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Proposed Re-evaluation Decision

PRVD2017-25

Piperine and Oil of Black Pepper and Their Associated End-use Products

Consultation Document

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Table of Contents

Proposed Re-evaluation Decision	1
Outcome of Science Evaluation	1
Proposed Regulatory Decision for Piperine and Oil of Black Pepper.....	2
International Context	2
Next Steps.....	2
Additional Scientific Information.....	2
Science Evaluation.....	3
1.0 Introduction.....	3
2.0 The Technical Grade Active Ingredient, Its Properties and Uses	3
2.1 Identity of the Technical Grade Active Ingredient.....	3
3.0 Human Health	4
3.1 Toxicological Summary	4
3.2 Residential Exposure and Risk.....	4
3.3 Bystander Exposure and Risk	5
3.4 Dietary Exposure and Risk.....	5
3.5 Aggregate Exposure	5
3.6 Cumulative Exposure	5
4.0 Environment.....	5
5.0 Value	6
6.0 Pest Control Product Policy Considerations	6
6.1 Toxic Substances Management Policy Considerations.....	6
7.0 Incident Report.....	6
8.0 Conclusion	6
Appendix I Registered Piperine and Oil of Black Pepper Products as of August 16, 2017	7
Appendix II Label Amendments for Products Containing Piperine and Oil of Black Pepper..	9
References.....	11

Proposed Re-evaluation Decision

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

Piperine and oil of black pepper are registered for use as animal repellents for application on indoor and outdoor sites. Piperine and oil of black pepper occur naturally in the black pepper plant.

This document presents the proposed regulatory decision for the re-evaluation of piperine and oil of black pepper as animal repellents, including the proposed updates to the label directions to further protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing piperine and oil of black pepper registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public including the pesticide manufacturers and stakeholders may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

Piperine and oil of black pepper are derived from black pepper. Piperine and oil of black pepper provide an additional non-conventional choice for users to repel animals.

With respect to human health, these actives are of low acute toxicity via oral, dermal and inhalation routes. They are non- to minimally irritating to the eyes, mildly irritating to the skin, and are potential skin sensitizers.

Residential exposures are not of concern for homeowners and bystanders from use of piperine and oil of pepper when the current label directions are observed. Piperine and oil of black pepper are not registered for use on food. Based on the use pattern, dietary exposure to piperine and oil of black pepper through the consumption of food and drinking water is not of concern.

When products containing piperine and oil of black pepper are used in accordance with the current label directions, risks of concern to non-target terrestrial and aquatic organisms are not expected.

Proposed Regulatory Decision for Piperine and Oil of Black Pepper

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, Health Canada is proposing that products containing piperine and oil of black pepper (used to repel animals) are acceptable for continued registration for use and sale in Canada, provided that the updates to label directions are in place.

Registered pesticide product labels include specific instructions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of piperine and oil of black pepper, no additional risk mitigation measures are proposed by the PMRA. To meet current labelling standards, the following label updates are proposed (see details in Appendix II):

- Storage label statements; and
- Disposal statement

International Context

Piperine and oil of black pepper are currently acceptable for use in the United States. Pepper dust is acceptable for use in the European Union. As of 9 August 2017, no decision by an Organisation for Economic Co-operation and Development member country to prohibit all uses of piperine and oil of black pepper for health or environmental reasons has been identified.

Next Steps

The public including the registrants and stakeholders are encouraged to submit comments during the 90-day public consultation period¹ upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document.² 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 PMRA's responses.

Additional Scientific Information

No additional data are required.

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

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

Science Evaluation

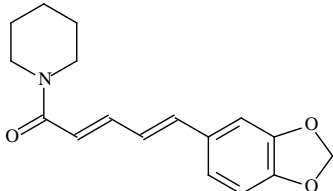
1.0 Introduction

Piperine and oil of black pepper are registered as animal repellents to repel cats, dogs, groundhogs, raccoons, skunks, and squirrels by causing irritation when animals touch or taste the products.

Currently there is one technical grade active ingredient for piperine, one technical grade active ingredient for oil of black pepper, and seven domestic class end-use products registered in Canada (Appendix I). All domestic end-use products contain piperine and oil of black pepper and are co-formulated with the active ingredients capsaicin and related capsaicinoids as granular or liquid products. They are applied using spray bottles or power sprayers for liquid formulations and by hand or by spreaders for granular formulations.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		Piperine	Oil of black pepper
Function		Animal repellent	Animal repellent
Chemical Family		Alkaloid	Essential oils
Chemical name			Not applicable
1	International Union of Pure and Applied Chemistry (IUPAC)	1-[(2 <i>E</i> ,4 <i>E</i>)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoyl]piperidine	
2	Chemical Abstracts Service (CAS)	2,4-Pentadien-1-one, 5-(1,3-benzodioxol-5-yl)-1-(1-piperidinyl)-, (2 <i>E</i> ,4 <i>E</i>)-	
CAS Registry Number		94-62-2	8006-82-4
Molecular Formula		C ₁₇ H ₁₉ NO ₃	Not applicable
Structural Formula			Not applicable

Molecular Weight	285.35	Not applicable
Purity of the Technical Grade Active Ingredient	40.2%	100%
Registration Number	29549	29551

3.0 Human Health

People could be exposed to piperine and oil of black pepper through applying end-use products and by entering treated areas. 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 levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Continued registration is only supported for uses that are determined to have no health risks of concern.

