg a.i./kg)		Dry weight (mg a.i./kg)		Fresh weight (mg a.i./kg)		Dry weight (mg a.i./kg)	
		On-field	Off-field	On-field	Off-field	On-field	Off-field	On-field	Off-field
short range grass	3.3[b]	122	90	403.1	298.3	43.0	32.1	143.2	105.9
long grass	4.4[b]	56	41	246.1	182.1	18.0	13.5	80.4	59.5
broadleaf plants	5.4[b]	69	51	372.9	275.9	23.0	16.9	123.3	91.2
pods with seeds	3.9[b]	7	5	28.9	21.4	4.0	2.6	13.8	10.2
insects	3.8[c]	48	35	182.2	134.8	33.0	24.5	125.8	93.1
grain and seeds	3.8[c]	7	5	28.2	20.9	4.0	2.6	13.5	10.0
fruit	7.6[c]	7	5	56.4	41.7	4.0	2.6	26.9	20.0

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
[b] Fresh/dry weight ratios from Harris (1975)
[c] Fresh/dry weight ratios from Spector (1956)

Table 8.7 Maximum/mean on-field and off-field estimated daily exposure (EEC and EDE) for birds and mammals, Direct over-spray – early season airblast (on-field and off-field)[1]

Generic Body weight (kg)	FIR[a] (kg dw diet/day)	Food Guild (food item)[b,c]	Maximum/mean nomogram residues			
			On-field		Off-field (early season airblast, 74% deposition)	
			EEC	EDE[d]	EEC	EDE
			(mg a.i./kg diet)	(mg a.i./kg bw)	(mg a.i./kg diet)	(mg a.i./kg bw)
BIRDS						
0.02	0.0051	Insectivore (small insect)	182.2/125.8	46.5/32.1	134.8/93.1	34.4/23.7
0.02	0.0051	Granivore (grain and seeds)	28.2/13.4	7.2/3.4	20.9/9.9	5.3/2.5
0.02	0.0051	Frugivore (fruit)	56.4/26.9	14.4/6.9	41.7/19.9	10.6/5.1
0.1	0.0199	Insectivore (large insect)	182.2/125.8	36.3/25.0	134.8/93.1	26.8/18.5
0.1	0.0199	Granivore (grain and seeds)	28.2/13.4	5.6/2.7	20.9/9.9	4.2/2.0
0.1	0.0199	Frugivore (fruit)	56.4/26.9	11.2/5.4	41.7/19.9	8.3/4.0
1	0.0581	Insectivore (small insect)	182.2/125.8	10.6/7.3	134.8/93.1	7.8/5.4
1	0.0581	Granivore (grain and seeds)	28.2/13.4	1.6/0.8	20.9/9.9	1.2/0.6
1	0.0581	Frugivore (fruit)	56.4/26.9	3.3/1.6	41.7/19.9	2.4/1.2
1	0.0581	Herbivore (short grass)	403.1/143.1	23.4/8.3	298.3/105.9	17.3/6.2
1	0.0581	Herbivore (long grass)	246.1/80.4	14.3/4.7	182.1/59.5	10.6/3.5
1	0.0581	Herbivore (Broadleaf plants)	372.9/123.3	21.7/7.2	275.9/91.2	16.0/5.3
MAMMALS						
0.015	0.0022	Insectivore (small insect)	182.2/125.8	26.7/18.4	134.8/93.1	19.8/13.7
0.015	0.0022	Granivore (grain and seeds)	28.2/13.4	4.1/2.0	20.9/10.0	3.1/1.5
0.015	0.0022	Frugivore (fruit)	56.4/26.9	8.3/4.0	41.7/20.0	6.1/3.0
0.035	0.0045	Insectivore	182.2/125.8	23.4/16.2	134.8/93.1	17.3/12.0
0.035	0.0045	Granivore (grain and seeds)	28.2/13.4	3.6/1.7	20.9/10.0	2.3/1.3
0.035	0.0045	Frugivore (fruit)	56.4/26.9	7.3/3.5	41.7/20.1	5.4/2.6
0.035	0.0045	Herbivore (short grass)	403.1/143.1	51.8/18.4	298.3/106.0	38.3/13.6
0.035	0.0045	Herbivore (long grass)	246.1/80.4	31.6/10.3	182.1/59.5	23.4/7.6
0.035	0.0045	Herbivore (forage crops)	373.0/123.3	48.0/16.0	276.0/91.2	35.5/11.7
1	0.0687	Insectivore	182.2/125.8	12.5/8.6	135.0/93.1	9.3/6.4
1	0.0687	Granivore (grain and seeds)	28.2/13.4	2.0/1.0	20.9/10.0	1.4/0.7

Generic Body weight (kg)	FIR[a] (kg dw diet/day)	Food Guild (food item)[b,c]	Maximum/mean nomogram residues			
			On-field		Off-field (early season airblast, 74% deposition)	
			EEC	EDE[d]	EEC	EDE
			(mg a.i./kg diet)	(mg a.i./kg bw)	(mg a.i./kg diet)	(mg a.i./kg bw)
1	0.0687	Frugivore (fruit)	56.4/26.9	3.9/1.8	41.7/20.0	2.9/1.4
1	0.0687	Herbivore (short grass)	403.1/143.1	27.7/9.8	298.3/106.0	20.5/7.3
1	0.0687	Herbivore (long grass)	246.1/80.4	17.0/5.5	182.1/59.5	12.5/4.1
1	0.0687	Herbivore (Broadleaf plants)	373.0/123.3	25.6/8.5	276.0/91.2	19.0/6.3

[1] Calculations based on the use on grapes (8 × 224 g a.i./ha, 7-day interval, foliar half-life 10 days)

[a] Food Ingestion Rates (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = 0.398(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 birds" equation was used: FIR (g dry weight/day) = 0.235(BW in g) $^{0.822}$

[b] large insects not considered to be a relevant food source for small birds and mammals,

[c] For granivorous species, only grains and seeds were considered as a relevant source of exposure (as opposed to seeds in pods, which were not considered),
EEC = Estimated environmental concentration,

[d] EDE = Estimated daily exposure; is calculated using the following formula: (FIR/BW) × EEC. At the screening level, food items representing the most conservative EEC are used.

Table 8.8 Summary of effects on terrestrial organisms

Test organisms	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA #
Invertebrates					
Earthworm					
Earthworm (*Eisenia fetida*)	Zoxamide	14-d Acute (artificial soil)	**LC_{50} >1070 mg a.i./kg soil**	Applied concentrations: 66.7, 134, 273, 520 and 1070 mg a.i./kg dw soil, Lethargy was observed in the 134 mg a.i./kg treatment and higher, but was not observed in the control, solvent control or 66.7 mg a.i./kg concentration, No toxic effects seen at the tested concentrations.	1194214 and 3173307
	Zoxamide	56-d Chronic (reproduction in (artificial soil)	**$NOEC_{repro}$ = 1.0 mg a.i./kg soil dw** (reduced number of	Applied concentrations: 0.5, 1, 5, 10 and 20 mg a.i./kg soil,	1194260

Test organisms	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA #
			offspring/adult earthworm)	No statistically significant mortality or negative effects on growth of adults at all tested concentrations, Statistically significant reduced reproduction at 5 mg a.i./kg or greater.	
	Zoxamide	56-d Chronic (reproduction in natural soil)	$NOEC_{repro}$ = 7 mg a.i./kg natural soil (reproduction)	Applied concentrations: 1, 2, 4, 5, 7 and 10 mg a.i./kg soil, No mortality in adults, Reduced reproduction at 10 mg a.i./L soil.	3173307
	RH-127450 (100%) (Major soil TP)	14-d Acute	**LC_{50}>1000 mg a.s./kg soil** (highest concentration tested)	No effects on survival or body weight, No toxic effects seen at the tested concentrationons.	3173307
Beneficial Arthropods					
Parasitic wasp (*Aphidius Rhopalosiphi*)	Zoxium 240 SC (formulated product, 22.35% a.i., zoxamide)	48-h Acute (glass plate) 10-d Chronic	**LR_{50} > 300 g a.i./ha** (based on lack of mortality) **NOECrepro <150 g a.i./ha** (based on effects on egg laying)	Applied rates: 150 and 300 g a.i./ha), Two phase study: Adult phase (survival and behaviour – 48 hours) – No mortality after 48 hours, Reproduction phase -10 days – Reduction of egg laying at 150 g a.i./ha and higher, No toxic effects seen at the tested rates.	2836501
Predacious mite (*Typhlodromus Pyri*)	Zoxium 240 SC (formulated product, 22.35% a.i., zoxamide)	14-d Acute contact (glass plate)	LR_{50} > 300 g a.i./ha NOEC <150 g a.i./ha (based on effects on egg laying)	Applied rates: 150 and 300 g a.i./ha), Statistically significant mortality of the treated mites in compare to the control (8.0%, 23.0%, 29.0% in control, 150 and 300 g a.i./ha, respectively), Females treated with 150 and 300 g a.i./ha produced significantly fewer eggs when compared to the control (1.23, 0.57, and 0.91 for the control, 150 g a.i./ha and 300 g a.i./ha, respectively), No toxic effects seen at the tested rates.	2836502

