Registration Decision RD2017-01

Beta-cyfluthrin

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Registration Decision Statement[1] for Beta-cyfluthrin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Beta-cyfluthrin Technical Insecticide and its end-use products, Temprid SC Insecticide and Temprid ReadySpray Insecticide containing the technical grade active ingredient beta-cyfluthrin. The end-use products are coformulated with the active ingredient, imidacloprid, to kill certain crawling and flying insects found indoors (including on mattresses) and outdoors on the exterior surfaces of structures.

This decision is consistent with the Proposed Registration Decision PRD2016-21, *Beta-cyfluthrin*, which contains a detailed evaluation of the information submitted in support of this registration. The evaluation found that, under the approved conditions of use, the products have value and do not present an unacceptable risk to human health or the environment. See Appendix I for a summary of comments received during the consultation process as well as the PMRA's response to these comments.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2016-21, *Beta-cyfluthrin)* are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[2] regarding this registration decision within 60 days from the date of publication of this Registration 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 the Health Canada's website (Request a Reconsideration of Decision) or contact the 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

1. Comments regarding the toxicological endpoints

Comment: A comment was received which expressed disagreement with the PMRA's selection of the NOAEL of 0.5 mg/kg bw from the guideline oral gavage acute neurotoxicity study as the point of departure for the acute and repeat oral/dietary risk assessments. The commenter considered the findings cited by the PMRA at the LOAEL of 2 mg/kg bw in this study not toxicologically significant. In addition, they indicated that at a given level of exposure, bolus gavage dosing results in greater acute toxicity compared to human-relevant dietary or hand-to-mouth exposures. Finally, it was suggested that the vehicle (Cremophor EL) used in the acute neurotoxicity study exacerbates the acute toxicity of beta-cyfluthrin, compared to other vehicles or dietary exposure. For the above-noted reasons, the commenter considered the endpoint selected by the PMRA as overly conservative.

PMRA response: In the guideline acute neurotoxicity study in rats conducted with beta-cyfluthrin, the following effects were observed at the 2 mg/kg bw dose level: decreased motor and locomotor activity in a figure-eight maze in females (motor and locomotor activity were decreased by 32% and 36%, respectively, relative to controls), perianal staining (both sexes), and changes in functional observational battery (FOB) parameters (decreased approach response and oral stains in males and decreased activity in the open field in females). All of these effects were considered by the PMRA to be treatment-related and adverse. As a point of note, the study authors also considered the decreased motor and locomotor activity in females at 2 mg/kg bw/day to be biologically significant.

The PMRA is of the opinion that the results obtained from studies using bolus gavage dosing are relevant for use in certain dietary and hand-to-mouth exposure scenarios. It is standard regulatory practice to consider these studies relevant for use in risk assessment.

The PMRA acknowledges the comment that the Cremophor EL vehicle enhanced absorption of beta-cyfluthrin, thus exacerbating toxicity. As noted in PRD2016-21, *Beta-cyfluthrin*, data were available which demonstrated that following oral gavage dosing, the rate and extent of absorption of cyfluthrin was increased when it was administered in Cremophor EL compared to polyethylene glycol. While it is not uncommon for vehicles to play a role in modulating pyrethroid toxicity, in the case of Cremophor EL, the enhancement of cyfluthrin toxicity was considerable.

The initial selection of the NOAEL of 0.5 mg/kg bw from the acute neurotoxicity study was supported by a $BMDL_{20}$ of 1.4 mg/kg bw generated from motor activity data in a published non-guideline acute neurotoxicity study (Wolansky et al., 2006) which used corn oil as the vehicle. Given i) that the vehicle may have led to a conservative NOAEL for neurotoxicity and, ii) that the $BMDL_{20}$ falls between the NOAEL and LOAEL established by the PMRA for the guideline acute neurotoxicity study, the PMRA considers it scientifically valid to revise the endpoint selected for risk assessment. Accordingly, the $BMDL_{20}$ of 1.4 mg/kg bw from the Wolansky study is now selected by the PMRA as the point of departure for use in the risk assessments for both the acute and repeat-dose scenarios (acute reference dose, acceptable daily intake, short-term non-dietary oral risk assessment, short- and intermediate-term aggregate assessments).

