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Organization

WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 4

PRONet Duo

(V.K.A. Polymers Private Limited)

P-12406

Safety Assessment

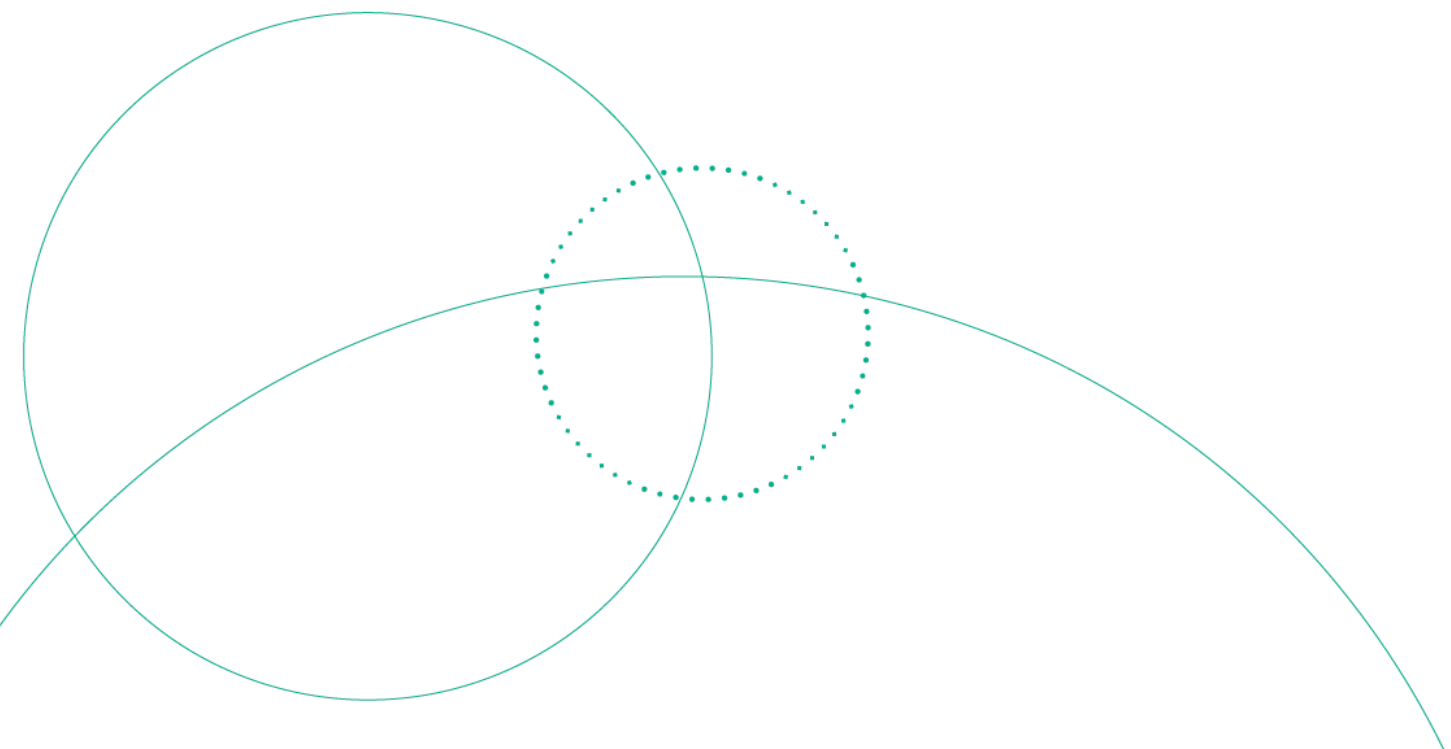


Table of Contents

1	Risk Assessment Summary.....	3
	1.1 Introduction	3
	1.2 Product Identification	3
	1.3 Active Ingredient (AI) Statement.....	3
	1.4 Summary of Findings.....	3
2	Human Health Risk Assessment	5
	2.1 Hazard Assessment	5
	2.1.1 PRONet Duo	5
	2.1.2 Active Ingredient – Bifenthrin	6
	2.1.3 Points of Departure (POD) and Reference Doses (RfD).....	8
	2.2 Exposure Assessment.....	10
	2.2.1 Sleeping Under Treated Net.....	12
	2.2.2 Washing Treated Nets.....	14
	2.2.3 Exposure via Breast Milk	15
	2.3 Risk Characterization.....	16
	2.4 Conclusions	18
3	References	20
4	Appendices	21
	Appendix A. Toxicity Profile: Bifenthrin Technical.....	21
	Appendix B. Hazard Assessment Bifenthrin	27

