UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **August 8, 2019**

SUBJECT: ***Tau*-fluvalinate**. Updated Draft Human Health Risk Assessment for Registration Review.

PC Code: 109302	**DP Barcode:** D453559
Decision Nos.: 553921	**Registration No.:** NA
Petition No.: NA	**Regulatory Action:** Registration Review
Risk Assessment Type: Single chemical aggregate	**Case No.:** 2295
TXR No.: NA	**CAS No.:** 102851-06-9
MRID No.: NA	**40 CFR:** §180.427

FROM: Danette Drew, Chemist/Risk Assessor
Risk Assessment Branch (RAB) V
Health Effects Division (7509P)

THROUGH: Michael S. Metzger, Branch Chief
RAB V/VII
Health Effects Division (7509P)

TO: Miguel Zavala, Chemical Review Manager
Risk Management and Implementation Branch 3
Pesticide Reevaluation Division (7508P)

This document is an update to the Human Health Draft Risk Assessment (DRA) in Support of Registration Review for *tau*-fluvalinate.

1.0 Executive Summary

Tau-fluvalinate (cyano-(3-phenoxyphenyl)methyl *N*-[2-chloro-4-(trifluoromethyl)phenyl]-D-valinate), a type II class pyrethroid, is registered as a post-emergent insecticide/miticide for the control of a variety of insects in beehives and various outdoor or greenhouse settings. *Tau*-fluvalinate also has two non-food use special local need (SLN) registrations for California on the following crops grown for seed: carrots, Brassica vegetables, and cole crops. There are two tolerances currently established for residues of *tau*-fluvalinate, one in honey, and one for wine

grapes, the latter associated with no U.S. registrations (40CFR §180.427). *Tau*-fluvalinate is the residue of concern for tolerance enforcement and risk assessment. *Tau*-fluvalinate also has uses in outdoor residential settings including outside surfaces (crack and crevice), ant mound treatments (spot application) and use on roses, flowers, houseplants, ground covers, vines, ornamentals, shrubs and trees that may result in handler or post-application exposures. Since there is no dermal hazard for *tau*-fluvalinate due to the low systemic toxicity, only inhalation exposures were quantitatively assessed.

Since the previous DRA (***Tau-fluvalinate****. Updated Draft Human Health Risk Assessment for Registration Review*, D. Drew, Sept 6, 2016, D427869, D425975), new information has been submitted which allows the database uncertainty factor to be reduced from 3X to 1X for children less than 6 years old. This information presented in *USEPA Office of Pesticide Programs' Re-Evaluation of the FQPA Safety Factor for Pyrethroids: Updated Literature and CAPHRA Program Data Review, July 1, 2018* (https://www.epa.gov/sites/production/files/2019-08/documents/2019-pyrethroid-fqpa-caphra.pdf) and is summarized in the hazard section below.

There have been no changes to the risk assessment endpoints or points of departure, exposure assessments (dietary, residential or occupational), aggregate, or cumulative assessments. No risks of concern were identified in the previous DRA, and since the database uncertainty factor is now removed, risk estimates are further reduced for children.

The only comments related to human health received by HED since completion of the DRA were from Wellmark International concerning the Data Evaluation Record (DER) for the study, "A Nose-Only Inhalation Exposure Neurotoxicity Study of *Tau*-fluvalinate in Rats" (MRID 49660601), which was submitted in support of the data call in (DCI) Requirements for GDCI-109302-1031. The rebuttal addressed the 1) differences in the conducting laboratory and HED conclusions regarding the no-observed-adverse-effect-concentration (NOAEC) and 2) deficiencies noted by HED. HED's responded to these comments (*Tau-fluvalinate: Response to Comments on the Data Evaluation Review (DER) for the Study, "A Nose-Only Inhalation Exposure Neurotoxicity Study of Tau-fluvalinate in Rats"*, S. Dobreniecki, Feb 5, 2018, D442722), and concluded that the previous conclusion, that the no-observed-adverse-effect concentration (NOAEC) could not be established for the study, remains correct. These comments did not change any conclusions drawn in the DRA.

Hazard Assessment

The hazard assessment for *tau*-fluvalinate can be found in the DRA (D. Drew, Sept 6, 2016, D427869, D425975); the reader is referred to that document for detailed information regarding hazard identification and endpoint selection.

