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Pest
Management
Regulatory
Agency

Agence de
réglementation
de la lutte
antiparasitaire

JAN 22 2018

ltordo@thorsp.com
Reference No.2017-3648

Lynn P. Tordo
Thor Specialties, Inc.
50 Waterview Drive
Shelton, CT
USA
06484

Dear Ms. Tordo:

Re: Notice of Objection to Re-evaluation Decision RVD2017-02 Octhilinone

Your notice of objection, filed under subsection 35(1) of the *Pest Control Products Act* (PCPA), regarding the re-evaluation decision of octhilinone has now been reviewed and assessed in accordance with the Act and regulations.

The purpose of a notice of objection is to identify the area of science supporting the registration or re-evaluation decision to which objection is taken, to provide the scientific basis of the objection and to request that the area of science in question be referred to a review panel for reconsideration and recommendation.

The Pest Management Regulatory Agency (PMRA) has taken all reasonable measures to ensure impartiality in determining if a panel should be established. The notice of objection, including the scientific rationale, was assessed by a team of PMRA evaluators who were not involved in the original re-evaluation decision. This team provided recommendations as to the requirement for a review panel based on the validity and the scientific plausibility of the issue(s) raised in the notice. The criteria for establishing a review panel are dependent on:

- whether the information in the notice raises scientific-founded doubt as to the validity of the evaluations, on which the decision was based, of the health and environmental risks and the value of the pesticide; and
- whether the advice of a review panel of expert scientists would assist in addressing the subject matter of the objection.

The following information was received and reviewed in support of your notice of objection:

- Notice of objection (rationale)

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The information which you submitted in support of your objection does not meet those requirements and, accordingly, fails to provide any basis for the establishing of a review panel. As a consequence, a review panel will not be established to reconsider the regulatory decision in response to your request.

The issues raised in the notice of objection are attached to this letter and are in **bold text**, PMRA responses are not (see Attachment 1).

Should you have any questions regarding this letter, please contact Jamie Munro at 613-736-3646 or jamie.munro2@canada.ca. Please quote Reference Number 2017-3648 in any correspondence regarding the Notice of Objection to re-evaluation of othilione.

Sincerely,

A handwritten signature in black ink, appearing to be 'P. Brander', written over the printed name.

Peter Brander
Chief Registrar
Pest Management Regulatory Agency

CC Joanne Ryder jryder@dow.com Dow Chemical Company
Adrian Krygsman KrygsmanA@troycorp.com

Attachment 1

Comment 1: Comments were received related to the dermal systemic NOAEL of 25 mg/kg bw/day used by the PMRA for dermal risk assessment. The systemic NOAEL was considered overly conservative since body weight reductions were considered secondary to local skin irritation, and effects on adrenal and heart weights were not toxicologically significant due to the absence of a dose-response. Since other isothiazolinones cause point-of-contact toxicity (irritation and/or corrosion) and do not demonstrate primary systemic toxicity, it was suggested that the same conclusion should apply to othilinone. A NOAEL for systemic toxicity of 125 mg/kg bw/day was proposed, similar to that derived by the study director and the “European evaluating competent authority”.

PMRA Response:

The PMRA acknowledges that adverse effects on body weight in the rat 90-day dermal toxicity study by Zuhlke, as well as the rat 14-day dermal toxicity study, were noted in the presence of point-of-contact irritation. Effects on body weight were also noted in the rat 90-day inhalation toxicity study, again in the presence of point-of-contact irritation. In the rat oral developmental toxicity study, salivation, possibly related to the irritating nature of the test substance, was noted at a dose level which also produced adverse effects on body weight. Although the irritating properties of othilinone may have contributed to the adverse reductions in body weight in these studies, the possibility that these effects were the result of direct systemic toxicity cannot be ruled out. This was further supported by the restriction of body weight effects to male rats at 125 mg/kg bw/day in the rat 90-day dermal toxicity study by Zuhlke, despite the fact that both sexes at this dose level exhibited similar irritation scores. With regards to the comments related to the effects on heart and adrenal weights in female rats in the 90-day dermal toxicity study, these effects were considered toxicologically significant by the PMRA; furthermore, as these organ weight effects were only noted at the highest dose tested, the absence of a dose-response is a moot point. Accordingly, maintaining the NOAEL of 25 mg/kg bw/day for the rat 90-day dermal toxicity study by Zuhlke is reasonable. No change to the reference values for the human health assessment of othilinone is proposed at this time.