1 Risk Assessment Summary

1.1 Introduction

The applicant, V.K.A. Polymers Private Limited (India), submitted a product dossier to the World Health Organization Prequalification Unit Vector Control Product Assessment Team PQT-VCP) containing supporting data for the proposed product PRONet Duo and requested WHO assessment for the purpose of prequalification. PRONet Duo is an insecticide treated net (ITN) product intended for use in malaria endemic regions. The fabric is made from mono filament polyethylene yarn incorporated with two pesticidal active ingredients, bifenthrin (CAS No. 82657-04-3) and chlorfenapyr (CAS No. 122453-73-0).

1.2 Product Identification

Applicant:	V.K.A. Polymers Private Limited
Product name:	PRONet Duo LN
Other names:	N/A
Active ingredients (AI):	Bifenthrin (7 g/kg) and Chlorfenapyr (8 g/kg)
Target concentration:	245 mg/m ² Bifenthrin and 280 mg/m ² Chlorfenapyr
CAS no.:	82657-04-3 and 122453-73-0, respectively
Product type:	Insecticide-Treated Net (ITN)

1.3 Active Ingredient (AI) Statement

Bifenthrin [2-methylbiphenyl-3-ylmethyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)- 2,2-dimethylcyclopropanecarboxylate], is a pyrethroid, and like other pyrethroids, causes neurotoxicity from via disruption the voltage-gated sodium channels in the nervous system. Bifenthrin lacks an alpha-cyano moiety and is classified as a type I pyrethroid. Clinical signs characteristic of type I involves the nervous system characterized by tremors, hyperactivity, elevated body temperature and altered FOB observations.

Chlorfenapyr (CAS No. 122453-73-0) is an N-substituted halogenated pyrrole. It is a pro-insecticide that is converted to its active metabolite by P450 monooxygenases mechanisms.

1.4 Summary of Findings

In this human health risk assessment, the estimated risk ratios for PRONet Duo ITN are based on the target concentration of 245 mg/m² (7 g/kg) bifenthrin and 280 mg/m² (8 g/kg) chlorfenapyr.

This human health risk assessment supports the following conclusions:

- The existing toxicology database for bifenthrin and chlorfenapyr, as pertaining to PRONet Duo, are adequate for risk assessment and support PRONet Duo for its intended use as a vector control product.
- The use of PRONet Duo as an ITN does not present any unacceptable risk for all populations (adults, children, toddlers, and infants) sleeping under treated nets, for adults and children sleeping under and washing treated nets under a repeated exposure scenario, and for infants and newborns sleeping under treated nets and exposed via breast milk.

2 Human Health Risk Assessment

This human health risk assessment for PRONet Duo is conducted according to the “A Generic Risk Assessment Model for Insecticide-Treated Nets, 2nd edition” (GRAM) (WHO, 2018).

Risk assessment involves three steps: Hazard assessment, Exposure assessment and Risk characterization.

- **Hazard assessment** is the identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed. Authoritative evaluations are used as starting points for the risk assessment of insecticides. Examples of authoritative evaluations are: Joint Meeting on Pesticide Residues (JMPR), International Programme on Chemical Safety (IPCS), International Agency for Research and Cancer (IARC), United States Environmental Protection Agency (USEPA), European Food Safety Authority (EFSA).
- **Exposure assessment** is assessed in a “guideline scenario” which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information. Conservative high-end point estimates of the default distributions are used as defaults. No account is taken of intended misuse. All relevant routes of exposure are covered.
- In **risk characterization**, estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.