Comment: A comment was received which expressed disagreement with the use of the results from an acute neurotoxicity study for repeat-exposure oral/dietary risk assessment. It was noted that the principal effect observed with beta-cyfluthrin is transient evidence of acute neurotoxicity, with limited or no evidence of cumulative toxicity. The commenter therefore felt that the use of a point of departure from an acute neurotoxicity study was overly conservative for a repeat-dose exposure scenario.

PMRA Response: Notwithstanding the issue of cumulative toxicity, it is necessary to protect for transient effects following either single or repeat exposures to a pesticide. The $BMDL_{20}$ of 1.4 mg/kg bw/day for motor activity from the acute oral neurotoxicity investigation by Wolansky et al. (2006) is the lowest point of departure in the beta-cyfluthrin/cyfluthrin database and is thus considered protective of all repeat-dose exposure scenarios. From a risk perspective, it would also not be appropriate to establish a higher point of departure for a repeat-dose scenario than for an acute scenario. For this reason, the PMRA considers the use of this endpoint appropriate for use in the repeat-exposure oral/dietary risk assessments.

Comment: A comment was received requesting that the PMRA harmonize toxicology endpoints for risk assessment with those established by the USEPA. The EPA selected the NOAELs of 2 mg/kg bw from the acute neurotoxicity study in rats and 2.36 mg/kg bw/day from the 90-day dietary study in dogs for the acute and repeat-exposure risk assessments, respectively.

PMRA Response: The PMRA takes into consideration points of departure established by other recognized pesticide regulatory authorities such as the USEPA during the evaluation process, but may not always concur on the selection of endpoints for risk assessment. The PMRA has revised the point of departure for the acute- and repeat-dose scenarios (acute reference dose, acceptable daily intake, short-term non-dietary oral risk assessment, short- and intermediate-term aggregate assessments), based on the scientific reasons discussed above. The revised PMRA toxicology endpoints are listed in the table below. Endpoints that have been revised are marked with an asterisk (*).

Summary of Toxicology Endpoints for Human Health Risk Assessment

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary (All populations)*	Acute neurotoxicity study in rats	$BMDL_{20}$ of 1.4 mg/kg bw/day; based on decreased motor activity	300
	ARfD = 0.005 mg/kg bw		
Repeated dietary (All populations)*	Acute neurotoxicity study in rats	$BMDL_{20}$ of 1.4 mg/kg bw/day; based on decreased motor activity	300
	ADI = 0.005 mg/kg bw/day		
Short-, intermediate- and long-term dermal (All populations)	21-day dermal toxicity study in rats	NOAEL = 376 mg/kg bw/day; based on clinical signs of toxicity, decreased food consumption.	300

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Short-term inhalation (All populations)	28-day inhalation toxicity study in rats	NOAEC = 0.0002 mg/L (0.07 mg/kg bw/day); based on decreased body weight and body weight gain.	300
Intermediate- and long-term inhalation (All populations)	90-day inhalation toxicity study in rats	NOAEC = 0.00009 mg/L (0.02 mg/kg bw/day); based on clinical signs of toxicity and decreased body weight.	300
Non-dietary incidental oral (short-term)*	Acute neurotoxicity study in rats	$BMDL_{20}$ of 1.4 mg/kg bw/day; based on decreased motor activity	300
Aggregate Exposure: Based on clinical signs of neurotoxicity			
All Durations Aggregate - Oral (All populations)*	Acute neurotoxicity study in rats	$BMDL_{20}$ of 1.4 mg/kg bw/day; based on decreased motor activity	300
Short-term Aggregate - Inhalation (All populations)	5-day inhalation toxicity study	NOAEC=0.00025 mg/L (0.07 mg/kg bw/day)	300
Intermediate- and Long-term Aggregate - Inhalation	90-day inhalation toxicity study	NOAEC = 0.00009 mg/L (0.02 mg/kg bw/day)	300
Cancer	Equivocal increase in the incidence of urinary bladder tumours in females in the rat chronic toxicity/oncogenicity study with cyfluthrin. Endpoints selected for the non-cancer risk assessment are protective of these equivocal findings.		