Test organisms	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA #
Predacious mite (Amblyseius andersoni)	Zoxium 240 SC (formulated product, 22.35% a.i., zoxamide)	14-d Acute contact (glass plate)	LR_{50} >300 g a.i./ha NOEC <150 g a.i./ha (based on adult mortality)	Applied rates: 150 and 300 g a.i./ha), The differences in percent cumulative mortality between the control and treated groups were statistically significant (2.0%, 12.8% and 17.8% in the control, 150 g a.i./ha, 300 g a.i./ha, respectively), No toxic effects seen at the tested rates.	2837856
Bees					
Honey bee (*Apis mellifera*)	Zoxamide (95% a.i.)	48-h Acute contact	**LD_{50} > 100 µg a.i./bee**	Concentrations applied: 0.25, 2.5, 25 and 100 µg a.i./bee, Practically non-toxic.	1194215
	Zoxium 240 SC (formulated product, 22.35% a.i., zoxamide)	72-h Acute oral 72-h Acute contact	Oral (formulation) LD_{50} > 147 µg formulation/bee Oral (based on % of zoxamide in formulation[4]) LD_{50} > 33 µg zoxamide/bee Contact (formulation) LD_{50} > 200 µg formulation/bee Contact (based on % of zoxamide in formulation[4]) > 44.7 µg a.i/bee	Zoxium 240 SC is registered product in Canada, Limit test with only one concentration, Acute oral: 147 µg formulation/bee, Acute contact: 200 µg formulation/bee, No statistically significant effects on bee mortality or behaviour were observed, Practically non-toxic.	2836497
	Zoxium 240 SC (formulated product,	10-d Chronic (adult)	NOEC = 5000 mg a.i./kg feeding solution	One concentration of 5000 mg a.i./kg feeding solution, corresponding to 174.8 µg a.i./bee/day, No mortality or behavioural abnormalities.	2836498

Test organisms	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA #
	22.35% a.i., zoxamide)		**NOEL = 174.8 µg a.i./bee/day**		
	Zoxamide (98.8% purity)	72-h Acute larval study	**LD_{50} > 115 µg a.i./larva** NOEL = <7.19 µg a.i/larva (based on mortality)	Concentrations applied: 7.19, 14.38, 28.75, 57.5 and 115 µg a.i./larvae, The mortality of treated groups of 7.19, 14.38, 28.75, 57.5 and 115 µg a.i/larva were 4.2, 4.2, 8.3, 10.4 and 6.3% , respectively, after 72 hours, Practically non-toxic.	2836507
	Zoxium 240 SC (formulated product, 22.35% a.i., zoxamide))	Brood/hive	NOEC = 3.47 g Zoxium 240 SC/L, corresponding to = 0.75 g a.i./L	Concentrations applied: 0.833 and 3.47 g Zoxium 240 SC/L corresponding to 0.18 and 0.75 g a.i./L on three bee colonies, No effects on bee brood development were observed at up to 0.75 g a.i./L.	3173308
Birds					
Bobwhite quail (*Colinus virginianus*)	Zoxamide	14-d Acute oral	LD_{50} >2000 mg a.i./kg bw	Concentrations applied: 305, 488, 781, 1250 and 2000 mg a.i./kg bw, No mortalities were observed, Practically non-toxic.	1193820
	Zoxamide	8-d Acute dietary	LC_{50} >5250 ppm LD_{50} > 1415.9 mg a.i./kg bw/day[5]	Concentrations applied: 328, 656, 1313, 2625 and 5250 ppm for 5 days, followed by a 3 day recovery period, No mortality or any other effects were observed, Practically non-toxic.	1193821

Test organisms	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA #
	Zoxamide	22-Weeks Reproduction	NOEC = 1000 mg a.i./kg food NOEL= 158.2 mg a.i./kg bw/day[5]	Concentrations applied: 75, 200, 500 and 1000 ppm (mg a.i./kg food), There were no statistically significant or treatment related were observed on adult body weight, survival, growth and reproductive parameters.	1193823
Mallard duck (*Anas plathyrhynchos*)	Zoxamide	8-d Acute dietary	LC_{50} >5250 ppm **LD_{50} >1167 mg a.i./kg bw/day[5]** NOEC = 2625 ppm (based on a single mortality at 5250 ppm)	Concentrations applied: of 328, 656, 1313, 2625 and 5250 ppm for a period of 5 days followed by a 3-day recovery period, No mortality or any other effects were observed, Practically non-toxic.	1193822
	Zoxamide	22-Weeks Reproduction	NOEC = 1000 mg a.i./kg food **NOEL = 114.3 mg a.i./kg bw/day[5]**	Concentrations applied: 75, 200, 500 and 1000 ppm (mg a.i./kg food), No statistically significant or treatment related were observed on adult body weight, survival, growth and reproductive parameters.	1194262
Mammals					
Rat	Zoxamide	Acute oral toxicity (gavage)	**LD_{50} > 5000 mg a.i./kg bw** (♂/♀)	No deaths or treatment-related adverse effects identified, Practically non-toxic.	3065671
Mouse	Zoxamide	Acute oral toxicity (gavage)	LD_{50} > 5000 mg a.i./kg bw (♂/♀)	No deaths or treatment-related adverse effects identified, Practically non-toxic.	3065671
Rat	Zoxamide	2-Generation reproductive toxicity (dietary)	**Parental Toxicity (P1)** **NOAEL = 360**//409 **mg a.i./kg bw/day** (♀/♂) (based on reduced body weight)	Reduced body weight in P_1, No adverse treatment-related effects on reproductive parameters,	3065671

Test organisms	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA #
			Reproductive Toxicity NOAEL = 1474/1624 mg/kg bw a.i./day (♂/♀) (based on no effects) Offspring Toxicity LOAEL = 82 mg a.i./kg bw/day	Evidence of increased sensitivity of the young in the 2-generation reproductive toxicity study in rats based on decreased body weight and reduced extramedullary hematopoiesis.[6]	
Terrestrial vascular plants					
Greenhouse screening on up to19 species	Zoxamide	14-d phytotoxicity	**NOEC ≥ 500 g a.i./ha**	Rates tested: 125, 250 and 500 g a.i./ha on broad-leaved, grass species and species of cereal crop plants (such as corn, cotton, wheat, rice, barley, cabbage, carrots, lettuce, melon, onion, peas, rape, rye, sugar beets, sunflower, tomato, and soybean), No adverse effects were seen at any rates.	1194268 and 1194263

P_1 = parental first generation,
a.i. = active ingredient, zoxamide; a.s. = active substance, transformation product,
[1] The endpoints for use in the risk assessment are highlighted **in bold**,
[2] Based on USEPA toxicity classification or IOBC toxicity classification,
[3]A description of observed effects for each study,
[4] The values were corrected for the a.i. [Endpoints calculated by multiplying the dose in µg formulation/bee (as reported) by the % a.i in the formulation],
[5] Conversion by EFSA,
[6] Based on the PMRA review these effects were not considered serious.

Table 8.9 Summary of effects on aquatic organisms.

Test organism	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA#
Freshwater Organisms					
Invertebrates					
Water flea (*Daphnia magna*)	Zoxamide (purity 94.2%)	48-hr Acute (flow-through)	**EC_{50} > 0.42 mg a.i./L** (mean measured) (highest soluble concentration)	Test concentrations: 0.092, 0.15, 0.25, 0.42 and 0.78 mg a.i./L, Concentration of 0.78 mg a.i./L was exceeded the functional solubility, 0.42 was used as the highest soluble concentration, No immobility or sublethal effects up to achievable solubility limit, Practically non-toxic up to achievable solubility limit.[4]	1194216
	Zoxamide (Purity 92.3%)	21-d Chronic (flow-through)	**NOEC = 0.039 mg a.i./L** (mean measured) (based on significant survival effects)	Test concentration: 0.009, 0.02, 0.039. 0.074 and 0.16 mg a.i./L (mean measured), Survival reduction at 0.074 and 0.16 mg a.i./L, Reproductive parameteres were unaffected by exposure to zoxamide.	1194218 and 3173307
	RH-127450 (99.27%, a major TP in aquatic system)	48-hr Acute (static)	**EC_{50} > 1.35 mg a.s./L** (highest soluble concentration)	Test concentrations: 0.31, 0.63, 1.3, 2.5 and 5.0 mg a.s./L, Concentrations of 2.5 and 5.0 mg a.s/L exceeded the functional solubility, No immobility or mortality or sublethal effects were observed up to achievable solubility limit, Practically non-toxic up to achievable solubility limit.[4]	11942217
Benthic (sediment-dwelling)					
Midge Larvae (*Chironomus riparius*)	Zoxamide (purity 92.3%)	28-d Chronic (static)	**NOEC = 0.45** mg a.i./L (nominal) (overlying	Concentrations tested: 0.45, 0.81, 1.5, 2.6, 4.7 and 8.5 mg a.i./L (nominal),	1194219

