Re-evaluation Decision RVD2017-02

Octhilinone

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Re-evaluation Decision

Octhilinone is an antimicrobial active ingredient registered in Canada for use as a material preservative in coatings (paints and stains), building materials (for example caulks, sealants, and stucco), wallpaper pastes and adhesives, aqueous emulsions and adhesives, fabric, leather, polymer and vinyl compounds. It is also registered for use as a mildewcide for wood freshly-treated with copper azole wood preservative. There are 20 products containing octhilinone currently registered in Canada under the authority of the *Pest Control Products Act*, including three technical grade active ingredients, 16 commercial class end-use products, and one manufacturing concentrate.

After a re-evaluation of octhilinone as a material preservative, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting continued registration of products containing octhilinone for sale and use in Canada. An evaluation of available scientific information found that most uses of octhilinone products do not present unacceptable risks to human health or the environment when used according to the revised conditions of registration, which include amended label directions. The use of octhilinone as a material preservative in coatings (paints and stains) is cancelled to address potential risks of concern to human health. Label amendments, as summarized below and listed in Appendix II, are required for all end-use products that are material preservatives. No additional data are requested at this time.

Human Health

- Hazard label statements on the technical grade product label
- Additional personal protective equipment to protect workers in industrial/manufacturing settings
- Cancellation of octhilinone use as a material preservative in coatings (paints and stains)
- Reduction of the maximum application rate in building materials, aqueous emulsions and adhesives, and polymer compounds
- Prohibition of use in adhesives, polymer and vinyl compounds for food contact materials
- Prohibition of use in polymer and vinyl compounds for children's toys

Environment

- Standard environmental hazard and advisory label statements.

The use of octhilinone as a mildewcide for wood freshly-treated with copper azole wood preservative was assessed by PMRA separately (Registration Decision RD2016-31, *Octhilinone*).

PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2012-02, *Re-evaluation Program Cyclical Re-evaluation*, presents the details of the cyclical re-evaluation approach, which is in line with the requirements of the *Pest Control Products Act*.

This re-evaluation decision[1] was proposed in the consultation document, Proposed Re-evaluation Decision PRVD2015-11, *Octhilinone*. Two comments were received during the consultation process. Appendix I summarizes the comments and PMRA's responses to them. This decision is consistent with the proposed re-evaluation decision stated in PRVD2015-11. A reference list for all data used as the basis for the re-evaluation decision is also included in PRVD2015-11.

To comply with this decision, the required mitigation measures must be implemented on all products labels sold by registrants no later than 24 months after the publication date of this decision document.

Other Information

Any person may file a notice of objection[2] regarding this decision on octhilinone within 60 days from the date of publication of this Re-evaluation Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision) or contact PMRA's Pest Management Information Service.

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

[2] As per subsection 35(1) of the *Pest Control Products Act*

Appendix I Comments and Responses

In response to the consultation document PRVD2015-11, *Octhilinone,* the following comments were received:

1. Comment relating to the toxicological endpoint for non-dietary oral ingestion

The gavage developmental study in rats is not the most appropriate study for selection of an endpoint for assessing short- to intermediate-term risks from non-dietary oral ingestion of octhilinone residues.

There are several animal oral studies available, which involved an assessment of a greater number of toxicological endpoints (including full clinical, haematological and pathological investigations) than standard developmental toxicity studies. Furthermore, the extended duration of dosing gives inherent conservatism when deriving toxicity benchmarks. The commenter points that use of the 90-day oral toxicity study in rats would result in a No Observed Adverse Effect Level (NOAEL) of 50 mg/kg bw/day.

PMRA Response

The toxicological endpoint selected for the assessment of risks to children from non-dietary (incidental) oral ingestion (short- to intermediate-term) of octhilinone residues was derived from the gavage developmental toxicity study in rats. In that study, the NOAEL for maternal toxicity was 5 mg/kg bw/day, based on salivation, reduced body weights and body weight gains, and the death of one maternal animal that were observed at the LOAEL of 30 mg/kg bw/day. Although these effects were observed in maternal animals, they were considered relevant endpoints in an assessment of risks to children and the available data did not suggest that pregnant animals were more sensitive than non-pregnant animals to the toxic effects from exposure to octhilinone.

It is acknowledged that subchronic toxicity studies by design assess a broader array of toxicological endpoints than are examined in maternal animals in developmental toxicity studies. However, the adverse effects observed in maternal animals in the gavage developmental toxicity study in rats conducted with octhilinone cannot be dismissed and must be considered in the determination of toxicological endpoints for use in human health risk assessment. When comparing the effects in rats when octhilinone was administered via the diet versus gavage, octhilinone demonstrated a higher level of toxicity via gavage. In addition, administration via gavage more closely simulates scenarios involving non-dietary oral ingestion by children, such as hand-to-mouth exposure to octhilinone in treated carpets and vinyl floors, as well as mouthing of octhilinone-treated clothing.