[1] CAF (Composite assessment factor) refers to the total of uncertainty and *Pest Control Products Act* factors for dietary risk assessments, MOE (margin of exposure) refers to target MOE for occupational assessments.
* denotes revised endpoint

2. Comments regarding the quantitative health risk assessment

Comment: A comment was received stating that the handler risk assessment for pest control operators (PCOs) utilized the data from The Pesticide Exposure Handlers Database (PHED) rather than the cyfluthrin PCO observational exposure study that was submitted by the commenter. The commenter stated that, in the cyfluthrin proposed re-evaluation decision document, the PMRA acknowledged receipt of the study after the completion of their assessment of cyfluthrin, and that the PMRA committed to reviewing the study for relevance prior to issuing a final re-evaluation decision for cyfluthrin. The commenter assumes that the PMRA will also review the study prior to issuing a final registration decision for beta-cyfluthrin.

PMRA Response: A passive dosimetry study was submitted, which monitored worker exposure during mixing, loading and applying (M/L/A) liquid structural pest control products indoors using a manually pressurized hand wand. The study has now been reviewed and considered acceptable for use in risk assessments. Also, information presented by the applicant, referencing the National Pest Management Association, indicated a PCO can apply upwards of 40 L/day depending on the location of use (commercial vs residential location) and pest infestation level.

This is a refinement from the 150 L/day used in the original assessment which is a default value used in agricultural scenarios.

Estimates of dermal and inhalation exposure were revised using the new unit exposure and amount handled per day values. The duration of exposure is expected to be intermediate-term. Dermal and inhalation risks for beta-cyfluthrin are not of concern (Table 5; revised values are bolded).

Table 5 PCO Dermal and Inhalation Exposure to Beta-cyfluthrin.

Application Equipment	Amount Handled Per Day[1]	Unit Exposure (µg/ kg ai handled)[2]		Dermal Exposure (mg/kg bw/day)[3]	Dermal MOE[4]	Inhalation Exposure (mg/kg bw/day)[3]	Inhalation MOE[4]
		Dermal	Inhalation				
Temprid SC Insecticide							
Manually pressurized hand wand	**40 L /day**	**92001.28**	**351.22**	**1.12×10^{-2}**	**33600**	**4.28×10^{-5}**	**468**
Backpack	150 L /day	5445.85	62.1	2.49×10^{-3}	151000	2.84×10^{-5}	705
Temprid ReadySpray Insecticide							
Aerosol	14 cans per day	146598.1	1646	2.85×10^{-3}	132000	3.19×10^{-5}	626

[1] Information submitted by the applicant under DACO 5.2.
[2] Single layer PPE with chemical gloves from the PCO passive dosimetry study
[3] Exposure (mg/kg bw/day) = [(Amount Handled Per Day (L/day) × Dilution Rate (2.0 mL product/L) × Density for Temprid SC Insecticide) **OR** (Amount Handled Per Day (cans/day) × Net Contents (mL/can) × Density for Temprid ReadySpray Insecticide)] × Guarantee (%) × Unit Exposure (µg/ kg ai handled) × Absorption Value (%) × Unit Conversion (mg/ 1000 µg)
[4] MOE = Intermediate-term NOAEL (mg/kg bw/day) ÷ Exposure (mg/kg bw/day); Target MOE = 300

Comment: A comment was received stating that the hand-to-mouth and object-to-mouth MOEs were calculated using the incidental oral NOAEL of 0.5 mg/kg/day which was derived from the acute neurotoxicity study, and that this point of departure is not appropriate for incidental oral ingestion for the reasons provided by the commenter in the comments regarding the selection of an appropriate oral toxicity endpoint. The comment stated that, although the incidental oral ingestion scenario is a short-term exposure scenario, the use of an endpoint obtained through bolus dosing will accentuate the potential toxicity effects compared to an oral ingestion scenario that is assumed to occur intermittently over a two- to four-hour duration, and that the most appropriate point of departure for the assessment of incidental oral exposure risk is a NOAEL of 2.0 mg/kg/day as discussed in the comments regarding the appropriate point of departure.