Test organism	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA#
			water, based on emergence rate)	Statistically significant less midges emerged attest concentrations of 0.81mg a.i./L and higher.	
Midge larvae (*Chironomus dilutus*)	Zoxamide (purity 98.8%)	10-d Chronic (static-renewal)	NOEC = 89 mg a.i./kg sediment dw and = 0.55 mg a.i./L (pore water) (based on survival and growth)	Test concentrations: 5, 10, 21, 45 and 89 mg a.i./kg sediment dw (measured), Zoxamide remained associated with the sediment for the duration of the exposure, No adverse effects on survival and growth at the highest concentration tested.	2837859
Amphipods (*Hyalella azteca*)	Zoxamide (purity 98.8%)	10-d Chronic (static-renewal)	NOEC = 21 mg a.i./kg sediment dw and **0.32 mg a.i./L (pore water)** (based on survival and growth)	Test concentrations: 5, 9.6, 21, 43 and 93 mg a.i./kg sediment dw (measured), Zoxamide remained associated with the sediment for the duration of the exposure, Reduction in percent survival was observed in 43 and 93 mg a.i./kg sediment dw treatments.	2837860
Fish					
Rainbow trout (*Oncorhynchus mykiss*)	Zoxamide (purity 94.2%)	96-hr Acute (flow-through)	**LC_{50} = 0.16 mg a.i./L** (mean measured)	Test concentrations: 51, 71, 140, 210 and 380 µg a.i./L (measured), Mortality and/or sublethal effects were noted in the 0.14 mg a.i./L and higher, Highly toxic.	1194224
Bluegill sunfish (*Lepomis macrochirus*)	Zoxamide (purity 94.2%)	96-hr Acute (flow-through)	LC_{50} > 0.79 mg a.i./L (mean measured)	Test concentrations: 0.10, 0.17, 0.29, 0.49 and 0.79 mg a.i./L (measured), Dose-related sublethal effects were noted at concentrations higher than 0.10 mg a.i./L, Practically non-toxic up to achievable solubility.[4]	1194225
Zebra fish (*Brachydanio rerio*)	Zoxamide (purity 92.3%)	96-hr Acute (flow-through)	LC_{50} > 0.73 mg a.i./L (mean measured)	Test concentrations: 0.16, 0.25, 0.40, 0.61 and 0.73 mg a.i./L (measured),	3173307

Test organism	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA#
				Practically non-toxic up to achievable solubility limit.[4]	
Fathead minnow (*Pimephales promelas*) – Benthic fish	Zoxamide (Purity 92.3%)	96-hr Acute (flow-through), Juvenile fathead	**LC_{50} > 0.21 mg a.i./L** (mean measured) (highest concentration tested)	Test concentrations: 37, 62, 112, 173 and 208 µg a.i./L (measured), No mortality up to highest concentration tested.	1193818
Rainbow trout (*Oncorhynchus mykiss*)	Zoxamide (purity 92.9%)	95-d Early Life Cycle (flow through)	**NOEC = 0.00348 mg a.i./L** (mean measured) (based on survival and sublethal effects)	Test concentrations: 0.403, 0.882, 1.70, 3.48 and 6.87 µg a.i./L (measured), Survival and abnormalities (discolouration and abnormal body posture) were significant at 6.87µg a.i./L.	1193812
Fathead minnow (*Pimephales promelas*) – Bentic fish	Zoxamide (purity 92.3%)	202-d Full Life Cycle (flow-through)	**NOEC = 0.06 mg a.i./L** (mean measured) (based on survival of first generation)	Test concentrations: 7.8, 15, 29, 60 and 121 µg a.i./L (measured) during the parental exposure, 8.1, 16, 28, 64 and 127 µg a.i./L (measured) for second generation exposure, Life-cycle impact: Reduction in first and second generation survival, Reduction in first generation length, Reduction in length and weight of male parental generation fish.	1193818
Rainbow trout (*Oncorhynchus mykiss*)	RH-127450 (purity 99.27%, major TP in water)	96-hr Acute (static)	**LC_{50} > 2.5 mg a.s./L** (highest soluble concentration tested)	Test concentrations: 0.31, 0.63, 1.3, 2.5 and 5.0 mg a.s./L, Functional water solubility under the test conditions had been exceeded for 5.0 mg a.i./L, 2.5 mg a.s./L was used as the highest soluble concentration, Sublethal effects observed at 1.3 mg a.s./L and higher (discolouration, resting on the bottom of the test	1194261 and 3173307

Test organism	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA#
				chamber, loss of equilibrium and remaining in the top quarter of the water column), Practically non-toxic up to achievable solubility limit.[4]	
Algae					
Green algae (*Selenastrum capricornutum*)	Zoxamide (purity 92.9%)	120-hr Acute (static)	ErC_{50} = 0.05 mg a.i./L (mean measured) (growth rate) E_bC_{50} = 0.02 mg a.i./L (biomass)	Test concentrations: 4.13, 8.58, 17.8, 31.9 and 65.6 µg a.i./L (measured), Statistically significant inhibition effect on growth rate and biomass, Highly toxic.	1193813
Green algae (*Scenedesmus subspicatus*)	Zoxamide (purity 92.3%)	96-hr Acute (static)	**EC_{50} = 0.01 mg a.i/L** (mean measured) (cell density and biomass) ErC_{50} = 0.02 mg a.i/L (growth rate)	Test concentrations: 1.6, 3.5, 7.0, 14 and 28 µg a.i./L (measured), Highly toxic.	1193814
Bluegreen algae (*Anabaena flos-aquae*)	Zoxamide (purity 92.3%)	96-hr Acute (static)	EC_{50} > 0.86 mg a.i/L (cell density) ErC_{50} > 0.86 mg a.i/L (growth rate) E_bC_{50} > 0.86 mg a.i/L (biomass) NOEC = 0.86 mg a.i./L (All endpoints are in mean measured)	Test concentrations: 0.05, 0.10, 0.20, 0.42 and 0.86 mg a.i./L (measured), No inhibitory effect was observed at the highest test concentration.	1193815
Diatom (*Navicula pelliculosa*)	Zoxamide (purity 92.3%)	96-hr Acute (static)	EC_{50} > 0.93 mg a.i/L (cell density) ErC_{50} > 0.93 mg a.i/L (growth rate)	Test concentrations: 0.058, 0.11, 0.21, 0.41 and 0.93 mg a.i./L (measured), Concentrations of 0.41 and 0.93 mg a.i./L have inhibitory effects on N. pelliculosa (37% and 44%, respectively),	1193816

Test organism	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA#
			E_bC_{50} > 0.93 mg a.i/L (biomass) NOEC = 0.21 mg a.i./L (All endpoints are in mean measured)	No ≥50% toxicity was observed up to highest concentration tested.	
Green algae (*Selenastrum capricornutum*)	RH-127450 (purity 99.27%, major TP in water)	96-hr Acute (static)	EC_{50} = 3.2 mg a.s/L (cell density) **E_bC_{50} = 2.8 mg a.s./L** (biomass) E_rC_{50} = 4.1 mg a.s/L (growth rate) NOEC = 2.4 mg a.s/L (growth rate) (All endpoints are in mean measured)	Test concentrations: 0.27, 0.52, 1.1, 2.4 and 4.1 mg a.i./L (measured).	1194234
Green algae (*Selenastrum subspicatus*)	RH-163353 (major TP in water)	96-hr Acute (static)	**EC_{50} >23 mg a.s./L** NOEC = 6.1 mg a.s./L (based on 96-hr growth rate) (All endpoints are in mean measured)	Test concentrations: 1.3, 2.9, 6.1, 12 and 23 mg a.s./L (measured).	3173307
Vascular plant					
Duckweed (*Lemna gibba* G3)	Zoxamide (purity 92.3%)	14-d Acute (static-renewal)	**IC_{50} = 0.017 mg a.i./L** (mean measured) NOEC = 0.009 mg a.i./L	Test concentrations: 1.1, 2.2, 4.4, 9.0 and 18 µg a.i./L (measured), Reduction of 49% in frond production in the 18 µg a.i./L treatment, Highly toxic.	1194269
Estuarine/Marine organisms					
Invertebrates					
Crustacean Mysid shrimp (*Mysidopsis bahia*)	Zoxamide (purity 92.3%)	96-hr Acute (flow-through)	**LC_{50} = 0.076 mg a.i./L** NOEC = 0.0306 mg a.i./L (based	Test concentrations: 0.017, 0.0306, 0.0469, 0.0763 and 0.132 mg a.i./L,	1194220

