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Proposed Registration Decision

PRD2012-23

Mandipropamid

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Overview

Proposed Registration Decision for Mandipropamid

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Mandipropamid Technical Fungicide and Revus Fungicide, containing the technical grade active ingredient mandipropamid, for control or suppression of various foliar diseases in Brassica vegetables, bulb vegetables, cucurbits, peppers, tomatoes, leafy vegetables and grapes.

Mandipropamid Technical Fungicide (Registration Number 29073) and Revus Fungicide (Registration Number 29074) are conditionally registered in Canada. The detailed review for Mandipropamid Technical Fungicide and Revus Fungicide can be found in Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide*. The current applications were submitted to convert Mandipropamid Technical Fungicide and Revus Fungicide from conditional registration to full registration.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Mandipropamid Technical Fungicide and Revus Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable¹ if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value² when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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

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

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

Before making a final registration decision on mandipropamid, the PMRA will consider all comments received from the public in response to this consultation document.³ The PMRA will then publish a Registration Decision⁴ on mandipropamid, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluations in this consultation document and within Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide*.

What Is Mandipropamid?

Mandipropamid is a Group 40 fungicide active ingredient and is classified as a carboxylic acid amide. It has a proposed mode of action that inhibits phospholipid biosynthesis, and interferes with cell wall division. It is rated as having a low to medium risk for resistance development in pathogen populations. It is the active ingredient in the end-use product Revus Fungicide for control or suppression of various foliar diseases in Brassica vegetables, bulb vegetables, cucurbits, peppers, tomatoes, leafy vegetables and grapes.

Health Considerations

Can Approved Uses of Mandipropamid Affect Human Health?

Mandipropamid is unlikely to affect your health when used according to the label directions.

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

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

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

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

Mandipropamid Technical Fungicide and the end-use product, Revus Fungicide, are not acutely toxic.

Mandipropamid did not cause cancer in animals and was not genotoxic. There was also no indication that mandipropamid caused damage to the nervous system and there were no effects on reproduction or fetal development. The first signs of toxicity in animals given daily doses of mandipropamid over longer periods of time were decreases in bodyweight gain and liver effects. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and children 1-2 years old, the subpopulation that would ingest the most mandipropamid relative to body weight, are expected to be exposed to less than 6% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from mandipropamid is not of concern for all population subgroups.

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

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

Residue trials conducted throughout the United States using mandipropamid on Brassica vegetables, cucurbits, dry bulb and green onion, fruiting vegetables, grapes, leafy vegetables and potato were acceptable. Residue trials conducted in Europe using mandipropamid on greenhouse vegetables (cucumber, lettuce and tomato) were acceptable. The MRLs for this active ingredient can be found in Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide*.

Occupational Risks From Handling Revus Fungicide

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

Farmers and custom applicators who mix, load or apply Revus Fungicide, as well as field workers re-entering freshly treated fields, nurseries and greenhouses, can come in direct contact with mandipropamid residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Revus Fungicide must wear a long sleeved shirt, long pants, and shoes plus socks. Additionally, workers must wear chemical-resistant gloves during mixing/loading. The label also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications, and the exposure duration for handlers and workers, risk to these workers is not of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Mandipropamid Is Introduced Into the Environment?

When used according to the label directions, which include precautionary statements, mandipropamid does not pose a risk to the environment.

Mandipropamid is slightly to moderately persistent in soil with the main route of dissipation being biotransformation. Mandipropamid is not expected to volatilize nor leach significantly. No major transformation products of mandipropamid were identified in the soil laboratory studies.

Mandipropamid can enter the aquatic environment through spray drift and runoff from the treatment area. Based on the environmental fate characteristics, limited runoff of mandipropamid and its transformation products is expected. Mandipropamid dissipates rapidly from the water layer mainly via partitioning to the sediments, but phototransformation will also contribute to this dissipation in the photic zone. Biotransformation is the main route of dissipation for mandipropamid in sediments. Mandipropamid is stable to hydrolysis and is not expected to volatilize; therefore, these two processes will not affect the dissipation of mandipropamid from the aquatic environment. In the total aquatic system, mandipropamid is classified as non-persistent to slightly persistent depending on the system and conditions present.

