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Regulatory
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Agence de
réglementation
de la lutte
antiparasitaire

December 13, 2021

e-mail: sspaulding@central.com
Reference No. 2021-1851

Steven R. Spaulding
Wellmark International D.B.A. Central Life Sciences
100 Stone Road West, Suite 111
Guelph, ON
N1G 5L3

Dear Steven R. Spaulding:

Re: Notice of Objection to Special Review Decision SRD2021-01, Special Review of Tetrachlorvinphos and Its Associated End-use Products

Your notice of objection regarding the special review decision for tetrachlorvinphos, specifically the cancellation of the flea and tick pet collar uses, filed under subsection 35(1) of the *Pest Control Products Act* (PCPA), has now been reviewed and assessed in accordance with the PCPA and Regulations.

The purpose of a Notice of Objection is to identify the area of science supporting the registration or re-evaluation/special review 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 assessing this Notice of Objection. The issues you raised and the PMRA responses are in Attachment 1.

The information which you submitted in support of your objection does not raise scientific-founded doubt as to the validity of the evaluations on which the decision was based, and, accordingly, fails to provide a basis for the establishment of a review panel. As a consequence, there will be no further action taken on this Notice of Objection.

The information available to the PMRA at the time of the final special review decision supported the decision outlined in SRD2021-01, *Special Review of Tetrachlorvinphos and Its Associated*

End-use Products. Registrants have the option to submit new studies and additional information to Health Canada to add/amend a registration. All new applications will be assessed according to the PMRA Guidance Document, Management of Submissions Policy. Registrants can request a pre-submission consultation to obtain guidance on data that may be required to add the cancelled uses.

Should you have any questions regarding this letter, please submit them to the Notice of Objection e-mail account (pmra.noo-ado.arla@hc-sc.gc.ca) and we will respond as soon as possible. Please quote Reference Number 2021-1851 in any correspondence regarding the Notice of Objection to the special review of tetrachlorvinphos.

Sincerely,



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Bissonnette, Frederic
Date: 2021.12.13 16:16:
26-05'00'

Frédéric Bissonnette
Chief Registrar
Pest Management Regulatory Agency

Attachment 1. PMRA responses to the issues raised in the NoO.

Notice of Objection - Comment I:

“PMRA’s Special Review did not include consideration of a 21-Day Dermal Study in Rats with TCVP that was reported in 1989 by WIL Research Laboratories, Inc. (Naas, 1989):

Naas, D.J. 1989. 21-Day Dermal Study in Rats with Rabon Technical. WIL Research Laboratories, Inc. WIL-149007. December 4, 1989. Sponsored by: E.I. DuPont de Nemours & Co., Inc. Wilmington, DE. EPA MRID # 41342001.”

“The dermal route of exposure should not be needed for risk assessment as there was no demonstration of hazard, and hence no quantification of risk is necessary. The USEPA concluded the same in their 2020 evaluation of TCVP. PMRA may not have been aware of this study as in their Special Review, they stated that a dermal study was not available. From PMRA Special Review: For exposure via the dermal or inhalation route (all 5 durations), no adequate route-specific studies were available (see Page 21; Proposed Special Review Decision – PSRD2019-04, dated 26 April 2019).”

PMRA Response:

The dermal exposure endpoint is currently based on the developmental neurotoxicity (DNT) study findings in the offspring. The Objectors attest that lack of findings in the dermal toxicity study would supersede the DNT and that the PMRA did not have the study nor did it evaluate the study. The 21-day dermal toxicity study was part of the USEPA RED document, EPA 738-R-95-041, published in September 1995. The PMRA HED toxicology re-evaluation document (PMRA# 2543910, 2002) called the study supplementary due to small group sizes and large standard deviations, as a result, it was not considered to be an adequate study. As such, the study was considered as part of the Special Review, which referenced the re-evaluation document and the USEPA RED. Additionally, the dermal study would not be considered appropriate for risk assessment, even if considered an acceptable study, as the effects observed on the young in the DNT study (brain morphometrics) were not assessed in the dermal study.