Test organism	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA#
			on erratic swimming)	Percent mortality in the 0.0469, 0.0763 and 0.132 mg a.i./L was 5%, 45% and 100%, respectively, Very highly toxic.	
	Zoxamide (purity 92.3%)	27-d Life-cycle (flow-through)	**NOEC = 0.007 mg a.i./L (7.2 µg a.i./L)** (mean measured) based on reproduction, length, dry weight) LOEC = 0.014 mg a.i./L (14 µg a.i./L)	Test concentrations: 1.7, 3.4, 7.2, 14 and 19 µg a.i./L (measured, Fewer young and decreased lengths and dry weights in 14 µg a.i./L. Reduced survival to pairing in 19 µg a.i./L.	1194222
Benthic (sediment-dwelling)					
Mollusc: Eastern oyster (*Crassostrea virginica*)	Zoxamide (purity 92.3%)	96-hr Acute (flow-through)	**EC_{50} = 0.72 mg a.i./L** NOEC = 0.123 mg a.i./L	Test concentrations: 0.0587, 0.123, 0.238, 0.507 and 0.863 mg a.i./L (measured), Oyster shell growth reduced significantly in 0.238 mg a.i./L and higher, Practically non-toxic up to achievable solubility limit.[4]	1194221
Amphipods (*Leptocherius plumulosus*)	Zoxamide (Purity 98.8%)	10-d Chronic (static)	**NOEC = 95 mg a.i./kg** sediment dw (maximum concentration tested).	Test concentrations: 1.5, 4.9, 12, 33 and 95 mg a.i./kg sediment dw, No effects were observed at any tested concentrations.	2837861
Marine Fish					
Sheepshead minnow (*Cyprinodon variegatus*)	Zoxamide (purity 92.3%)	96-hr Acute (flow-through)	**LC_{50} > 0.86 mg a.i./L** (highest concentration tested.	Test concentrations: 0.136, 0.235, 0.349, 0.482 and 0.855 mg a.i./L (measured), No toxic effects were observed up to achievable solubility limit.[4]	1194226
	Zoxamide	Early life-stage (34 days)	**NOEC = 0.004 mg a.i./L** (based on wet body weight)	Test concentrations: 19, 40, 78, 150 and 250 µg a.i./L (measured), Growth was the most sensitive biological factor.	1193817

Test organism	Test substance	Exposure	Endpoint[1]	Degree of toxicity[2]/comments[3]	PMRA#
Marine alga					
Marine diatom (*Skeletonema costatum*)	Zoxamide	96-hr Acute (static)	**EC_{50} > 0.91 mg a.i./L** NOEC = 0.49 mg a.i./L	Test concentrations: 0.052, 0.11, 0.24, 0.49 and 0.91 mg a.i./L (measured), NOEC was based on the highest concentration with no inhibitory effects on alga growth, No toxic effects were observed up to achievable solubility limit.[4]	1194251

TP = major transformation product in water/sediment,
a.i.= active ingredient, zoxamide; a.s. = active substance, transformation product or end-use product,
[1]The endpoints for use in the risk assessment are highlighted **in bold**,
[2]USEPA classification, where applicable,
[3]A description of observed effects for each study,
[4] Toxicity endpoint is higher than maximum achievable test concentration; therefore, zoxamide considered not to be toxic up to its functional solubility limit within the test system.

Table 8.10 Selected endpoints used in the risk assessment

Organism	Test substance/Exposure	Endpoint	Value
Earthworm (*Eisenia fetida*)	Zoxamide/Acute	14-d LC_{50}	>1070 mg a.i./kg dw soil
	Zoxamide/Chronic	56-d NOEC	1.0 mg a.i./kg dw soil
	RH-127450 (major TP in soil)/Acute	14-d LC_{50}	>1000 mg a.s./kg soil
Honeybee	Zoxamide (95% a.i.)/Acute contact	48-h LD_{50}	>100 µg a.i./bee
	Zoxium 240 SC (formulated product, 22.35% a.i.)/Acute oral	72-h LD_{50}	>33 µg a.i./bee
	Zoxium 240 SC (formulated product, 22.35% a.i.)/Acute contact	72-h LD_{50}	> 44.7 µg a.i/bee
	Zoxium 240 SC (formulated product, 22.35% a.i.)/Adult feeding	10-d NOEL	174.8 µg a.i./bee/d
	Zoxamide (98.8% purity)/Acute larval toxicity	72-h LD_{50}	>115 µg a.i./larva
Parasitic wasp (*Aphidius Rhopalosiphi*)	Zoxium 240 SC (formulated product, 22.35% a.i.)/glass plate	48-h LR_{50} NOEC	>300 g a.i./ha <150 g a.i./L
Predacious mite (*Typhlodromus Pyri*)	Zoxium 240 SC (formulated product, 22.35% a.i.)/Acute glass plate	10-d LR_{50}	>300g a.i./ha
Bobwhite quail (*Colinus virginianus*)	Zoxamide/Acute oral	14-d LD_{50}	>2000 mg a.i./kg bw
Mallard duck (*Anas plathyrhynchos*)	Zoxamide/Acute dietary	8-d LD_{50}	>1167 mg a.i./kg bw/d
	Zoxamide/Reproduction	22-week NOEL	114.3 mg a.i./kg bw/day
Mammals - Rat	Zoxamide/Acute oral	LD_{50}	> 5000 mg a.i./kg bw
	Zoxamide/2-generation)	NOAEL	360 mg a.i./kg bw/d

Organism	Test substance/Exposure	Endpoint	Value
		(parental) LOEL (offspring)[1]	82 mg a.i./kg bw/day
Terrestrial vascular plants	Zoxamide/Screening phytotoxicity	NOEC	500 g a.i./ha
Water flea (*Daphnia magna*)	Zoxamide/Acute	48-h EC_{50}	>0.42 mg a.i./L (highest soluble concentration)
	Zoxamide/Chronic	21-d NOEC	0.039 mg a.i./L
	RH-127450 (99.27%, a major TP in aquatic system)/Acute	48-h EC_{50}	>1.35 mg a.s./L (highest soluable concentration)
Midge Larvae (*Chironomus riparius*)	Zoxamide/Chronic	28-d NOEC	0.45 mg a.i./L
Amphipods (*Hyalella azteca*)	Zoxamide/Chronic	10-d NOEC	0.32 mg a.i./L
Freshwater fish Rainbow trout (*Oncorhynchus mykiss*)	Zoxamide/Acute	96-h LC_{50}	0.16 mg a.i./L
	Zoxamide/Early life stage	95-d NOEC	0.004 mg a.i./L
	RH-127450 (27%, a major TP in aquatic system)/Acute	96-h LC_{50}	>2.5 mg a.s./L
Amphibians[2]	Zoxamide/Acute (Rainbow trout)	96-h LC_{50}	0.16 mg a.i./L
	Zoxamide/Chronic ELS (Rainbow Trout)	95-d NOEC	0.004 mg a.i./L
Aquatic vascular plants (*Lemna gibba*)	Zoxamide/Acute	14-d IC_{50}	0.017 mg a.i./L
Green algae (*Scenedesmus subspicatus*)	Zoxamide/Acute	96-h EC_{50}	0.01 mg a.i./L
Green algae (*Selenastrum capricornutum*)	RH-127450 (purity 99.27%, major TP in water)/Acute	96-h E_bC_{50}	2.8 mg a.s./L
Green algae (*Selenastrum subspicatus*)	RH-163353 (major TP in water)/Acute	96-h EC_{50}	>23 mg a.s./L
Saltwater Crustacean Mysid shrimp (*Mysidopsis bahia*)	Zoxamide/Acute	96-h LC_{50}	0.076 mg a.i./L
	Zoxamide/Chronic life-cycle	27-d NOEC	0.007 mg a.i./L
Marine fish Sheepshead minnow (*Cyprinodon variegatus*)	Zoxamide/Acute	96-h LC_{50}	>0.86 mg a.i./L(highest soluable concentration)
	Zoxamide/Early life stage	34-d NOEC	0.004 mg a.i./L
Marine diatom (*Skeletonema costatum*)	Zoxamide/Acute	96-h EC_{50}	0.19 mg a.i./L (highest soluable concentration)

a.s. = used for active substance of transformation product,

[1] A NOEL was not determined,

[2] No information was submitted or found in a literature on toxicity to amphibians. Therefore, toxicity data for rainbow trout were used as a surrogate.

Table 8.11 Screening level risk assessment to soil invertebrates as a result of direct in-field exposure

Organism	Test substance	Exposure	Endpoint value (mg test item/kg soil dw)/UF[2]	EEC[3] (mg a.i./kg) soil dw)	RQ	LOC exceeded?
Earthworm (*Eisenia fetida*)	Zoxamide	Acute 14-d artificial soil	LC_{50}/2 >535	0.409	<0.01	No
		Chronic 56-d reproduction test - artificial soil	NOEC/1 = 1	0.409	= 0.41	No
	RH-127450	Acute 14-d	LC_{50}/2 >500	0.7153	<0.01	No

[1] Based on the highest use pattern (224 g a.i./ha × 8, 7 days interval on grape),
[2] UF = uncertainity factor,
[3] EEC in soil calculated using a half-life of 21.2 days for parent and 11.7 days for RH-127450, respectively. The EEC is calculated for a soil depth of 15 cm and density equal to 1.5 g/cm^3. The screening EEC for transformation products are calculated by multiplying the total applied a.i. concentration by the TP/a.i. molecular weight ratio (= 0.9), assuming 100% conversion of the parent to the TP.