3.1 Toxicological Summary

Both active ingredients have a long history of safe use as food flavouring agents. The active ingredients in the end-use products are also derived from food. All currently registered end-use products are a mixture of the active ingredients piperine, oil of black pepper, capsaicin and related capsaicinoids. The products are of low acute toxicity via the oral, dermal and inhalation routes, non- to minimally irritating to the eyes, mildly irritating to the skin and potential skin sensitizers.

A review of a published scientific toxicological review on piperine and oil of black pepper found that piperine appears to be non-genotoxic in the Ames test at multiple concentrations with and without metabolic activation in multiple strains of *Salmonella typhimurium*. Piperine was also negative in an in vivo bone marrow micronucleus test and failed to induce mutations in male mouse germ cells. Piperine and black pepper have been shown to have antioxidant effects through the inhibition or quenching of free radicals, reduction of lipid peroxidation and beneficial effects on cellular thiols, and antioxidant molecules and enzymes. Piperine has also been demonstrated to stimulate pancreatic enzymes, enhance digestive capacity and reduce gastrointestinal transit time.

No short-term or intermediate-term toxicological effects are anticipated from the current use of piperine and oil of black pepper; therefore, toxicological end-points for quantitative risk assessment purposes have not been established by the PMRA. No additional toxicology data are required for re-evaluation.

3.2 Residential Exposure and Risk

There is potential for exposure of piperine and oil of black pepper to people handling the end use products through dermal and inhalation routes. However, because of the low toxicity of the products, and existing risk reduction measures currently included on the product labels (for

example, recommendation to use water proof gloves during application; other precautionary measures such as to avoid ingestion and contact with eyes or skin), the potential risk to residential users is not expected to be of concern under the current conditions of use.

No additional mitigation measures are proposed.

3.3 Bystander Exposure and Risk

Based on the use pattern, there is a potential for bystander dermal and inhalation exposure from the use of these products. As the toxicity of the products is low, and the product labels include risk reduction measures (for example, request to keep children and pets away from sites of application until sprayed solution has dried), the potential risk to bystanders is not expected to be of concern under the current conditions of use.

No additional mitigation measures are proposed.

3.4 Dietary Exposure and Risk

Piperine and oil of black pepper have a long history of safe use as food flavouring agents. The concentrations of these actives in the end use products are low, the products have low toxicity, and they are registered for non-food uses. Based on this, potential dietary risk (food and water) is not expected to be of concern under the current conditions of use.

3.5 Aggregate Exposure

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible routes (oral, dermal and inhalation). For piperine and oil of black pepper, aggregate exposure is not expected to be of concern under the current conditions of use.

3.6 Cumulative Exposure

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. The PMRA did not identify information indicating that piperine and oil of black pepper share a common mechanism of toxicity with other pest control products. Furthermore, the potential risks from cumulative exposure of piperine and oil of black pepper with other such pest control products are not of concern, given the inherent low toxicity profile of the active ingredients.

4.0 Environment

Piperine and oil of black pepper occur naturally in the black pepper plant (*Piper nigrum L.*). Based on the current use pattern, potential environmental exposure is minimal. The end-use products were found to be practically non-toxic to birds and mammals on an acute basis. Based on this, potential risk to the environment is not expected to be of concern under the current

conditions of use. No additional mitigation measures are proposed. Storage and disposal statements are proposed as per current labelling standards (Appendix II).

5.0 Value

Piperine and oil of black pepper are co-formulated with capsaicin and related capsaicinoids, and are used to repel cats, dogs, groundhogs, raccoons, skunks, and squirrels. Only a limited number of active ingredients are registered for use by homeowners to repel raccoons, skunks, and squirrels, and no alternative active ingredients are registered to repel groundhogs. These nonconventional active ingredients provide another option for homeowners to use, along with other control measures such as prevention and non-chemical control measures.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

Piperine and oil of black pepper were assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, and they do not meet the Track 1 criteria.

7.0 Incident Report

As of 16 August 2017, one minor environmental incident was reported to the PMRA (a cedar tree dead when a product containing oil of black pepper and piperine was applied; a herbicide was applied at the same time). This incident involved multiple active ingredients, which confounds any active ingredient-specific conclusions regarding adverse effects. No additional risk reduction measures are proposed.