Major transformation products of mandipropamid were identified in the aquatic fate studies. These transformation products will only form in significant levels in the aquatic environment if large quantities of mandipropamid enter the aquatic environment as they are not expected to be present in runoff. Further discussion regarding these transformation products occurs in Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide*.

Risk to non-target species is considered negligible based on the uses of mandipropamid.

Value Considerations

What Is the Value of Revus Fungicide?

Revus Fungicide controls or suppresses downy mildew, late blight and phytophthora blight on various field and greenhouse-grown crops.

Revus Fungicide is a reduced-risk product for use on leafy vegetables, grapes, tomatoes, cucurbits, bulb vegetables, and Brassica head and stem crops. It is currently the only fungicide registered in Canada for suppression of phytophthora blight on field peppers. Revus Fungicide can be tank mixed with Bravo 500 Agricultural Fungicide (registration number 15723) for resistance management, or to increase the disease spectrum on crops that are registered on both product labels. In addition, Revus Fungicide can be applied by ground and aerial application equipment.

Sensitivity monitoring studies have suggested that populations of *Phytophthora infestans*, the causative pathogen of potato late blight, have not developed resistance to mandipropamid. However, certain isolates of *Plasmopara viticola*, the causative pathogen for downy mildew of grape, have been found to be simultaneously resistant to all Group 40 active ingredients. Therefore, resistance management practices are required when using Revus Fungicide on grapes for control of downy mildew and are highly recommended when using Revus Fungicide on other labelled crops.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Revus Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Given there is a concern with users coming into direct contact with Revus Fungicide on their skin or through inhalation of spray mists, anyone mixing, loading or applying Revus Fungicide must wear a long-sleeved shirt, long pants, and shoes plus socks. Additionally, workers must wear chemical-resistant gloves during mixing/loading. In addition, standard label statements to protect against drift during application have been added to the label.

Next Steps

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

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on mandipropamid (based on the Science Evaluation sections of this consultation document and Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide*). In addition, the test data referenced in this consultation document and Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Mandipropamid

1.0 The Active Ingredient, Its Properties and Uses

Please refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for a detailed assessment of the active ingredient, its properties and uses.

As conditions of conversion to full registration, additional analytical data to address the requirements for five representative commercial-scale batches of the technical product and for confirmation of identity were submitted and assessed to be acceptable.

2.0 Methods of Analysis

Please refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for a detailed assessment of the methods of analysis.

The final study report demonstrating the stability of the analytical standards was submitted and confirmed the stability of the analytical standards.

An acceptable method was developed for the determination of mandipropamid in plant matrices based on the multiresidue method DFG S-19, as part of the confirmatory data package to convert the active ingredient mandipropamid from conditional to full registration. The liquid chromatography method with tandem mass spectrometry (LC-MS/MS) provides an alternative chromatographic column and mobile phase, and two MS/MS transitions compared to the enforcement method RAM 415/01 (LC-MS/MS). The method fulfilled the requirements with regards to specificity, accuracy and precision at the limit of quantitation.

Analytical methodologies for detection of the major transformation products of mandipropamid in sediment and water were submitted as a condition of conversion to full registration. The analytical methodologies have been validated and were determined to be acceptable as post-registration monitoring methods (Appendix I, Table 1).

3.0 Impact on Human and Animal Health

Please refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for a detailed assessment of the impact on human health.

3.1 Food Residues Exposure Assessment

3.1.1 Residues in Plant and Animal Foodstuffs

The storage stability data requirements identified in Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* were submitted and deemed to be adequate. The data demonstrate that the storage conditions and intervals in the potato processing study are acceptable. Acceptable confirmatory supervised residue trials were conducted in Canada on greenhouse lettuce using an end-use product containing mandipropamid. The maximum residue limit (MRL) of 20 ppm (Established Maximum Residue Limit EMRL2010-01, *Mandipropamid*) established for mandipropamid in leafy vegetables, except Brassica (Crop Group 4) does not need to be revised as a result of this assessment.

3.1.2 Dietary Risk Assessment

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994-1996 and 1998.