PMRA Response: Comments on the appropriateness of the incidental oral NOAEL of 0.5 mg/kg/day are provided under the toxicology responses above. As such, this section will focus on the changes to the risk assessment.

Based on the changes made to the toxicological endpoints, the risk assessments were updated using the $BMDL_{20}$ of 1.4 mg/kg bw. Corrections to the original risk assessment are presented below as revisions to the original Table 9, Table 10 and Table 11 in PRD2016-21, *Beta-cyfluthrin*.

The hand-to-mouth equation was refined to represent exposure after an hour of residue accumulation on a child's hands prior to the commencement of hand-to-mouth activity rather than the existing assumption of an entire day of residue accumulation. As such, the incidental oral exposure via the hand-to-mouth route was reduced and the risk was no longer considered to be of concern. Therefore, it was no longer necessary to use the refined transfer values of 4% and 6% for soft and hard surfaces, respectively. As such, the standard values from the USEPA 2012 Residential SOPs of 6% for soft surfaces and 8% for hard surfaces were used.

With the MOEs now exceeding the target MOE of 300, Temprid ReadySpray Insecticide no longer must to be restricted for use in areas where children are not present and Temprid SC Insecticide can be applied for control of bed bugs at the same dilution rate as all other pests at 2 mL product/L water. Also, both products are now permitted for use for void, crack and crevice and spot treatments. Exposure to void application was not calculated as exposure is expected to be minimal.

Table 9 Child (1-2 years) Hand-to-Mouth Exposure to Beta-cyfluthrin.

Exposure Scenario	Deposited Residue (µg a.i./cm^2)	Dermal Exposure (mg/hr)	Hand residue loading (mg/hr)	Fraction of hand mouthed	Exposure Time (hours/day)	Incidental Oral Exposure (mg/kg/day)	Incidental Oral MOE
Indoor Perimeter/Spot / Bed Bugs							
Soft Surface	0.5	0.0540	0.004050	0.13	4	0.000184	7600
Hard Surface		0.0720	0.005400		2	0.000123	11400
Bed bugs (crack and crevice)							
Soft Surface	0.25	0.0270	0.002025	0.13	4	0.000092	15200
Hard Surface		0.0360	0.002700		2	0.000061	22800
Crack and crevice							
Soft Surfaces	0.1	0.0108	0.000810	0.13	4	0.000037	38000
Hard Surfaces		0.0144	0.001080		2	0.000025	57000

For a full review of calculations, refer to the USEPA Section 7 Indoor Environments SOP.

Table 10 Child (1 < 2 year) Object-to-Mouth Exposure to Beta-cyfluthrin.

Exposure Scenario	Deposited Residue (µg/cm^2)	Fraction of residue transferred to object	Object Residue (µg/cm^2)	Exposure Time (hours/day)	Extraction by Saliva	Incidental Oral Exposure (mg/kg/day)	Incidental Oral MOE
Indoor Perimeter/Spot (All pests including bed bugs)							
Soft Surface	0.50	0.06	0.030	4	0.48	0.000392	3570
Hard Surface		0.08	0.040	2		0.000261	5360
Bed bug (crack and crevice)							
Soft Surfaces	0.25	0.06	0.015	4	0.48	0.000196	7140
Hard Surface		0.08	0.02	2		0.000131	10700
Crack and crevice (All pests, excluding bed bugs)							
Soft Surfaces	0.1	0.06	0.006	4	0.48	0.000078	17900
Hard Surfaces		0.08	0.008	2		0.000052	26800

For a full review of calculations, refer to the USEPA Section 7 Indoor Environments SOP.