2.1 Hazard Assessment

The toxicology databases for bifenthrin and chlorfenapyr are adequate to determine the health hazard and to assess the risks associated with the proposed uses of PRONet Duo as an ITN.

Additionally, the human health risk assessment of chlorfenapyr is discussed and summarized in the “Generic Risk Assessment – Human Health – Chlorfenapyr (CAS No. 122453-73-0)” published by WHO in 2024 (WHO, 2024). This GRA-Chlorfenapyr is intended to be used as an example of the implementation of the “Generic Risk Assessment Model for Insecticide-Treated Nets, 2nd edition” (GRAM) (WHO, 2018) and points of reference for the assessment of new products which are formulated with these active ingredients. As such, model inputs for chlorfenapyr are taken from its respective GRA (WHO, 2024). Specific values for the GRA rely on conservative assumptions to formulate default values, therefore, this assessment does not use the refined specific inputs of chlorfenapyr in PRONet Duo.

2.1.1 PRONet Duo

WHO prequalification assessments incorporate acute toxicity information for technical materials, intermediate formulants, and end-use products. Generally, National Regulatory Authorities rely on acute toxicity data to serve as a basis for precautionary labeling. However, as an insecticide treated net (ITN) is both the formulation and the delivery mechanism of the active ingredient (AI), direct testing may not be possible using common methods for acute toxicity studies. Additionally, physically altering the ITN via shredding of products or extracting the AI content from the ITN is not recommended as it does not represent actual exposure scenarios. Generally, waivers are considered when a toxicity endpoint is not relevant to an end-use product based on the use scenarios and exposure potential. WHO PQT/VCP has outlined *Considerations for fulfilling the acute 6-pack requirement for insecticide-treated nets* necessary

for applicants to meet waiver approval for PQT/VCP (WHO, 2023). The applicant for PRONet Duo, V.K.A. Polymers Pvt. Ltd. (India), submitted a dossier to the WHO PQT/VCP containing supporting data and rationale in favor of being granted a waiver for the entirety of the standard 6-pack acute toxicity battery for the product PRONet Duo.

The WHO/PQT supports waiving the required 6-pack acute toxicity testing battery for the end-use product, PRONet Duo, based on the guidance from national and international authorities, current WHO/PQT practices, and the following weight of evidence argument:

- a) There are valid data available on each of the components in the product allowing for classification of the product by current practices.
- b) Synergistic effects between the two AIs, bifenthrin and chlorfenapyr, are not anticipated given that both AIs have different target organs and pesticidal modes of action, and that risk ratios are not of concern for either AI individually following WHO/PQT risk assessment analysis.
- c) Data demonstrating the toxic potential of the AIs are available and individual risk assessments for the AIs, as well as product exposure risk ratios, demonstrate generally low toxicity.
- d) The PRONet Duo ITN is both the formulation and the delivery mechanism of the AIs. Direct testing of the ITN is not possible using common methods for acute toxicity studies without obtaining inaccurate and misrepresentative data (physically altering the ITN via shredding of products or extracting the AI content from the ITN is not recommended as it does not represent actual exposure scenarios).
- e) Data from 6-pack acute toxicity studies on the end-use formulation would not impact the current risk ratios and conclusions of the WHO/PQT risk assessment.

2.1.2 Active Ingredient – Bifenthrin

This risk assessment relies heavily on toxicity studies conducted on the AI, bifenthrin, itself as it is one of the biologically active substances that produces a targeted pesticidal effect but can also have the potential to produce toxic biological effects. Bifenthrin is an active ingredient in the pyrethroid chemical class and toxicology studies have been evaluated by the Joint Meeting on Pesticide Residues (JMPR, 2009) and the United States Environmental Protection Agency (USEPA, 2020). Furthermore, a human health hazard on bifenthrin and an evaluation of pesticide residues in food are available from USEPA (2020) and JMPR (2009). The toxicity profile of bifenthrin is presented in Appendix A and the complete Hazard Assessment of bifenthrin is presented in Appendix B.