Notice of Objection - Comment II:

“PMRA and the USEPA have both used linear low-dose extrapolation to calculate a cancer potency factor (i.e., Q1*) of 1.83×10^{-3} (mg/kg/day), although their respective bases and endpoints differ from each other along with differences from the conclusions of the oncogenicity study report. We are including this discussion as it would appear that there are multiple bases for questioning the use of combined hepatocellular adenomas/carcinomas as an endpoint for cancer risk assessment and whether the linear low-dose extrapolation method is appropriate given the excessive dosing employed and the

lack of a dose-response for tumor formation. The study report associated with the oncogenicity study in B6C3F1 mice indicated excessive toxicity at the two highest dose levels as evidenced by body weight decrements ranging from 15-40%. The USEPA noted these dose levels as slightly excessive (8000 ppm) to excessive (16000 ppm) and historically a body weight decrement greater than 10% is evidence of excessive toxicity/dosing which is associated as having exceeded the maximum tolerated dose. As such, any/all findings, including tumor response, should be considered secondary or conflicted owing to excessive toxicity.”

PMRA Response:

The PMRA response to this objection is three-fold.

- 1) All information referenced by the objectors were already considered during the Special Review to support their claim.
- 2) According to PMRA# 2543910, decreased body weight compared to control started at 1200 mg/kg bw/d in mice in the 92-week study; however, liver tumour were increased in females at 240 mg/kg bw/d and in males at 2400 mg/kg bw/d. The q* is based on the liver tumours in female mice, which occurred at lower doses than the body weight effects. As such, any excessive toxicity at the highest doses tested would not have an effect on the cancer risk assessment.
- 3) Combining hepatocellular adenomas and carcinomas is standard practice used by both the PMRA and USEPA, and no information was provided to support a different approach.

Notice of Objection - Comment III:

Concern over the assumptions related to pet collar use during a lifetime used in the risk assessment:

“By using a conservative assumption of long-term pet collar use, the PMRA exaggerated the assumed dermal route contribution to theoretical lifetime excess cancer risk. PMRA has only estimated marginally unacceptable lifetime excess cancer risk estimates, based on the assumptions adults are exposed to tetrachlorvinphos residues from pet collars every day for 90 days per year, each year for 35 years. With more realistic scientific values and assumptions for pet collar lifetime use, the cancer risk estimates would be within the acceptable range.”

PMRA Response:

The exposure frequency of 90 days/year used in the cancer risk assessment was based on the USEPA estimate of 180 days/year (USEPA, 2016) and assuming the flea and tick season is shorter in Canada when compared to the US, due to colder climatic conditions. Pet ownership was assumed to occur over a period of 50 years during an entire lifetime, consistent with that

used by the USEPA, with exposure durations of 35 years for adults, 5 years for youth, and 5 years for children. Pet collar use data is currently unavailable in the Residential Exposure Joint Ventures' latest survey provided to the Agency, nor was any other reference/source submitted to refine these exposure durations. Therefore, while the PMRA acknowledges that these exposure frequencies and durations represent uncertainties and conservatisms in the risk assessments, in the absence of frequency and duration-specific exposure information to pet collars, these values cannot be refined further.

Notice of Objection - Comment IV:

Concern over the overestimation of human dermal absorption in the risk assessment:

“Through its designation of the magnitude of tetrachlorvinphos dermal absorption through human skin based on rat studies, the PMRA overestimated the products’ risks. It has long been known that the higher permeability of rat skin makes rats a poor model for assessing the permeability of compounds through human skin. Based on the GastroPlus® modeling program, dermal absorption of tetrachlorvinphos through human skin is predicted to be approximately 3- to 4-fold lower than rat skin at all application levels. When a more reasonable estimation of risk is considered, the products would be found to be acceptable for continued use. We have been advised that Hartz is prepared to conduct a rat versus human in vitro dermal absorption study for radiolabeled TCVP to provide further evidence to the PMRA that the dermal risks associated with the flea and tick pet collars for residential uses are acceptable.”

PMRA Response:

The PMRA recognizes that there are conservatisms and limitations in using results from an in vivo rat dermal absorption study in the risk assessment, which may overestimate human dermal absorption. The PMRA also received the GastroPlus® modelling that Hartz Canada Inc. submitted as part of their notice of objection for tetrachlorvinphos. However, results from the GastroPlus® modeling program cannot be used to refine the dermal absorption value, since the PMRA has not yet established an approach on incorporating in silico modelling to assess dermal absorption. As such, without additional dermal absorption data, the difference of dermal absorption between rats and humans for tetrachlorvinphos cannot be quantified nor applied to the risk assessment.

As mentioned in SRD2021-01, the current exposure and risk assessment for tetrachlorvinphos was based on the data available at the time. However, registrants have the option to submit studies, such as an in vitro rat vs. human dermal absorption study, and additional information to Health Canada to add/amend a registration. All new applications will be assessed according to the [PMRA Guidance Document, Management of Submissions Policy](#).