Table 8.12 Screening level (in-field) risk to beneficial arthropods (foliar-dwelling organisms)

Application scenario		Test substance EER[1] (g a.i./ha)	RQ		LOC exceeded?
			Parasitic wasp (*A. rhopalosiphi*) 48h-LR_{50}[2] > 300 g a.i./ha	Predatory mite (*T. pyri*) 10 d-LR_{50} > 300 g a.i./ha	
In-field	Direct foliar application 8 × 224 g a.i./ha with 7 days interval	570.8	< 1.9	< 1.9	No

[1] EER (Estimated Exposure rate) on leaves is calculated, using the highest use pattern (224 g a.i./ha × 8, 7 days interval on grape), a half-life of 10-d. The EER for direct over spray is 570.8 g a.i./ha,
[2]LR = lethal rate.

Table 8.13 Screening Level EECs and RQ values for honeybees based on foliar application[1]

Endpoint	Exposure route	Test substance	Maximum single application rate (kg a.i./ha)	Exposure Estimate (µg a.i./bee)	Acute or Chronic Effect Endpoint (µg a.i./bee)	RQ	LOC exceeded?
Individual Survival (adult)	Acute Contact	Zoxamide	0.224	0.54	>100	<0.005	No
		Zoxium 240 SC			>44.7	<0.012	No
Individual Survival (adult)	Acute Oral	Zoxium 240 SC		6.5	>33	<02	No
Bee larvae	Acute oral	Zoxium 240 SC		6.5	>115	<0.06	No
Adult feeding	Chronic Dietary	Zoxium 240 SC		6.5	174.8	0.04	No
Honeybee brood feeding study	21 days exposure	Zoxium 240 SC	No adverse effects on the survival of the exposed adult worker bees and the colony conditions and health at concentration up to solubility limit of zoxamide (0.75 g a.i./L)				

[1] Tier I assessment for foliar application: the highest single spray application rate was used to estimate the EEC.

Table 8.14 Screening level risk of zoxamide to birds and mammals

Organism	Study type	Substance	Endpoint value (mg a.i./kg bw/day) divided by UF	Food guild[1]	Estimated daily intake (assuming high residue level on food, a.i./kg bw/day	RQ	LOC Exceeded?
Bobwhite quail (*Colinus virginianus*)	Acute oral	Zoxamide	$LD_{50}/10 > 200$	Small insectivore birds	46.3	< 0.23	No
				Medium insectivore birds	36.3	< 0.18	
				Large herbivore birds	23.4	< 0.12	
Mallard duck (*Anas plathyrhynchos*)	Dietary	Zoxamide	$LD_{50}/10 > 116.7$	Small insectivore birds	46.3	< 0.4	No
				Medium insectivore birds	36.3	< 0.31	
				Large herbivore birds	23.4	< 0.2	
Mallard duck (*Anas plathyrhynchos*)	Reproduction	Zoxamide	NOEL/1 = 114.3	Small insectivore birds	46.3	= 0.4	No
				Medium insectivore birds	36.3	= 0.32	
				Large herbivore Birds	23.4	= 0.21	
Mammals - Rat	Acute oral	Zoxamide	$LD_{50}/10 > 500$	Small insectivore mammals	26.4	< 0.05	No
				Medium herbivore mammals	50.3	< 0.1	
				Large herbivore mammals	27.7	< 0.06	

Organism	Study type	Substance	Endpoint value (mg a.i./kg bw/day) divided by UF	Food guild[1]	Estimated daily intake (assuming high residue level on food, a.i./kg bw/day	RQ	LOC Exceeded?
Mammals - Rat	Reproduction (parent)	Zoxamide	NOAEL/1 = 360	Small insectivore mammals	26.4	= 0.07	No
				Medium herbivore mammals	50.3	= 0.14	
				Large herbivore mammals	27.7	= 0.08	
Mammals - Rat	Reproduction (offspring)	Zoxamide	LOAEL/1 = 82	Small insectivore mammals	26.4	= 0.32	No
				Medium herbivore mammals	50.3	= 0.61	
				Large herbivore mammals	27.7	= 0.34	

UF = Uncertainty factor,

[1] Concentrations of zoxamide on different food guilds (EDE) are calculated based on the highest rate for airblast application to grape (in other words, 8 × 224 g a.i./ha) with a 7-day interval and a default foliar half-life of 10 days.

Table 8.15 Screening level risk of zoxamide to terrestrial plants

Representative crop and maximum seasonal application parameters	On-field foliar cumulative rate (g a.i./ha)	Toxicity endpointg a.i./ha	On-field RQ	LOC exceeded?	Off-field RQ (74% drift)	LOC exceeded?
Grape: 224 g a.i/ha × 8 applications, 7-d interval; applied with airblast equipment (early season, 74% drift)	571	500	**1.1**	**Yes**	< 1	NO
Onion: 190 g a.i./ha × 8 applications, 7-d interval; applied by field sprayer (groundboom) with medium spray droplet size (6% drift)	484	500	0.9	No	Not calculated	
Potato: 186 g a.i/ha × 6 applications, 7-d interval; applied by aerial equipment with medium spray droplet size (23% drift)	458	500	0.8	No	Not calculated	

Table 8.16 Screening (on-field) and drift (off-field) risk to aquatic organisms [224 g a.i./ha × 8 ,7-d interval on grape applied with early season airblast (74% drift)]

Organism	Exposure	Test Substance	Endpoint value (mg test substance/L)	Screening EEC* (mg a.i./L)	RQ	LOC exceeded?	Drift EEC (mg a.i./L)	Drift RQ	Drift LOC exceeded?
Freshwater invertebrates									
Water fleas (*Daphnia magna*) free-swimming	48-h Acute	Zoxamide	1/2EC_{50} >0.21	0.2	<1	No	Not calculated		
	21-d Chronic	Zoxamide	NOEC = 0.04	0.2	**= 5**	**Yes**	0.148	**= 3.7**	**Yes**
	48-h Acute	RH-127450	1/2EC_{50} >0.68	0.2	<0.3	No	Not calculated		
Midge (*Chironomus riparius* (sediment-dwelling)	28-d Chronic	Zoxamide	NOEC = 0.45 (spiked water study)	0.2 (overlying water)	= 0.44	No	Not calculated		
Amphipods (*Hyalella azteca*) (sediment-dwelling)	10-d Chronic	Zoxamide	NOEC = 0.32 mg a.i./L	0.2	= 06.2	No	Not calculated		
Freshwater fish									
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Zoxamide	1/10 LC_{50} = 0.016	0.2	**= 12**	**Yes**	0.148	**= 9.2**	**Yes**
	95-d ELS		NOEC = 0.004	0.2	**= 50**	**Yes**	0.148	**= 37**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	RH-127450	1/10 LC_{50} >0.25	0.2	<084	No	Not calculated		
Amphibians									
Amphibians	96-h Acute	Zoxamide	1/10 LC_{50} = 0.02	1.07	**= 66.9**	**Yes**	0.788	**= 49.3**	**Yes**
	95-d Chronic	Zoxamide	NOEC = 0.004	1.07	**= 268**	**Yes**	0.788	**= 197**	**Yes**
Aquatic plants									
Aquatic vascular plants (*Lemna gibba*)	14-d Acute	Zoxamide	1/2IC_{50} = 0.0085	0.2	**= 23**	**Yes**	0.148	**= 17**	**Yes**
Green algae (*Scenedesmus subspicatus*)	96-h Acute	Zoxamide	1/2EC_{50} = 0.005	0.2	**= 40**	**Yes**	0.148	**= 30**	**Yes**

Organism	Exposure	Test Substance	Endpoint value (mg test substance/L)	Screening EEC* (mg a.i./L)	RQ	LOC exceeded?	Drift EEC (mg a.i./L)	Drift RQ	Drift LOC exceeded?
Green algae (*Selenastrum capricornutum*)	96-h Acute	RH-127450	1/2EbC_{50} = 1.4	0.2	= 0.14	No	Not calculated		
Green algae (*Selenastrum subspicatus*)	96-h Acute	RH-163353	1/2EC_{50} >11.5	0.2	<0.02	No	Not calculated		
Marine/estuarine invertebrates									
Saltwater Crustacean Mysid shrimp (*Mysidopsis bahia*)	96-h Acute	Zoxamide	1/2LC_{50} = 0.04	0.2	**= 5**	**Yes**	0.021**	= 0.52	No
	27-d Chronic	Zoxamide	NOEC = 0.007	0.2	**= 29**	**Yes**	Acute endpoints only are used for spray drift assessment for marine habitats.		
Marine/estuarine fish									
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Zoxamide	1/10LC_{50} >0.086	0.2	**< 2.3**	**Yes**	0.021**	<0.2	No
	34-d ELS	Zoxamide	NOEC = 0.004	0.2	**= 50**	**Yes**	Acute endpoints only are used for spray drift assessment for marine habitats.		
Marine algae									
Marine diatom (*Skeletonema costatum*)	96-h Acute	Zoxamide	1/2EC_{50} = 0.455	0.2	**0.44**	No	Not calculated		