The intent of the hazard assessment of each AI (Appendix B) is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. For the active ingredient, PQT/VCP relies on these authoritative evaluations, does not state specific data requirements on behalf of VCP, and focuses on the studies and endpoints applicable to the risk assessment of the use patterns of VCPs. As such, the hazard assessment is not exhaustive in its summary of publicly available information characterizing the hazard of the AI. The toxicity database of bifenthrin has adequate studies for hazard characterization.

2.1.2.1 Bifenthrin Profile Statement

The target organ in mammalian toxicity studies on bifenthrin is the nervous system with the rat being the most sensitive species. There was no evidence of gender-related differences in the effects of bifenthrin exposure. Administration of bifenthrin to rats, mice, and dogs by the oral route resulted in characteristic type I pyrethroid neurotoxicity: tremors, staggered gait, loss of muscle coordination, twitching, and

changes in motor activity and functional observation battery (FOB) as the most common adverse effects. No reports of histopathological observation were noted in the nervous system. Bifenthrin did not cause developmental or reproductive toxicity. There is weak evidence for mutagenicity. The USEPA has classified bifenthrin as a Group C “Possible human carcinogen” based on an increased incidence of urinary bladder tumors in mice. Quantification of risk using a non-linear approach [i.e., reference dose (RfD)] will adequately account for all chronic toxicity, including potential carcinogenicity, that could result from exposure to bifenthrin (2020).

2.1.2.2 Acute Toxicity

Bifenthrin has moderate acute toxicity via the oral and inhalation route of exposure (GHS Category 3) and low toxicity (GHS Category 4) via the dermal route of exposure. It is not irritating to the eye and non-irritating to the skin. It resulted as a skin sensitizer in one dermal sensitization assay and not a sensitizer in another dermal sensitization assay (JMPR, 2009).

Table 2. Acute Toxicity of Bifenthrin Technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD ₅₀ > 50 ≤ 300 mg/kg	3	JMPR, 2009
Acute dermal toxicity	Rabbit and Rat	LD ₅₀ > 2000 mg/kg	4	JMPR, 2009
Acute Inhalation (nose only)	Rat	LC ₅₀ > 0.5 ≤ 1.0 mg/L	3	JMPR, 2009
Dermal irritation	Rabbit	Non-irritant	Not classified	JMPR, 2009
Eye irritation	Rabbit (female)	Non-irritant	Not classified	JMPR, 2009
Skin sensitization, Buehler	Guinea pigs (male)	Non-sensitizer	Not classified	JMPR, 2009
Skin sensitization, maximization test	Guinea pigs (female)	Positive	N/A	JMPR, 2009

2.1.2.3 Absorption, Distribution, Metabolism, and Excretion (ADME)

Further details on ADME for bifenthrin are available in Appendix B.

Oral absorption: According to a study reviewed by EFSA, 50% of administered bifenthrin was bioavailable based on bile cannulated rats showing 50% of compound excreted via the feces (EFSA, 2011). However, for purposes of ITNs, absorption estimates regarding the intake/external dose, as opposed to the systemic/bioavailability amount, result in more accurate predictions of risk ratios for PQT/VCP risk assessments. Therefore, 100% oral absorption has been retained for this assessment.

Dermal absorption: 26% selected based on a weight of evidence approach incorporating study results for bifenthrin from available dermal absorption studies having been considered in authoritative evaluations relied upon by WHO PQT/VCP.

Inhalation absorption: Absorption via the inhalation route is assumed to be 100% that via the oral route. Due to the lack of a long-term inhalation study, oral equivalent is used for inhalation risk assessment.