Furthermore, in several dietary studies conducted with octhilinone, including the 90-day dietary toxicity study in rats, there were issues with stability of the test material in the diet and with palatability of the test diet, the latter resulting in a high degree of food scatter. Although the doses in the dietary studies were corrected for analytical recovery of test material and food scatter, the administration of octhilinone via gavage reduces the influence of these confounding factors on the systemic exposure of octhilinone.

For the reasons outlined above, the NOAEL from the gavage developmental toxicity study in rats is considered to be the most appropriate point of departure for assessing risks to children from non-dietary oral ingestion of octhilinone.

2. Comment relating to uncertainty factors used in the human health risk assessment

The type of toxicity observed following administration of octhilinone is predominantly local and does not involve metabolic processes. Systemic effects are observed only secondary to local effects. The toxicokinetic components of both the 10-fold uncertainty factor to account for the interspecies extrapolation and the 10-fold uncertainty factor to account for intraspecies variability should be removed as they are deemed not relevant when the primary effect is irritation/corrosion or sensitization.

The application of an additional uncertainty factor to extrapolate from a short-term to a long-term exposure scenario is not warranted when the primary toxic effects are irritation or corrosion, given that such effects are mediated by direct physical destruction of tissues local to the dosing site. The effects are considered predominantly concentration-based findings for which duration of exposure is not relevant.

A target MOE of 10 would be appropriate for all exposure scenarios. The target MOE of 10 would encompass the toxicodynamic components of the 10-fold uncertainty factor to account for the interspecies extrapolation and the 10-fold uncertainty factor to account for intraspecies variability.

PMRA Response

The toxicological endpoints selected for the human health risk assessment of octhilinone were based on effects observed in a 90-day dermal toxicity study in rats, a 90-day inhalation toxicity study in rats, a gavage developmental toxicity study in rats, and a local lymph node assay in mice. The effects noted in the 90-day dermal and inhalation toxicity studies as well as the rat gavage developmental toxicity study included systemic effects such as reductions in body weight and body weight gain, and changes in adrenal gland and heart weight. In the 90-day dermal and inhalation toxicity studies, these effects on body weight and organ weight occurred in the presence of dermal and respiratory tract irritation. In the rat developmental toxicity study, salivation, possibly a response to the irritating nature of the test substance, was noted at the same dose level that resulted in reduced body weight. Although the irritating properties of octhilinone likely contributed to these findings, the possibility that systemic toxicity is also occurring cannot be ruled out.

In the PMRA octhilinone human health risk assessment, the target MOE for the long-term dermal and inhalation exposure scenarios was 300, which included a 3-fold uncertainty factor to extrapolate from a short-term to a long-term exposure scenario. The toxicological endpoints selected for the long-term dermal and inhalation exposure scenarios were derived from rat studies of 90-day duration. As indicated above, the toxicological endpoints selected for human health risk assessment were based in part on systemic effects. There was also evidence in the toxicological database for increased toxicity with increased duration of dosing. Therefore, the incorporation of this additional 3-fold uncertainty factor for long-term risk assessments was deemed appropriate.

Appendix II Label Amendments for Products Containing Octhilinone

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. Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

TECHNICAL GRADE PRODUCT LABEL

I) The following statements must be included on the primary panel of the technical grade products:

CORROSIVE TO THE EYES AND SKIN
POTENTIAL SKIN SENSITIZER

II) The following statements must be included in a section entitled **PRECAUTIONS** on the technical grade product label:

DANGER – POISON
CORROSIVE TO THE EYES AND SKIN
POTENTIAL SKIN SENSITIZER
DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans, or other waters.

III) The following statements must be included in a section entitled **ENVIRONMENTAL HAZARD** on the technical grade product label:

TOXIC to aquatic organisms.

IV) The following statements must be included in a section entitled **DISPOSAL** on the technical grade product label:

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

COMMERCIAL END-USE PRODUCT LABELS (MATERIAL PRESERVATIVES)

I) The following use of octhilinone is to be removed from the end-use product labels (Registration Nos. 24167 and 25630) as it is no longer supported by the registrants:

i. Polymer compounds

II) The following use of octhilinone is to be removed from the end-use products labels (Registration Nos. 23955; 24167; 25630; 27271) due to concerns for human health:

i. Coatings

III) The maximum application rate for the following uses is to be reduced to 0.54 g a.i./L:

Registration No.	Use	Guarantee	Proposed product application rate
23955	Building materials Aqueous adhesives and tackifier preservation	45%	1.2 kg/1000L
24167	Caulks and sealants Aqueous emulsion and adhesives	45%	1.2 kg/1000L
25630	Caulks and sealants Aqueous emulsions and adhesives	25%	2.16 kg/1000L
27271	Caulks and sealants Aqueous emulsions and adhesives Polymer compounds	45%	1.2 kg/1000L

IV) Detailed use directions, including end-uses, application rates and methods (for example, open pour or a closed mixing/loading system), must be added to the KATHON 893 Microbiocide (Registration No. 24167), MICRO-CHECK 11P Industrial Mildewcide (Registration No. 24920), MICRO-CHECK 11 Industrial Mildewcide (Registration No. 24925), and MICRO-CHECK 11 DIDP Industrial Mildewcide (Registration No. 24930) product labels.