Table 11 Aggregate Exposure for Beta-cyfluthrin[1]

	Hard Surface MOEs				Soft Surface MOEs			
	Incidental Oral	Inhala-tion	Dietary	Aggregate	Incidental Oral	Inhala-tion	Dietary	Aggregate
Indoor Perimeter / Spot / Bed Bug	5360	520000	1280	1030	3570	520000	1280	938
Bed bugs (crack and crevice)	10700	520000	1280	1140	7140	520000	1280	1080
Crack and crevice (excluding bed bugs)	26800	520000	1280	1200	17900	520000	1280	1190

[1] The $BMDL_{20}$ of 1.4 mg/kg bw for oral exposure and 0.07 mg/kg bw/day for short-term inhalation exposure; target MOE = 300

The aggregate MOE was calculated by $= \frac{1}{[(1/MOE_{OtM}) + (1/MOE_{Inhalation}) + (1/MOE_{Dietary})]}$

3. Comments regarding the incident reports

Comment: A comment was received regarding the types of incidents that were used in the review, in particular, respondents questioned if the reported effects were consistent with exposure to cyfluthrin/beta-cyfluthrin, and if the exposure scenarios were consistent with the proposed use patterns for Temprid SC Insecticide and Temprid ReadySpray Insecticide.

PMRA Response: The proposed use pattern for Temprid SC Insecticide and Temprid ReadySpray Insecticide is for indoor, structural application to cracks and crevices as well as spot treatments. To support the risk assessment, only incidents where the product was applied in a similar manner were considered.

Three databases (PMRA, California Department of Pesticide Regulation, and National Institute of Occupational Health and Safety) were searched for incidents relevant to the proposed products. In all three databases, there was a high degree of repetition for respiratory effects following re-entry into structural areas that had been treated with cyfluthrin or beta-cyfluthrin.

In the PMRA database, 34 individuals were affected in six incidents when they were either present or re-entered a home or business treated with cyfluthrin. These incidents were found to be consistent with cyfluthrin exposure.

The California Department of Pesticide Regulation's database had 175 incidents reported and the National Institute of Occupational Health and Safety database had 97 incidents following the same exposure scenario (i.e. after entering structural areas that had been treated with cyfluthin or beta-cyfluthrin). Respiratory effects were the most frequently reported symptoms in both US databases. All of the US incidents were considered to be consistent with exposure to cyfluthrin or beta-cyfluthrin. In addition, a search of the California Department of Pesticide Regulation website also revealed a review of inhalation exposure of orange harvesters to cyfluthrin following re-entry into treated orchards 3-10 days after treatment (California Department of Pesticide Regulation, 1998). This review also highlighted the respiratory effects following re-entry, even in an outdoor application setting. It resulted in the initiation of a reevaluation of cyfluthrin and generation of a respiratory irritation study, worker exposure study, and monitoring data for structural application.

Comment: A comment was received pointing out that the rate of incidents reported for cyfluthrin/beta-cyfluthrin, in both the PMRA database and the California database, were so low in comparison to product sales that they could not justify the risk mitigation being proposed.

PMRA Response: The proposed mitigation is based on the risk of respiratory effects that was identified in the PMRA database, and is supported by post-market data from two US databases.

A low number of reported incidents compared to product sales cannot be used to imply a lack of risk. In addition, under-reporting of incidents has been documented in the pharmaceutical, agricultural pesticide, and veterinary drug world (Hazzell and Shakir, 2006; Bell et al., 2005; Fresnay et al., 2015), with estimates indicating that only 10% or less of adverse effects are reported. Hence, comparing the rate of these incidents to product sales could grossly underestimate the issue, which is another reason why the PMRA also relied upon information from the two US databases.

4. Comments regarding the re-entry interval

Comment: Comments were received that indicated the proposed re-entry of 8 hours was not necessary since the quantitative risk assessment showed no risk for postapplication inhalation exposure. In addition, the feasibility of applications that require an 8-hour re-entry interval was questioned, as it could displace occupants late into the evening or would restrict applicators to early morning applications only.