Comment 2: Comments on the current application rate range suggest that a broad range of concentrations is required to account for different environmental conditions, formulation differences as well as for dry-film vs. in can applications.

According to the Re-evaluation Decision for othilinone (RVD2017-02), the PMRA has cancelled the use of othilinone in coatings and limited the maximum amount of othilinone in Building Materials, Polymers, and Adhesives to 0.54 g a.i./L (540 ppm a.i.).

We are unaware of any occurrences (where othilinone has been used in a coating) in over five decades of any adverse human exposure due to the use of othilinone in coatings – this includes use at very much higher concentrations than the current maximum that was previously approved by the PMRA in coatings (2160 ppm othilinone).

PMRA Response:

Exposure to secondary workers is expected when handling/ applying treated products. In the absence of specific exposure data for each use scenario, the re-evaluation has conducted a risk assessment for these workers based on paint application. For professional painters using paintbrush, short- to long-term risks were not of concern. However, for professional painters using an airless sprayer, long-term risks were of concern. Therefore, as a result of the re-evaluation, the PMRA requires risk-reduction measures to protect human health: 1) Cancel the material preservative use in coating (paint and stain), and 2) Reduce the application rate in building materials, aqueous emulsions and adhesives, and polymer compounds.

The absence of incident reports for othilinone, could be related to the lack of the consumers' knowledge/ understanding that othilinone is used as an in-can preservative in paint, since these paints are not considered pest control products and are not labelled as such.

Comment 3: Comments on Dermal Absorption; The OIT Task Force considers that a dermal absorption value of 100%, which they state was used by PMRA, is overly conservative.

In reference to two unpublished dermal absorption studies:

Together this data therefore indicates that application of 100% dermal bioavailability in the risk assessment is not warranted and that for standard formulations a dermal absorption value of 40% is more applicable. Furthermore, when formulated in paints due to the matrix effects and significantly attenuated exposure potential, a dermal absorption value of 10% would be appropriate for use in risk assessment. As such the unit exposures applied should be adjusted accordingly.

PMRA Response:

Although the agency has not received the *in vivo* rat dermal absorption study nor the guinea pigs dermal bioavailability study, referenced by the registrants, a dermal absorption factor was not required in the original assessment, as the endpoint used for all exposure scenarios is based on a 90-day dermal toxicity study in rats.

Comment 4: Comments on the PMRA Risk Assessment; information provided to refine the risk assessment.

As a first-pass investigation of how the existing exposures might be refined, updated UEs based on relevant measured BHED® data were applied to the scenario with the highest risk of concern, airless spray application by professional painters at the maximum use concentration. UEs were recalculated using the BHED® SciBin Unit Exposure Tool for the “Applicator – Latex Paint – Exterior Airless Spray” scenario, geometric mean. The recommended dermal absorption factor of 10%, also based on measured data, was then applied to the unit exposure. This value was substituted for the PHED UE values in the table provided in the PMRA re-evaluation decision document. All other existing parameters used by the PMRA were carried forward with no change: 80 kg bodyweight, daily use volume of 187.5 L, containing the maximum concentration of 2.16 g a.i./L. Benchmarks and target MOEs used by PMRA were also carried forward without change.

The revised exposure estimates result in MOEs that significantly exceed the targets required by PMRA and therefore place risk well below the level of concern.

PMRA Response:

Although the risk assessment for professional painters was based on surrogate unit exposure values from the Canadian Pesticide Handler Exposure Database (PHED; Version 1.1), the Agency has acknowledged the uncertainty that may be associated with using PHED. In the absence of chemical-specific data, it was assumed that this database provided the best available information to conduct the risk assessment. However, should the registrant wish to submit a chemical-specific study or scenario specific units of exposure they can do so via a category B submission.