2.1.3 Points of Departure (POD) and Reference Doses (RfD)

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

2.1.3.1 Reference Doses

A reference dose (RfD) is an estimate of daily oral exposure (acute, aRfD) for a duration of 24 hours or less or chronic oral exposure (cRfD) for a duration of several months to a lifetime that is likely to be without an appreciable risk of deleterious effects during a lifetime. Both an aRfD and a cRfD can be derived from a NOAEL, LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

2.1.3.1.1 Acute Reference Dose (aRfD)

Bifenthrin was evaluated by the JMPR in 2009, at which time an aRfD of 0.01 mg/kg bw was established from a NOAEL of 1.3 mg/kg bw in an acute oral motor activity assessment study in rat (Wolansky, 2006). The NOAEL of 1.3 mg/kg bw is based on motor activity. An uncertainty factor of 100 to account for interspecies extrapolation (10) and intraspecies variabilities (10) is applied.

The USEPA (2020) used the BMDL_{1SD} of 3.1 mg/kg bw based on the decreased locomotor activity observed at BMD_{1SD} of 4.1 mg/kg bw in the acute neurotoxicity study by Wolansky *et al.*, 2006. This study/endpoint/dose was selected because it utilized a rat strain (Long-Evans) sensitive to neurotoxicity and measured an objective apical endpoint (locomotor activity) as the toxicity endpoint of concern. The BMD data analysis was utilized as a standardized method to address concerns of dose selection and dose spacing. An uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variation) was used to derive the aRfD.

$$\text{aRfD} = 3.1 \text{ mg/kg bw} \div 100 = 0.03 \text{ mg/kg bw}$$

2.1.3.1.2 Chronic Reference Dose (cRfD)

The USEPA (2020) did not establish a cRfD since the single-dose and repeated-dose studies with bifenthrin showed that repeat exposures did not result in lower PODs, i.e., there is no evidence of increasing toxicity with an increased duration of exposure. Therefore, the exposure assessments are conducted as a series of acute exposures, and these are protective scenarios in which exposure occurs for multiple days. Therefore, a cRfD was not established (USEPA, 2020).

cRfD = Not Established

2.1.3.1.3 Acceptable Daily Intake (ADI)

JMPR (2009) established an ADI of 0.01 mg/kg bw/day based on the NOAEL of 1.0 mg/kg bw/day established in the prenatal developmental toxicity study in rats based on maternal toxicity (increased incidence of tremors) and developmental toxicity (increased incidence of hydronephrosis without hydronephrosis in fetuses) at 2.0 mg/kg bw/day and the application of a 100-fold uncertainty factor.

$$ADI = 1.0 \text{ mg/kg bw/day} \div 100 = 0.01 \text{ mg/kg bw/day}$$

2.1.3.2 Selection of the Tolerable Systemic Dose (TSD)

The PQT/VCP selected the aRfD of 0.03 mg/kg bw established by the USEPA as the tolerable systemic dose (TSD_{AC}) for acute risk characterization.

$$TSD_{AC} = 0.03 \text{ mg/kg bw}$$

The PQT/VCP selected the cRfD of 0.01 mg/kg bw/day established by JMPR as the TSD for long-term risk characterization.

$$TSD = 0.01 \text{ mg/kg bw/day}$$

2.2 Exposure Assessment

The second step in performing a risk assessment is to estimate exposure to the insecticide AI chemical in the various groups of people potentially at risk. Exposure must take various parameters into consideration, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality and whether this exposure is intermittent or continuous.

Conservative, high-end point estimates of the default distributions are used as defaults in the exposure assessment. The default values may be modified by users of the models on a case-by-case basis and replaced with appropriate measured or otherwise improved point estimates or distributions, when applicable. Similarly, application of anthropometric and physiological datasets derived from the true target population, when available, is likely to yield more accurate exposure predictions.

The exposure assessment (i.e., exposure calculations) is evaluated according to the WHO-GRAM (2018) and chemical-specific data. The exposure assessment includes the appropriate subpopulations (adults, children [6-11 years], toddlers [1-2 years], infants [< 1 year]), the routes of exposure (oral, dermal, inhalation, and oral via breast milk), and the relevant scenarios (sleeping under the ITN, washing the ITN, and combined exposures). In the total exposure assessments, all relevant routes and different scenarios are summed to derive the total systemic dose (TSD). When an insecticide has significant acute toxicity (e.g. an aRfD) has been established by a regulatory authority, the risk is also estimated for acute exposure (TSD_{AC}). Exposure is assessed in a “guideline scenario”, which assumes that the insecticide is used according to the instructions given on the product label and in the WHO guideline information.