3.1.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic analysis: default and experimental processing factors, median values for certain commodities and United States tolerances for all other commodities. The refined chronic dietary exposure from all supported mandipropamid food uses (alone) for the total population and all representative population subgroups is $\leq 5.0\%$ of the acceptable daily intake (ADI). The PMRA estimates that chronic dietary exposure to mandipropamid from food and water is 3.6% (0.001822 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years at 5.3% (0.002669 mg/kg bw/day) of the ADI. Aggregate exposure from food and water is considered acceptable.

3.1.2.2 Acute Dietary Exposure Results and Characterization

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

3.1.3 Aggregate Exposure and Risk

The aggregate risk for mandipropamid consists of exposure from food and drinking water sources only; there are no residential uses. Aggregate risks were calculated based on chronic endpoints. There was no acute endpoint identified for the general population, including infants and children.

3.1.4 Maximum Residue Limits

Refer to Established Maximum Residue Limit EMRL2010-01, *Mandipropamid* for a list of the MRLs established for mandipropamid. Based on this assessment, no revision to the established MRLs is required.

4.0 Impact on the Environment

Please refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for a detailed assessment of the impact on the environment.

5.0 Value

Please refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for a detailed assessment of value.

Confirmatory efficacy trials to examine efficacy at the higher rate (150 g a.i./ha) for control of downy mildew on green bunching onions, leaks and Welch onions were required as a condition of conversion to full registration. No additional trial was provided to confirm the efficacy of Revus Fungicide on green onion and the high rate on bulb vegetables, nor was the requirement effectively addressed by a rationale. Instead, the applicant has elected to remove the subgroup and high use rate from the product label.

Confirmatory efficacy trials for control of downy mildew on crops within the brassica leafy green subgroup (two trials on Chinese cabbage and one trial on mustard green) were submitted as a condition of conversion to full registration. Revus Fungicide significantly decreased disease compared to the untreated control under high disease pressure in two trials on cabbage. The same efficacy was also confirmed in one trial on mustard green under low disease pressure. The use on the brassica leafy green subgroup is supported.

Confirmatory efficacy trials for suppression of phytophthora blight on crops within the fruiting vegetables group (two trials on bell peppers and one trial on eggplant) were submitted as a condition of conversion to full registration. Revus Fungicide significantly reduced plant mortality and disease severity in one trial on bell pepper, and increased the number of marketable fruit and decreased the number of infected fruit in another trial on bell pepper. A confirmatory trial on eggplant conducted also indicated that Revus effectively suppressed the development of phytophthora blight. The use on the fruiting vegetables is supported.

6.0 Pest Control Product Policy Considerations

Please refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for a detailed assessment of pest control product policy considerations.

7.0 Summary

Please refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for a summary of the impacts on human health and safety, environmental risk, and the value of Revus Fungicide. Data identified as a condition of registration were submitted and were determined to be acceptable.

7.1 Human Health and Safety

The nature of the residue in plants and animals is adequately understood. Refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for information pertaining to the residue definition. The proposed uses of mandipropamid do not constitute a risk of concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits, both domestic and import, to protect human health. Refer to Established Maximum Residue Limit EMRL2010-01, *Mandipropamid* for the list of MRLs established for mandipropamid.

7.2 Value Assessment

The value conditions of registration were addressed by either efficacy trials or scientific rationale. The use of Revus Fungicide on brassica leafy green subgroup and on the fruiting vegetables is supported.

The use of Revus Fungicide on green onion and the high rate of 150 g a.i./ha. on bulb vegetables were not supported by the rationale provided. The applicant has elected to remove the subgroup and high use rates for bulb vegetables from the current label.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Mandipropamid Technical Fungicide and Revus Fungicide, containing the technical grade active ingredient mandipropamid, for control or suppression of various foliar diseases in Brassica vegetables, bulb vegetables, cucurbits, peppers, tomatoes, leafy vegetables and grapes.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

μg	micrograms
ADI	acceptable daily intake
a.i.	active ingredient
bw	body weight
DEEM-FCID™	dietary exposure evaluation model
g	grams
ha	hectare(s)
HAFT	highest average field trial
HPLC	high-performance liquid chromatography
kg	kilogram(s)
L	litre(s)
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LOD	limit of detection
LOQ	limit of quantitation
n	number
max	maximum
mg	milligram(s)
min	minimum
MRL	maximum residue limit
MS	mass spectrometry
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
ppm	parts per million
Std. Dev.	standard deviation
STMdR	supervised trial median residue
STMR	supervised trial mean residue
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Analyte	Method Type	LOQ	Reference
Sediment	SYN 500003	HPLC-MS-MS	1 µg/kg	2095182
	SYN 504851			2095183
	SYN 521195			
	SYN 539678			
Water	SYN 500003	HPLC-MS-MS	0.05 µg/L	2095184
	SYN 504851			2095185