There were no cases reported to the United States Environmental Protection Agency Ecological Incident Information System, as of 5 October 2015.

8.0 Conclusion

Piperine and oil of black pepper are derived from black pepper. Piperine and oil of black pepper provide an additional non-conventional choice for animal repellent users.

Piperine and oil of black pepper are of low acute toxicity, non- to minimally irritating to the eyes, mildly irritating to the skin, and potential skin sensitizers. When used according to the current label directions, the potential residential and dietary (food and water) risks are not expected to be of concern.

When products containing piperine and oil of black pepper are used in accordance with the labels, risks of concern to non-target terrestrial and aquatic organisms are not expected.

Updates to label directions are being proposed to meet the current labelling standards.

Appendix I Registered Piperine and Oil of Black Pepper Products as of 16 August 2017

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (%)
29549	Technical	Passion-Krafts Int'l	Passion Krafts Oleoresin Of Black Pepper Technical	Liquid	40.2 (CAT*)
29551	Technical	Passion-Krafts Int'l	Passion Krafts Oil Of Black Pepper Technical	Liquid	100 (CAU*)
25789	Domestic	Passion-Krafts Int'l	Scentagone Animal Repellent	Granular	0.480 (CAU) 0.018 (CAT) 0.0015 (RCS*) 0.0017 (CAS*)
25829	Domestic	Woodstream Canada Corporation	Chemfree Critter Ridder	Granular	0.480 (CAU) 0.018 (CAT) 0.0015 (RCS) 0.0017 (CAS)
29630	Domestic	Passion-Krafts Int'l	Scent-A-Gone Animal Repellent Liquid Concentrate	Liquid	3.84 (CAU) 1.48 (CAT) 0.121 (RCS) 0.136 (CAS)
29631	Domestic	Passion-Krafts Int'l	Scent-A-Gone Animal Repellent Ready-To-Use Spray	Liquid	0.480 (CAU) 0.018 (CAT) 0.0015 (RCS) 0.0017 (CAS)
29741	Domestic	Woodstream Canada Corporation	Chemfree Critter Ridder Concentrate	Liquid	3.84 (CAU) 1.48 (CAT) 0.121 (RCS) 0.136 (CAS)
29743	Domestic	Woodstream Canada Corporation	Chemfree Critter Ridder Ready To Use	Liquid	0.480 (CAU) 0.018 (CAT) 0.0015 (RCS) 0.0017 (CAS)
29858	Domestic	Woodstream Canada Corporation	Chemfree Critter Ridder	Granular	0.480 (CAU) 0.018 (CAT) 0.0015 (RCS) 0.0017 (CAS)

* CAT: piperine; CAU: oil of black pepper; CAS: capsaicin; RCS; related capsaicinoids

Appendix II Label Amendments for Products Containing Piperine and Oil of Black Pepper

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements given below.

1. Add the following statement to all domestic end use products under the STORAGE heading:

“To prevent contamination store this product away from food or feed.”

2. Add the following statement to all domestic end use products under the DISPOSAL heading:

*“DO NOT reuse the empty containers. Dispose in household garbage.
Unused or partially used products should be disposed at provincially or municipally
designated hazardous waste disposal sites.”*

References

A. Information Considered in the Chemistry Assessment

List of Studies/Information Submitted by the Registrant

PMRA No.	Reference
1602744	2008, 2.11 Manufacturing Oil of black pepper, DACO: 2.11, 2.11.1,2.11.2, 2.11.3, 2.11.4 CBI
1602750	2008, DACO 2.14 Oil of black pepper. Physical/Chemical Properties, DACO: 2.14, 2.14.1, 2.14.10, 2.14.11, 2.14.12,2.14.13 ,2.14.2, 2.14.3,2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8,2 .14.9 CBI
1602751	2008, DACO 2.14.14 Oil of black pepper. Storage Stability, DACO: 2.14.14 CBI
1602673	2008, 2.11 Manufacturing Oleoresin of black pepper, DACO: 2.11, 2.11.1, 2.11.2, 2.11.3, 2.11.4 CBI
1602676	2006, DACO 2.13.2 - 2.13.4 Oleoresin of black pepper, DACO: 2.13, 2.13.2, 2.13.3, 2.13.4 CBI
1602677	2008, DACO 2.14 Oleoresin of black pepper, DACO: 2.14, 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9 CBI
1602678	2008, DACO 2.14.14 Oleoresin of black pepper, DACO: 2.14.14 CBI
1813334	2009, 2.11.3, DACO 2.11.3 CBI