* combined residues= zoxamide+RH-127450 and RH-163353,

** Refined drift EEC for the acute marine assessment was conducted using only one application.

Table 8.17 Screening (on-field) and drift (off-field) risk to aquatic organisms [190 g a.i./ha × 8 ,7-d interval on onion applied with field sprayer (6% drift)]

Organism	Exposure	Test Substance	Endpoint value (mg test substance/L)	Screening EEC* (mg a.i./L)	RQ	LOC exceeded?	Drift EEC (mg a.i./L)	Drift RQ	Drift LOC exceeded?
Freshwater invertebrates									
Water fleas (*Daphnia magna*) free-swimming	48- h Acute	Zoxamide	1/2EC_{50} >0.21	0.169	<0.8	No	Not calculated		
	21-d Chronic	Zoxamide	NOEC = 0.04	0.169	**= 4.2**	**Yes**	0.01	= 0.23	No
	48-h Acute	RH-127450	1/2EC_{50} >0.68	0.169	< 0.2	No	Not calculated		
Midge (*Chironomus riparius*	28-d Chronic	Zoxamide	NOEC = 0.45 (spiked water study)	0.169	= 0.4	No	Not calculated		

Organism	Exposure	Test Substance	Endpoint value (mg test substance/L)	Screening EEC* (mg a.i./L)	RQ	LOC exceeded?	Drift EEC (mg a.i./L)	Drift RQ	Drift LOC exceeded?
(sediment-dwelling)									
Freshwater fish									
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Zoxamide	1/10 LC_{50} = 0.016	0.169	**= 11**	**Yes**	0.01	= 0.63	No
	95-d ELS		NOEC = 0.004	0.169	**= 42**	**Yes**	0.01	**= 2.5**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	RH-127450	1/10 LC_{50} >0.25	0.169	<0.8	No	Not calculated		
Amphibians									
Amphibians	96-h Acute	Zoxamide	1/10 LC_{50} = 0.016	0.903	**= 56**	**Yes**	0.054	**= 3.4**	**Yes**
	95-d Chronic	Zoxamide	NOEC = 0.004	0.903	**= 225**	**Yes**	0.054	**= 13.5**	**Yes**
Aquatic plants									
Aquatic vascular plants (*Lemna gibba*)	14-d Acute	Zoxamide	1/2IC_{50} = 0.0085	0.169	**= 19.9**	**Yes**	0.01	**= 1**	**Yes**
Green algae (*Scenedesmus subspicatus*)	96-h Acute	Zoxamide	1/2EC_{50} = 0.005	0.169	**= 34**	**Yes**	0.01	**= 2**	**Yes**
Green algae (*Selenastrum capricornutum*)	96-h Acute	RH-127450	1/2EbC_{50} = 1.4	0.169	=0.12	No	Not calculated		
Green algae (*Selenastrum subspicatus*)	96-h Acute	RH-163353	1/2EC_{50} >11.5	0.169	<0.01	No	Not calculated		
Saltwater/marine invertebrates									
Saltwater Crustacean Mysid shrimp (*Mysidopsis bahia*)	96-h Acute	Zoxamide	1/2LC_{50} = 0.04	0.169	**= 4.2**	**Yes**	0.001**	= 0.03	No
	27-d Chronic	Zoxamide	NOEC = 0.007	0.169	**= 24**	**Yes**	Acute endpoints only are used for spray drift assessment for marine habitats.		
Marine fish									
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Zoxamide	1/10LC_{50} >0.086	0.169	**< 2**	**Yes**	0.001**	<0.01	No
	34-d ELS	Zoxamide	NOEC = 0.004	0.169	**= 42**	**Yes**	Acute endpoints only are used for spray drift assessment for marine habitats.		

Organism	Exposure	Test Substance	Endpoint value (mg test substance/L)	Screening EEC* (mg a.i./L)	RQ	LOC exceeded?	Drift EEC (mg a.i./L)	Drift RQ	Drift LOC exceeded?
Marine algae									
Marine diatom (*Skeletonema costatum*)	96-h Acute	Zoxamide	1/2EC_{50} = 0.455	0.169	**0.4**	**No**	Not calculated		

* combined residues= zoxamide, RH-127450 and RH-163353,

** Refined drift EEC for the acute marine assessment was conducted using only one application.

Table 8.18 Screening (on-field) and drift (off-field) risk to aquatic organisms [204 g a.i./ha × 3,7-d interval on potato applied with aerial equipment [medium spray droplet size, 23% drift)]

Organism	Exposure	Test Substance	Endpoint value (mg test substance/L)	Screening EEC* (mg a.i./L)	RQ	LOC exceeded?	Drift EEC (mg a.i./L	Drift RQ	Drift LOC exceeded?
Freshwater invertebrates									
Water fleas (*Daphnia magna*) free-swimming	48- h Acute	Zoxamide	1/2EC_{50} >0.21	0.074	<0.4	No	Not calculated		
	21-d Chronic	Zoxamide	NOEC = 0.04	0.074	**= 1.8**	**Yes**	0.017	= 0.43	No
	48-h Acute	RH-127450	1/2EC_{50} >0.68	0.074	<0.01	No	Not calculated		
Midge (*Chironomus riparius* (sediment-dwelling)	28-d Chronic	Zoxamide	NOEC = 0.45	0.074	= 0.16	No	Not calculated		
Freshwater fish									
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Zoxamide	1/10 LC_{50} = 0.016	0.074	**= 4.6**	**Yes**	0.017	**= 1.1**	**Yes**
	95-d ELS		NOEC = 0.004	0.074	**= 18.5**	**Yes**	0.017	**= 4.3**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	RH-127450	1/10 LC_{50} >0.25	0.074	<0.3	No	Not calculated		
Amphibians									
Amphibians	96-h Acute	Zoxamide	1/10 LC_{50} = 0.016	0.395	**= 24.7**	**Yes**	0.091	**= 5.8**	**Yes**
	95-d Chronic	Zoxamide	NOEC = 0.004	0.395	**= 98.8**	**Yes**	0.091	**= 22.8**	**Yes**

Organism	Exposure	Test Substance	Endpoint value (mg test substance/L)	Screening EEC* (mg a.i./L)	RQ	LOC exceeded?	Drift EEC (mg a.i./L	Drift RQ	Drift LOC exceeded?
Aquatic plants									
Aquatic vascular plants (*Lemna gibba*)	14-d Acute	Zoxamide	$1/2IC_{50}$ = 0.0085	0.074	**= 8.7**	**Yes**	0.017	**= 2**	**Yes**
Green algae (*Scenedesmus subspicatus*)	96-h Acute	Zoxamide	$1/2EC_{50}$ = 0.005	0.074	**= 15**	**Yes**	0.017	**= 3.4**	**Yes**
Green algae (*Selenastrum capricornutum*)	96-h Acute	RH-127450	$1/2EbC_{50}$ = 1.4	0.074	= 0.05	No	Not calculated		
Green algae (*Selenastrum subspicatus*)	96-h Acute	RH-163353	$1/2EC_{50}$ >11.5	0.075	<0.006	No	Not calculated		
Saltwater/marine invertebrates									
Saltwater Crustacean Mysid shrimp (*Mysidopsis bahia*)	96-h Acute	Zoxamide	$1/2LC_{50}$ = 0.04	0.074	**= 1.8**	**Yes**	0.006**	= 0.15	No
	27-d Chronic	Zoxamide	NOEC = 0.007	0.074	**= 11**	**Yes**	Acute endpoints only are used for spray drift assessment for marine habitats.		
Marine fish									
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Zoxamide	$1/10LC_{50}$ >0.086	0.074	<0.86	No	Not calculated		
	34-d ELS	Zoxamide	NOEC = 0.004	0.074	**= 18**	**Yes**	Acute endpoints only are used for spray drift assessment for marine habitats.		
Marine algae									
Marine diatom (*Skeletonema costatum*)	96-h Acute	Zoxamide	$1/2EC_{50}$ = 0.455	0.074	= 0.2	No	Not calculated		

* combined residues= zoxamide+RH-127450 and RH-163353,

** Refined drift EEC for the acute marine assessment was conducted using only one application.

Table 8.19 Risk to aquatic organisms due to runoff.

Organism	Exposure	Endpoint value (mg/L)	Refined EEC* (mg a.i./L)	RQ[a]	LOC exceeded?
190 g a.i./ha × 6 applications, 7-day interval; use on potatoes					
Waterfleas (*Daphnia magna*)	21-d Chronic	NOEC = 0.04	21-d EEC = 0.026	0.65	No
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	1/10 LC_{50} = 0.016	96-h EEC = 0.037	**2.3**	**Yes**
	95-d Early-life stage	NOEC = 0.004	21-d EEC = 0.026	**6.5**	**Yes**
	95-d Chronic	NOEC = 0.004	21-d EEC = 0.114	**28.5**	**Yes**
Lemna gibba	14-d Acute	½ IC_{50} = 0.0085	21-d EEC = 0.026	**3**	**Yes**
Green algae (*Scenedesmus subspicatus*)	96-h Acute	½ EC_{50} = 0.005	96-h EEC = 0.037	**7.4**	**Yes**
Mysid shrimp (*Mysidopsis bahia*)	96-h Acute	½ LC_{50} = 0.04	96-h EEC = 0.037	0.9	No
	27-d Chronic	NOEC = 0.007	21-d EEC = 0.026	**3.7**	**Yes**
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	1/10 LC_{50} >0.086	21-d EEC = 0.026	< 0.3	No
	34-d Early life stage	NOEC = 0.004	21-d EEC = 0.026	**6.5**	**Yes**

*Modelled EEC values for runoff for zoxamide were calculated by considering input to water from a 10-ha field adjacent to 1-ha waterbody of two different depths, 80 cm and 15 cm, using the Pesticide in Water Calculator (PWC) version 1.52.