Table 2 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Plant	DFG Method S-19	Mandipropamid	LC-MS/MS (enforcement)	0.01 ppm	1983164, 1983169, 1983170, 1983175

Note: refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for methods previously reviewed.

Table 3 Residue Summary

STORAGE STABILITY- POTATO AND PROCESSED COMMODITIES	Reference 1983171
<p>Samples of homogenized potato tubers, granules/flakes, chips and wet peel each spiked at 0.5 ppm with SYN500003 (metabolite of mandipropamid) were stored at ~-20°C for 0 months(0 days), ~3 months (99-103 days), ~7 months (227-231 days), ~12 months (377-381 days), ~18 months (560-564 days), ~21 months (643-647 days), ~26 months (812-816 days) and ~32 months (983-987 days). Method number GRM 001.01.B was used for the determination of SYN500003 residues in potato commodities. The data indicate that residues of SYN500003 are stable under frozen storage for up to ~32 months (983-987 days) in potatoes and potato processed commodities.</p>	

CROP FIELD TRIALS ON GREENHOUSE LETTUCE						Reference 1983174		
Confirmatory trials were conducted during the 2010 growing season at two greenhouses in British Columbia that were representative of commercial greenhouse lettuce production in Canada.								
Revus 250SC (250 g mandipropamid/L) was applied four times as a broadcast foliar application at 159.1-181.7 g a.i./ha/application for total seasonal rates of 648.5-688.3 g a.i./ha. A non-ionic surfactant (Agral 90) was included in all spray applications at 0.25% (v/v). Samples of mature greenhouse lettuce heads were collected at a preharvest interval (PHI) of 6 days. One sample from the control plot and four samples from each treated plot were collected.								
Residues of mandipropamid were determined using a liquid chromatography method with tandem mass spectrometric detection (LC-MS/MS), referred to as Method No. RAM 415/01. The limit of quantitation (LOQ) and the limit of detection (LOD) were reported as 0.01 ppm and 0.0031 ppm, respectively.								
Commodity	Total application (g a.i./ha)	n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Greenhouse Lettuce Heads	648.5-688.3	8	2.7	4.5	4.4	3.9	3.8	0.73

Note: refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for the studies previously reviewed.

Table 4 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)	
		Food Only	Food and Water
Refined chronic non-cancer dietary risk ADI = 0.05 mg/kg bw/day Estimated chronic drinking water concentration = 5.9 µg/L for total residues of mandipropamid and the transformation products SYN 500003 and SYN 504851	All infants < 1 year	3.4	4.2
	Children 1-2 years	5.0	5.3
	Children 3 to 5 years	4.3	4.7
	Children 6-12 years	3.1	3.3
	Youth 13-19 years	2.5	2.6
	Adults 20-49 years	3.3	3.6
	Adults 50+ years	3.7	3.9
	Females 13-49 years	3.4	3.7
	Total population	3.4	3.6

Note: refer to Evaluation Report ERC2009-01, *Mandipropamid Technical Fungicide* for the metabolism studies previously reviewed.

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

Refer to Established Maximum Residue Limit EMRL2010-01, *Mandipropamid* for the list of MRLs established for mandipropamid.

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A. List of Studies/Information Submitted by Registrant

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- 1964727 2007, Analysis of five representative production batches, DACO: 2.13.3, CBI
- 2069520 2007, Analytical method for determination of an impurity by LC/MS, DACO: 2.13.1, CBI
- 2069521 2007, Validation of analytical method for determination of an impurity by LC/MS, DACO: 2.13.1, CBI
- 2069522 2011, Identity of impurities, DACO: 2.13.2, CBI
- 2069523 2011, Clarification on specifications, DACO: 2.12.1, 3.3.2, CBI

2.0 Human and Animal Health

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3.0 Environment

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4.0 Value

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