B. Information Considered in the Human Health Assessment

List of Studies/Information Submitted by the Registrant

PMRA No.	Reference
1531255	2007, 4.1 Summary, N/A, MRID: N/A, DACO: 4.1
1531256	2004, Acute Oral Toxicity Up and Down Procedure in Rats, 16095, MRID: N/A, DACO: 4.6.1
1531257	2004, Acute Dermal Toxicity Study in Rats - Limited Test, 16096, MRID: N/A, DACO: 4.6.2
1531258	2004, Acute Inhalation Toxicity Study in Rats - Limit Test, 16097, MRID: N/A, DACO: 4.6.3
1531259	2004, Primary Eye Irritation Study in Rabbits, 16098, MRID: N/A, DACO: 4.6.4
1531260	2004, Primary Skin Irritation Study in Rabbits, 16099, MRID: N/A, DACO: 4.6.5
1531261	2004, Dermal Sensitization Study in Guinea Pigs (Buehler Method), 16100, MRID: N/A, DACO: 4.6.6
1603376	2008, 10.2.1 Mode of Action, DACO: 10.2.1
1603387	New York State Bureau of Pesticides Management, 2004, NYS DEC Letter -

1773806	Registration of Havahart Critter Ridder Registration, DACO: 12.5 2009, 2008-0020 Critter Ridder Concentrate English Draft label updated, DACO: 1.2.1
1531293	2007, 4.1 Summary, DACO: 4.1
1773824	2009, 2008-0020 Critter Ridder Ready to Use Spray English Draft label updated, DACO: 1.2.1
1609469	2008, 2008-0020 SPSF 23May2008, DACO: 0.1.6003
1676042	DACO: Clarification_Email
1531285	2007, 071210 Cover letter Critter Ridder Animal Repellent Ready to Use Spray Cat B, DACO: 0.8
1602273	2008, 10.2.1 Mode of Action, DACO: 10.2.1
1635667	2008, 2008-0021 SPS 23May2008, DACO: 0.1.6003

Additional Published Information

PMRA No.	Reference
1603383	US EPA, 1992, EPA RED Capsaicin, DACO: 12.5
1603384	US EPA, 2002, EPA BioPesticides Registration Action Document Piperine, DACO: 12.5
1603386	US EPA, 2002, EPA BioPesticides Registration Action Document Oil of Black Pepper, DACO: 12.5
1765047	2007, Crit Rev Food Sci Nutr 47: 735-748. Black Pepper and its Pungent Principle-Piperine: A Review of Diverse Physiological Effects, DACO: 4.8
1765053	2007, Int J Toxicol 26 (Suppl. 1): 3-106, Final Report on the Safety Assessment of Capsicum Annuum Extract, Capsicum Annuum Fruit Extract, Capsicum Annuum Resin, Capsicum Annuum Fruit Powder, Capsicum Frutescens Fruit, Capsicum Frutescens Fruit Extract, Capsicum, DACO: 4.8
1779027	US Food and Drug Administration, HHS - Common Name, Scientific Name, Limitations 21 CFR 172.515 Ch. I (4-1-06 Edition), DACO: 4.8
1779032	US Food and Drug Administration, HHS - Common Name and Botanical name of plant source. 21 CFR 182.10 Ch. I (4-1-06 Edition), DACO: 4.8
1779041	US Food and Drug Administration, HHS - Common Name and Botanical name of plant source. 21 CFR 182.20 Ch. I (4-1-06 Edition), DACO: 4.8
1779043	US Environmental Protection Agency - Inert ingredients, Limits, Uses 40 CFR 180.910 Ch. I (7-1-08 Edition), DACO: 4.8
1779044	US Environmental Protection Agency - Inert ingredients, Limits, Uses 40 CFR 180.930 Ch. I (7-1-08 Edition), DACO: 4.8
1779046	US Environmental Protection Agency - Polymer, CAS No. 40 CFR 180.960 Ch. I (7-1-08 Edition), DACO: 4.8
1779047	US Environmental Protection Agency 2009, Inert Ingredients Eligible for FIFRA 25(b) Pesticide Products - Last Updated March 3, 2009, DACO: 4.8
1779055	US Environmental Protection Agency Inert Ingredients Permitted for Use in Nonfood Use Pesticide Products - Last Updated January 27, 2009, DACO: 4.8

1779058 US Environmental Protection Agency 2000, Pesticide Registration (PR) Notice 2000-6 Minimum Risk Pesticides Exempted under FIFRA Section 25(b) - Clarification of Issues - NOTICE TO MANUFACTURERS, FORMULATORS, PRODUCERS AND REGISTRANTS OF PESTICIDE PRODUCTS, DACO: 4.8

C. Information Considered in Environmental Assessment

Additional Published Information

PMRA No.	Reference
1603383	US EPA, 1992, EPA RED Capsaicin, DACO: 12.5
1603384	US EPA, 2002, EPA BioPesticides Registration Action Document Piperine, DACO: 12.5
1603386	US EPA, 2002, EPA BioPesticides Registration Action Document Oil of Black Pepper, DACO: 12.5