Table 8.20 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria.

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Zoxamide	Major soil and aquatic transformation products (TPs)		
				RH-127450 (soil and aquatic TP)	RH-163353 (soil and aquatic TP)	RH-24549 (soil TP)
CEPA-toxic or CEPA-toxic equivalent[1]	Yes		Yes	Yes	Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes	Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	Does not meet DT_{50}: 2.03–23.9 days	Does not meet (DT_{50} = 3.94–21.5 days	Does not meet (DT_{50} = 8.45–12.4 days	Does not meet DT_{50} = 7.37–10.3 days
	Water/sediment Whole system	Half-life ≥ 182 days	Does not meet DT_{50}: 6.06–6.09 days	Meet (DT_{50} = 148.4–326.1 days	NA	NA
	Air	Half-life ≥ 2 days or evidence	NA DT_{50}: < 12 hours	NA	NA	NA

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Zoxamide	Major soil and aquatic transformation products (TPs)		
				RH-127450 (soil and aquatic TP)	RH-163353 (soil and aquatic TP)	RH-24549 (soil TP)
		of long range transport				
Bioaccumulation[4]	Log $K_{ow} \geq 5$		Does not meet Log K_{ow} = 3.76	Does not meet Log K_{ow} = 3.5	1.43 (pH 2.5)	Does not meet Log K_{ow} = 3.83 (pH 4) and -0.43 (pH 7)
	BCF ≥ 5000		No: 95–136 (whole fish)	NA	NA	NA
	BAF ≥ 5000		NA	NA	NA	NA
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet all TSMP Track 1 criteria.	No, does not meet all TSMP Track 1 criteria.	No, does not meet all TSMP Track 1 criteria.	No, does not meet all TSMP Track 1 criteria.

NA = not available

[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}).

Appendix IX Proposed label amendment for products containing zoxamide

The label amendments proposed below do not include all label requirements for individual products, such as disposal statements, and precautionary statements. Information on labels of currently registered products should not be removed unless it contradicts the following label statements.

1.0 Label Amendments for Zoxamide Technical Products

1.1 Under the title "ENVIRONMENTAL PRECAUTIONS" add the following statements:

TOXIC to aquatic organisms

"DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters."

1.2 Under the title "DISPOSAL", include the following statements:

Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal and provincial regulations. For additional details and clean up of spills, contact the manufacturer and the provincial regulatory agency.

2.0 Label Amendments for Zoxamide Commercial End-Use Products

2.1 Under the title "ENVIRONMENTAL PRECAUTIONS" add the following statements:

TOXIC to aquatic organisms. Observe spray buffer zones specified under DIRECTIONS FOR USE.

To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.

Avoid application when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative filter strip between the treated area and the edge of the water body.

2.2 Under the title "DIRECTIONS FOR USE" add the following statements:

As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

Field sprayer application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. DO NOT apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

Aerial application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT apply when wind speed is greater than 16 km/h at flying height at the site of application. DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Apply only by fixed-wing or rotary aircraft equipment which has been functionally and operationally calibrated for the atmospheric conditions of the area and the application rates and conditions of this label.

Label rates, conditions and precautions are product specific. Read and understand the entire label before opening this product. Apply only at the rate recommended for aerial application on this label. Where no rate for aerial application appears for the specific use, this product cannot be applied by any type of aerial equipment.

Ensure uniform application. To avoid streaked, uneven or overlapped application, use appropriate marking devices.

Spray Buffer Zones:

A spray buffer zone is NOT required for uses with hand-held application equipment permitted on this label.

The spray buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Buffer zones for PCP# 26840 (zoxamide only):

Method of application	Crop		Spray Buffer Zones (metres) required for the protection of:				
			Freshwater habitat of depths:		Estuarine/Marine habitat of depths:		Terrestrial habitat:
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Potato		5	1	0	0	0
Airblast	Grape	Early growth stage	45	20	0	0	0
		Late growth stage	35	10	0	0	0
Aerial	Potato	Fixed wing	125	10	0	0	0
		Rotary wing	100	10	0	0	0

When tank mixes are permitted, consult the labels of the tank-mix partners and observe the largest (most restrictive) spray buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The spray buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Spray Buffer Zone Calculator on the Pesticides portion of the Canada.ca website.

Buffer zones for PCP# 26842 based on application rates for zoxamide:

Method of application	Crop		Spray Buffer Zones (metres) required for the protection of:				
			Freshwater habitat of depths:		Estuarine/Marine habitat of depths:		Terrestrial habitat:
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Potato		5	1	0	0	0
	Onion		10	1	0	0	0
Airblast	Grape	Early growth stage	40	15	0	0	0
		Late growth stage	30	5	0	0	0
Aerial	Potato	Fixed wing	350	10	0	0	0
		Rotary wing	175	10	0	0	0

When tank mixes are permitted, consult the labels of the tank-mix partners and observe the largest (most restrictive) spray buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The spray buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Spray Buffer Zone Calculator on the Pesticides portion of the Canada.ca website.

Buffer zones for PCP# 32363 based on application rates for zoxamide:

Method of application	Crop		Spray Buffer Zones (metres) Required for the Protection of:				
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Potato		4	1	0	0	0
Aerial	Potato	Fixed wing	200	10	0	0	0
		Rotary wing	125	5	0	0	0

When tank mixes are permitted, consult the labels of the tank-mix partners and observe the largest (most restrictive) spray buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.The spray buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Spray Buffer Zone Calculator on the Pesticides portion of the Canada.ca website.

3.0 Additional Label amendments

3.1 For Reg. No. 26842 add the following statement on the commercial-class product label:

Ground application only.

3.2 For Reg. Nos. 26840 and 26842 in the "PRECAUTIONS" section replace the following drift statement on the commercial-class product labels

> Use good pesticide application practices and apply only when the potential for drift to non-target or sensitive areas is minimal. Take into consideration residential areas, areas of human activities, bodies of water, meteorological conditions including wind speed, wind direction, temperature inversions, application equipment and sprayer settings used for application. Do not spray when the wind is blowing towards adjacent residential areas or areas of human activity, e.g., schools, parks

With the standard drift statement:

> Apply only when the potential for drift beyond the area to be treated is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.

References

A. Information Considered in the Updated Chemistry Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Title
1262069	1998, Product Chemistry Series 830 Group B, Physical and Chemical Characteristics in RH-117281 Technical, DACO: 2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4, 2.14.6,2.14.7,2.14.8,2.14.9,2.16
2785841	2017, Zoxamide, DACO: 2.13.3,2.13.4
2785842	2016, Comparative QSAR analysis of Zoxamide in OECD QSAR Toolbox version 3.4.0.17, DACO: 2.13.3,2.13.4
2785843	2015, Analytical Profile of Five Production Batches of Zoxamide, DACO: 2.13.3,2.13.4
2785844	2014, Comparative QSAR analysis of Zoxamide against in OECD QSAR Toolbox version 3.2.0.103, DACO: 2.13.3,2.13.4

B. Information Considered for the Updated Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Title
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1193549	1996. RH-117,281 Technical: Acute dermal toxicity study in male and female rats. DACO 4.2.2
1193550	1996. RH-117,281 Technical: Acute inhalation toxicity study in rats. DACO 4.2.3
1193551	1996. RH-117,281 Technical: Eye irritation study in rabbits. DACO 4.2.4
1193552	1996. RH-117,281 Technical: Skin irritation study in rabbits. DACO 4.2.5
1193556	1996. RH-117,281: Three-month dietary toxicity study in mice. DACO 4.3.1
1193557	1996. RH-117,281: Three-month dietary toxicity/neurotoxicity study in rats. DACO 4.3.1, 4.5.11
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1193565	1998. Summary of toxicology studies and selection of toxicological endpoints for human health risk assessment. RH-117281 Technical, RH-7281 80W and RH-7281 MZ, 75 DF fungicide. DACO 4.1
1193566	1996. RH-117,281 Technical: Acute oral toxicity study in male and female rats. DACO 4.2.1
1193567	1998. RH-117,281 Technical: Acute oral toxicity study in male and female mice. DACO 4.2.1
1193568	1998. RH-117,281 Technical: One-year chronic dietary toxicity study in dogs. DACO 4.3.2
1193569	1998. RH-117,281 Technical: Twenty-eight day dermal toxicity study in rats. DACO 4.3.5
1193570 1193571	1998. RH-117,281 Technical: Eighteen-month dietary oncogenicity study in mice. DACO 4.4.3
1193572 1193573 1193574 1193575	1998. RH-117,281 Technical: 24-month dietary chronic/oncogenicity study in rats. DACO 4.4.2, 4.4.4
1193576 1193577	1998. RH-117,281 Technical: Two-generation reproductive toxicity study in rats. DACO 4.5.1