V) The following statements must be included on the primary panel of the end-use product labels for use in

- adhesives (Registration Nos. 23955; 24167; 25630; 27271)
- polymer compounds (Registration No.27271)
- vinyl compounds (Registration Nos. 24920; 24925; 24930; 25161; 25174; 31196; 31197)

For use as a material preservative in non-food contact materials and products

VI) The following statements must be included in the **DIRECTIONS FOR USE** section of the end-use product labels registered for use in polymer and vinyl compounds:

DO NOT use for polymer compounds for toys (Registration No. 27271).
OR
DO NOT use for vinyl compounds for toys (Registration Nos. 24920; 24925; 24930; 25161; 25174; 31196; 31197)

VII) The following statements must be included in the **DIRECTIONS FOR USE** section of all end-use product labels:

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

DO NOT discharge effluents containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans, and other waters unless the effluent has been detoxified to suitable means.

VIII) The following statement must be included in the **PRECAUTIONS** section of the end-use product labels:

End-use products formulated as solutions (Registration Nos. 23955; 24167; 24850; 25174; 24925; 24930; 25628; 25630; 26177; 27271; 27397; 31196):

Wear a long-sleeved shirt, long pants, chemical-resistant gloves, goggles or face shield, and a NIOSH-approved organic vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides during mixing, loading, application, clean up, maintenance, and repair. A respirator is not required for mixers/loaders/applicators using a closed mixing/loading system.

End-use products formulated as granules or pellets (Registration Nos. 24920; 25161; and 31197):

Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, and a NIOSH-approved organic vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides during mixing, loading, application, clean up, maintenance, and repair. A respirator is not required for mixers/loaders/applicators using a closed mixing/loading system.

IX) In the **ENVIRONMENTAL HAZARDS** section of all end-use product labels, the existing statement “This product is toxic to fish and wildlife” must be replaced with the following statement:

TOXIC to aquatic organisms. It is not to be used in circumstances that would cause or allow it to enter lakes, streams, ponds, estuaries, oceans, or other waters in contravention of federal or provincial regulatory requirements. The requirements of applicable laws should be determined before using the product.

X) In the **DISPOSAL** section (Reg. Nos. 24920, 24925, 24930) the existing statements must be replaced with the following statements:

1. Triple- or pressure-rinse the empty container. Add the rinsings to the treatment site.

2. Follow provincial instruction for any required additional cleaning of the container prior to its disposal.

3. Make the empty container unsuitable for further use.

4. Dispose of the container in accordance with provincial requirements.

5. For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills.

Appendix III Registered Octhilinone Products as of 22 March 2016

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (w/w)
24126	T	ROHM AND HAAS CANADA LP	KATHON TM 893T TECHNICAL MICROBICIDE	Liquid	99.4%
27038	T	THOR GMBH	ACTICIDE OIT TECHNICAL INDUSTRIAL MICROBICIDE	Solution	98%
31812	T	Troy Chemical Corporation	MERGAL OIT TECHNICAL MICROBICIDE	Solution	99.4%
31254	MC	THOR GMBH	ACTICIDE 45-F		45%
23955	C	ROHM AND HAAS CANADA LP	SKANE (TM) M-8 MICROBICIDE	Solution	45%
24167	C	ROHM AND HAAS CANADA LP	KATHON TM 893 MICROBICIDE	Solution	45%
24850	C	ROHM AND HAAS CANADA LP	BIOBAN^{TM} O 5P5 ANTIMICROBIAL	Solution	5%
24920	C	FERRO CHEMICALS GROUP	MICRO-CHEK 11P INDUSTRIAL MILDEWCIDE	Granular	4%
24925	C	FERRO CHEMICALS GROUP	MICRO-CHEK 11 INDUSTRIAL MILDEWCIDE	Solution	4%
24930	C	FERRO CHEMICALS GROUP	MICRO- CHEK 11 DIDP INDUSTRIAL MILDEWCIDE	Solution	4%
25161	C	MORTON INTERNATIONAL INC.	VINYZENE TM SB-8 BIOCIDE	Pellet	10%
25174	C	MORTON INTERNATIONAL INC.	VINYZENE IT 3010 DIDP BIOCIDE	Solution	10%
25628	C	ROHM AND HAAS CANADA LP	KATHON TM 4200 MICROBICIDE	Solution	25%
25630	C	ROHM AND HAAS CANADA LP*	KATHON TM TP 25% MICROBICIDE	Solution	25%
26177	C	THOMSON RESEARCH ASSOCIATES	ULTRA-FRESH DM-25	Solution	25%
27271	C	THOR GMBH	THOR ACTICIDE 45 MILDEWCIDE	Solution	45%
27397	C	ECOLAB CO.	TEX-STAT II	Solution	5%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (w/w)
31196	C	AKCROS CHEMICALS INC.	INTERCIDE(R) OBF-10 DIDP	Solution	10%
31197	C	AKCROS CHEMICALS INC.	INTERCIDE(R) OBF-10 SVC	Pellet	10%
32557*	C	ARCH WOOD PROTECTION CANADA CORP.	MOLDICIDE WE	Solution	45%

*Wood preservative