The hazard database for *tau*-fluvalinate is complete. Data are now available allowing reduction of the Food Quality Protection Act (FQPA) safety factor for children < 6 years old from 3X to 1X. This revision is summarized in Appendix A in an updated Summary of Toxicological Doses and Endpoints for *tau*-fluvalinate for Use in Human Health Risk Assessments.

FFDCA section 408 requires the Agency to apply an additional 10X safety factor to account for the potential pre- and post-natal toxicity and completeness of the data with respect to infants and children unless, based on reliable data, EPA can conclude that another safety factor will be "safe." The Agency considers the FQPA safety factor as having two components, with 3X assigned to pharmacokinetic (PK) and 3X to pharmacodynamic (PD) differences. Previously, EPA's Office of Pesticide Programs (OPP) retained a 3X FQPA Safety Factor (1X for PD and 3X for PK differences) for children < 6 years old based on concerns for PK differences between adults and children (E. Scollon, DP381210, 2011). OPP has re-evaluated the need for an FQPA Safety Factor for human health risk assessments for pyrethroid pesticides based on a review of the available guideline and literature studies as well as data from the Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) program. Because no new information of suitable quality was available on the age-related PD properties of the pyrethroids, the PD contribution to the FQPA safety factor remains at 1X. Regarding PK, recent data including human physiologically based pharmacokinetic (PBPK) models as well as *in vivo* and *in vitro* data on protein binding, enzyme ontogeny, and metabolic clearance, support the conclusion that the PK contribution to the FQPA safety factor can be reduced to 1X for all populations[1]. Therefore, the Agency concludes that the default 10X FQPA safety factor can be reduced to 1X for all populations for the pyrethroid pesticides.

Dietary Assessment

The table below shows the updated dietary risks with removal of the 3X FQPA safety factor for children < 6 y/o. There are no dietary risk concerns. The population with the highest risk estimate (adults 50-99 y/o) remains the same.

Summary of Acute Dietary (Food and Drinking Water) Exposure and Risk for *Tau*-Fluvalinate			
Population Subgroup[1]	aPAD mg/kg/day	Acute 95th Percentile	
		Exposure (mkd)	% aPAD
General U.S. Population	0.01	0.000365	3.7
All Infants (<1 yr. old)		0.000411	4.1
Children 1-2 yrs. old		0.000217	2.2
Children 3-5 yrs. old		0.000177	1.8
Children 6-12 yrs. old		0.000138	1.4
Youth 13-19 yrs. old		0.000125	1.3
Adults 20-49 yrs. old		0.000911	9.1
Adults 50-99 yrs. old		0.001992	**20**
Females 13-49 yrs. old		0.000623	6.2

[1] The most highly exposed population subgroup is in bold.

[1] USEPA Office of Pesticide Programs' Re-Evaluation of the FQPA Safety Factor for Pyrethroids: Updated Literature and CAPHRA Program Data Review (2019).). https://www.epa.gov/sites/production/files/2019-08/documents/2019-pyrethroid-fqpa-caphra.pdf

Residential and Aggregate Assessment

The acute aggregate exposure and risk estimates are equivalent to the acute dietary (food and drinking water) exposure and risk estimates. Acute aggregate risk is not of concern for the general U.S. population or any population subgroup.

Neurotoxic effects, the most sensitive effects observed in the toxicity database, attributable to chronic exposure to *tau*-fluvalinate have not been identified (neurotoxic effects do not progress over time), and *tau*-fluvalinate has been classified as "not likely to be a human carcinogen"; therefore, quantitative chronic and cancer aggregate risk assessments are not required.

There is potential for residential exposure from the existing registered uses of *tau*-fluvalinate. Current uses in outdoor residential settings include outside surfaces (crack and crevice), ant mound treatments (spot application) and use on roses, flowers, houseplants, ground covers, vines, ornamentals, shrubs and trees. These registered use patterns for *tau*-fluvalinate will not result in any non-dietary exposures to children. Therefore, since the only new information requiring this risk assessment update is the reduction of the FQPA safety factor for children < 6 y/o from 3X to 1X, there are no changes in the short- or intermediate-term residential or aggregate assessments from those previously presented in the DRA (Drew, 2016).

Spray Drift

Spray drift assessment results were presented in the DRA (D. Drew, Sept 6, 2016, D427869, D425975) and indicate that there are no risks are of concern at edge of treated fields. While there is a new turf transferable residue study available for tau-fluvalinate, it will not change the conclusion that there are no risks of concern at the field edge. Risk estimates from aerial and groundboom applications are not of concern past field edge for all registered uses.