PMRA Document Number	Title
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1193579	1997. RH-117,281 Technical: Oral (gavage) developmental toxicity study in rabbits. DACO 4.5.3
1193580	1996. RH-117,281 Technical: Salmonella typhimurium gene mutation assay (Ames test). DACO 4.5.4
1193581	1994. RH-117,281: Test for chemical induction of gene mutation at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation. DACO 4.5.5
1193582	1998. RH-117,281: Test for chemical induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells. DACO 4.5.6
1193583	1996. RH-117,281 Technical: Micronucleus assay in CD-1 mouse bone marrow cells. DACO 4.5.7
1193584 1193794	1998, 14C-RH-117,281: Pharmacokinetic and metabolism study in rats. DACO 4.5.9
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1193805	1997. RH-117,281 Technical: Acute oral (gavage) neurotoxicity study in rats. DACO 4.5.10
1193806	1998. RH-141,455: Acute oral toxicity study in male and female mice. DACO 4.2.1
1193807	1998. RH-141,455: Salmonella typhimurium gene mutation assay (Ames test). DACO 4.5.4
1193808	1998. [^{14}C]-RH-141,455: Rat metabolism study, tier 1 testing. DACO 4.5.9
1194265	1999. RH-117,281 Technical: Eighteen-month dietary oncogenicity study in mice. Historical control data: body weights, convulsions in the CD-1 mouse and spontaneous neoplastic lesions. DACO 4.4.3
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1288701	2006. Request for waiver of Canada Pest Management Regulatory Agency (PMRA) request for a local lymph node assay for zoxamide. DACO 4.6.6
1288702	1997. Dermal sensitization study of RH-117,281 technical in guinea pigs - maximization test. DACO 4.6.6
1288707	1998. RH-117,281 Technical: Delayed Hypersensitivity Study in Guinea Pigs, DACO: 4.6.6
1288708	1998. RH-117,281 Technical: Delayed Contact Hypersensitivity (Dilution) Study in Guinea Pigs. DACO 4.6.6
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1424761	1998. 14C-RH 117, 281, 80WP and 14C-RH-117, 281 2F formulations: dermal absorption study in male rats. DACO 4.8, 5.8
1424762	1998. Mechanism of action of the oomycete fungicides RH-54032 and RH-117281 on Phytophthora capsici, tobacco, mouse lymphoma cells and isolated bovine tubulin. DACO 10.2.1,4.8
1424763	1998. RH-141,452: Acute oral toxicity study in male and female mice. DACO 4.2.1, 4.8
1424764	1998. RH-141,452: Salmonella typhimurium gene mutation assay. DACO 4.5.4, 4.8
2785842	2016. Comparative QSAR analysis of Zoxamide and three impurities in OECD QSAR Toolbox version 3.4.0.17. DACO 2.13.3,2.13.4 CBI
2785843	2015. Analytical Profile of Five Production Batches of Zoxamide, DACO: 2.13.3,2.13.4 CBI
2785844	2014. Comparative QSAR analysis of Zoxamide against six impurities in OECD QSAR Toolbox version 3.2.0.103. DACO 2.13.3, 2.13.4 CBI
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PMRA Document Number	Title
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2929340	2002. Zoxamide: mammalian erythrocyte micronucleus test with kinetochore analyses. DACO 4.5.6
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3056421	2018. Human Health Aggregate Risk Assessment for the Proposed New Uses on Pepper/Eggplant Subgroup 8-10B
3056419	2019. Draft Human Health Risk Assessment in Support of Registration Review
3056417	2004. Review report for the active substance zoxamide.
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C. Information Considered in the Updated Dietary Assessment

Studies/Information Submitted by the Registrant

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2281462	1999. RH-117,281: Nature of Residues in Fruiting Tomato Plants. DACO 6.3
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2218750	1999. Preliminary Residue Analytical Method for Parent RH-7281 in Cucurbits. DACO 7.2.1
1191376	2000. Tolerance Enforcement Method for Parent RH-7281 and Its Two Acid Metabolites, RH-1452 and RH-1455, in Potato Peel Waste. DACO 7.2.1
1194284	1998. Preliminary Residue Analytical Method for RH-7281 and Its Two Acid Metabolites, RH-1452 and RH-1455, in Potato Chips and Flakes. DACO 7.2.1

PMRA Document Number	Reference
1194285	1996. Preliminary Residue Analytical Method for Parent RH-7281 in Grapes. DACO 7.2.1
1194287	1998. Preliminary Residue Analytical Method for Parent RH-7281in Grape Juice. DACO 7.2.1
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2218754	1999. Storage Stability of RH.117.281 Residues in Cucurbits Samples under Conditions of Frozen Storage. DACO 7.3
2281465	2001. Storage Stability of RH-117,281 Residues in Cucurbit Samples under Conditions of Frozen Storage. DACO 7.3
2281463	1999. Preliminary Residue Analytical Method for Parent RH-117, 281 in Tomato Juice. DACO 7.2.1
2218747	1999. Preliminary Residue Analytical Method for Parent RH-117, 281 in Tomato juice. DACO 7.2.1
2218748	1999. Preliminary Residue Analytical Method for Parent RH-117,281 in Tomato. DACO 7.2.1
2218753	2000.Validation of the residue Analytical Method for Parent RH-117281 in/on Tomato. DACO 7.2.1
2218751	1999. Preliminary Residue Analytical Method for Parent-7281 in Tomato Puree and Paste. DACO 7.2.1
2218750	1999. Preliminary Residue Analytical Method for Parent RH-7281 in Cucurbits. DACO 7.2.1
2218754	1999. Storage Stability of RH-117.281 Residues in Cucurbits Samples under Conditions of Frozen Storage. DACO 7.3
2281466	2001. Storage Stability of RH-117,281 Residues in Tomato RAC under Conditions of Frozen Storage: Supplement to TR34-99-171 (MRID No. 45012115) . DACO 7.3
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2281468	1999. Storage Stability Study: RH-117281 in Tomato Paste under conditions of Frozen Storage. DACO 7.3
2281470	2002. Storage stability in Tomato Juice. DACO 7.3
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1194295	1998. Stability of RH-141,455 and RH-141,452 Residues in Potatoes, Potato Flakes Under Conditions of Frozen Storage. DACO 7.3
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1480863	1999. RH-117281 Fungicide Field Residue Trials in the Cucurbit Vegetable. DACO 7.4.1
2218757	1999. RH-117281 Fungicide Field Residue Trials in Tomatoes and Tomato Processed Fractions. DACO 7.3, 7.4.1
1193834	1998. Nature of the Residue in Confined Rotational Crop. DACO 7.4.3
1193826	1998. Magnitude of residue of RH-7281 and Mancozeb in potatoes following treatment with RH-7281 80W and an RH-7281/Mancozeb pre-mix formulation. DACO 7.4.1
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1194289	1998. Tolerance Enforcement Method for RH-7281 and Its Two Acid Metabolites, RH-1452 and RH-1455, in Potato and Potato Processed Fractions. DACO 7.2.2

PMRA Document Number	Reference
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3056420	2016. Human health aggregate risk assessment for the proposed new uses on ginseng, tomato subgroup 8-10A; small fruit, vine climbing, except fuzzy kiwifruit, subgroup 13-07F; and tuberous and corm vegetable subgroup 1C. DACO 12.5.7
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D. Information Considered in the Updated Occupational and Non-Occupational Assessment

Studies/Information Submitted by Task Forces

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Additional Information Considered

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PMRA Document Number	Reference
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E. Information Considered in the Updated Environmental Assessment

Studies/Information Submitted by the Registrant

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2836501	1998. RH-117281 (240 SC): laboratory acute toxicity test with the parasitic wasp, *Aphidius rhopalosiphi* (Hyenopters: Braconidea). DACO 9.2.6
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712926	1997. Anaerobic Soil Metabolism of [^{14}C]RH-117-281. DACO 8.2.3.4.4
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1193801	1998. Hydrolysis of [^{14}C]RH-117281 in Water at pH 4, 7, and 9. DACO 8.2.3.2
1193803	1997. Soil Photolysis of [^{14}C]RH-117281. DACO 8.2.3.3.1
1194217	1998. Acute toxicity of RH-127450 to *Daphnia magna* in a range-finding test under static conditions. DACO 9.3.2
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1194234	1998. Acute toxicity of RH-127450 to the green alga (*Selenastrum capricornutum).* DACO 9.8.2
1194258	1998. Acute flow-through toxicity of Dithane/RH-117281 75 DG Blend to Rainbow trout (*Oncorhynchus mykiss*). DACO 9.5.2.1
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1193821	1997. RH-117281 technical: 8 day acute dietary LC_{50} study in bobwhite quail (*Colinus virginianus*). DACO 9.6.2.4

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Additional Information Considered

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