PMRA Response: The PMRA acknowledges that the data assessed for the pre-market risk assessment of beta-cyfluthrin did not result in the identification of the human health risk concerns, as characterized from the evaluation of the incident reports. However, it is also not uncommon for pre- and post-market data to have different results given the very different nature of the data. For example, incident reports are from real-life circumstances, which may not be the case for the data that is assessed during the pre-market evaluation. Having said that, the review and consideration of both types of data is essential in determining whether there is reasonable certainty that no harm to human health will result from exposure to or use of the pesticide when used in accordance to the conditions of registration.

With respect to the feasibility of having an 8-hour re-entry interval, the PMRA has again considered all available information (including pre- and post-market data, as well as publicly available literature and federal and provincial industry standards and practices). Cyfluthrin residue transfer data available in the public literature (Williams et al., 2003) indicates that a lower percentage is transferred once residues have dried. Residue transfer was monitored at 3, 7, 12, 23, 47.5 and 407.5 hours after application; and from 3 to 7 hours, residue transfer reduced from 8.5% to less than 2%, with minimal decreases thereafter. Current national best management practices following indoor commercial applications of pesticides recommend a re-entry of 2-6 hours. In Quebec, guidelines recommend a re-entry after 6 hours for cyfluthrin based on toxicology data (Ville de Montreal, 2010). Pest control operators in the province indicated that, although restrictive, this re-entry was suitable for cyfluthrin. The incidents reviewed indicate that adverse health effects occurred when individuals were present during and up to 24 hours after application. Although a few incidents reportedly occurred 24 hours after application, it is unknown if the areas had been ventilated or if the product had been used according to label directions.

Based on the available information, scientific literature and the incident report data, the PMRA has determined that reducing the re-entry interval to 6 hours is appropriate given the overall required risk mitigation, which also includes ensuring adequate ventilation and the requirement for applicators to leave an information sheet for occupants (informing them of the product that was applied, the re-entry interval, and possible adverse effects and what to do if they experience them). Combined, these measures should address the potential for respiratory effects when the product is applied according to label directions while, at the same time, maximizing the usability of the product to the extent possible.

5. Comments regarding the listing of adverse effects on product labels

Overall, respondents agreed with listing adverse effects on product labels.

6. Comments regarding the requirement to leave an information sheet

Comment: Overall, respondents were supportive of leaving an information sheet for occupants, but concerns were raised that adding potential adverse effects to the Information Sheet left for occupants could result in a placebo effect.

PMRA Response: The potential for placebo effects should be balanced with the fact that occupants need to be informed of health-risk related information, in a clear and transparent manner, so that they can take additional measures, if necessary, to further protect their health.

In the incident report data, occupants re-entering areas that had been treated with cyfluthrin or beta-cyfluthrin frequently experienced respiratory effects such as coughing, sore throat, and shortness of breath, along with nausea, dizziness and eye irritation. The purpose of the information sheet is to provide the occupants with the necessary information so they will know what to do if they experience these effects. While the adverse health effects will be listed on the product label, as Temprid SC and Temprid ReadySpray are applied by professional applicators, the occupants do not see the product label. To that end, it is important for occupants to know what effects could occur following re-entry into a treated area and what they should do if they experience those effects.

The availability for the consumer to have real-time access to this type of information is also consistent with other product types (for example, pharmaceuticals and veterinary drugs).

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2449137	2014, Observational Study to Determine Dermal and Inhalation Exposure to Pest Control Operator (PCO) Workers Applying Deltamethrin and/or β-Cyfluthrin Using Hand-held Equipment in a Crack and Crevice Application, DACO: 5.4
2445310	Williams R.L., Bernard C.E., Krieger R.I. (2003). Human Exposure to Indoor Residential Cyfluthrin Residues During a Structured Activity Program. *Journal of Exposure Analysis and Environmental Epidemiology*, 13, p.112 – 119

B. Additional Information Considered

i) Published Information

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