Occupational Exposure and Risk

Tau-fluvalinate formulations currently include liquid, ready-to-use, and impregnated materials. This chemical may be applied as a perimeter treatment, crack and crevice treatment, and mound treatment around commercial and domestic dwellings. For treatment of landscape ornamentals and nursery uses, *tau*-fluvalinate may be applied using a broadcast spray, foliar spray, dip treatment, containerized treatment, and basal spray treatment. Greenhouse applications include broadcast, fogger, and bench treatments. For agricultural uses on carrots, and on *Brassica* and cole crops (CA SLNs), *tau*-fluvalinate may be applied using aerial or ground equipment. *Tau*-fluvalinate is also labeled for use in the brood chambers of bee hives. Treatments to bee hives are made using impregnated strips. The REI for all crops is 12 hours.

Occupational exposures and risks were previously estimated (Drew, 2016) and found not to be of concern. Therefore, since the only new information requiring this risk assessment update is the reduction of the FQPA safety factor for children < 6 y/o from 3X to 1X, there are no changes in the short- or intermediate-term occupational assessments from those previously presented in the DRA.

Appendix A: Summary of Toxicological Doses and Endpoints for *tau*-fluvalinate for Use in Human Health Risk Assessments

Summary of Toxicological Doses and Endpoints for *Tau*-fluvalinate for Use in Dietary and Non-Occupational Human Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/ Safety Factors**	**RfD/PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Children < 6 years old)	NOAEL = 1.0 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = X	Acute RfD = 0.01 mg/kg/day aPAD = 0.01 mg/kg/day	Combined chronic gavage/carcinogenicity study LOAEL = 2.5 mg/kg/day. Clinical signs of neurotoxicity including excessive salivation, pawing, abnormal stance, excessive lacrimation, ruffling and hyperactivity followed by hypoactivity.
Acute Dietary (Adults and Children ≥ 6 years old)	NOAEL = 1.0 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 0.01 mg/kg/day aPAD = 0.01 mg/kg/day	Combined chronic gavage/carcinogenicity study LOAEL = 2.5 mg/kg/day. Clinical signs of neurotoxicity including excessive salivation, pawing, abnormal stance, excessive lacrimation, ruffling and hyperactivity followed by hypoactivity.
Incidental Oral (Short-term)	NOAEL = 1.0 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100 (Children < 6 years old)	Combined chronic gavage/carcinogenicity study LOAEL = 2.5 mg/kg/day. Clinical signs of neurotoxicity including excessive salivation, pawing, abnormal stance, excessive lacrimation, ruffling and hyperactivity followed by hypoactivity.
Inhalation (Short- and intermediate - term)	LOAEC = 20 mg/m^3 (LDT) See Table 4.5.1 of DRA for HED calculations	UF_A = 3X UF_H = 10X UF_L = 10X FQPA SF= 1X (all populations)	Residential LOC for MOE = 300 (all populations)	Acute inhalation study LOAEL = 20 mg/m^3 (LDT). Increased glucose levels and decreased body temperature, rearing and forelimb grip strength in females in addition to soiled fur appearance.

Summary of Toxicological Doses and Endpoints for *Tau*-fluvalinate for Use in Dietary and Non-Occupational Human Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/ Safety Factors**	**RfD/PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animals to humans (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_S = sensitivity among children <6 years old (FQPA). UF_L = use of a LOAEL to extrapolate a NOAEL. aPAD = acute population adjusted dose. RfD = reference dose. N/A = not applicable. HEC = human equivalent concentration. HED = human equivalent dose. LDT = lowest dose tested.

Summary of Toxicological Doses and Endpoints for *Tau*-fluvalinate for Use in Occupational Human Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/ Safety Factors**	**RfD/PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (Short- and intermediate - term)	LOAEC = 20 mg/m^3 (LDT) See Table 4.5.1 for HED calculations	UF_A = 3X UF_H = 10X UF_L = 10X	Occupational LOC for MOE = 300	LOAEL = 20 mg/m^3 (LDT). Increased glucose levels and decreased body temperature, rearing and forelimb grip strength in females in addition to soiled fur appearance.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animals to humans (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_S = sensitivity among children <6 years old (FQPA). UF_L = use of a LOAEL to extrapolate a NOAEL. aPAD = acute population adjusted dose. RfD = reference dose. N/A = not applicable. HEC = human equivalent concentration. HED = human equivalent dose. LDT = lowest dose tested. FQPA SF = FQPA Safety Factor.