PRONet Duo contains bifenthrin (7 g/kg) and chlorfenapyr (8 g/kg), among other non-pesticidal ingredients. PRONet Duo is intended to be used for malaria control as an Insecticide Treated Net (ITN). The target doses of the product are 245 and 280 mg/m², for bifenthrin and chlorfenapyr, respectively.

The estimated systemic doses from inhalation, dermal and oral (hand-to-mouth and direct contact) exposures due to sleeping under and washing treated PRONet Duo nets, and from exposure through breast milk to chlorfenapyr were calculated in the chlorfenapyr GRA (WHO, 2024). Table 3 compares the characteristics of PRONet Duo to those selected as representative values for the GRA. While the total concentration of PRONet Duo is slightly higher than the values assessed in the GRA, a higher wash resistance index (WRI) indicates a lower fraction released in the wash (SF). Therefore, this product risk assessment can bridge the chlorfenapyr exposure assessment to its respective generic risk assessment.

Table 3. Comparison of the PRONet Duo Chlorfenapyr Characteristics vs. GRA selected representative values

Attribute	PRONet Duo	Chlorfenapyr GRA
Concentration by weight	8 g/kg net	6.5 g/kg net
Fabric Weight	35 g/m ²	40 g/m ²
Concentration by net area	280 mg/m ²	260 mg/m ²
Wash resistance index	97%	90%

The exposure assessment below evaluates exposure scenarios of the active ingredient, bifenthrin only.

The following abbreviations and default values are used throughout the bifenthrin exposure assessment*:

Abbreviation	Definition	Value	Data derived or Default Value
Abs _D	Dermal absorption	26%	Data derived
Abs _{inh}	Inhalation absorption	100%	Default, GRAM
Abs _O	Oral absorption	100%	Default, GRAM
AT	Average time	365days	Default, GRAM
BW	Body weight	60 kg/adult, 23.9 kg/children 10 kg/toddlers, 8 kg/infants 4.2 kg/newborns	Default, GRAM
Dose _{Mbw}	Maternal daily dose	0.001 µg/kg bw/day	Calculated
EHA	Exposed hand area	0.008 toddlers; 0.007 infants	Default, GRAM
ESA	Exposed skin areas	ITN: 0.408 m ² for adults; 0.225m ² for children; 0.115m ² for toddlers; 0.100 m ² for infants	Default, GRAM
FHM	Fraction of hand area mouthed	0.164 (75 th percentile)	Default, GRAM
H	Average time spent under net each day (hours)	Average sleeping times: Adult: 9 hours, Child: 10 hours Toddler: 12 hours, Infant (0-1 yr): 13 hours	Default, GRAM
IR	Ingestion rate of milk	0.66 kg/day	Default, GRAM
NoN	Number of nets washed per day	5	Default, GRAM
NoW	Number of washes per year (default 20 washes/3 years)	6.67	Default, GRAM
NM	net mouthed	m ² : 0.0014 m ² ; 75th percentile	Default, GRAM
SC	Surface concentration	245 mg/m ²	Data derived
SE	Salivary extraction fraction	57%; 75th percentile	Default, GRAM
SF	Surface fraction = fraction released in a wash	3%	Data derived
SN	Size of the net	15 m ² (default)	Default, GRAM
SoIC	Solubility constant	0.361 for lipid-soluble	Default, GRAM
SysD _{TWA}	TWA systemic dose	µg/kg bw/day	Calculated
SysD _{MAX}	Maximal systemic dose	µg/kg bw/day	Calculated
T _½	First-order kinetics half time in the body of the insecticide.	2 days	Data derived
TC	Target concentration	245 mg /m ² bifenthrin * 15% specification uncertainty = 281.8 mg /m ²	Data derived
Transl	Fraction translodged onto skin	6% of the amount on the surface (75% percentile)	Default, GRAM
VLH	Volume of liquid on hands	Adults: 8.2 mL Children: 4.3 mL	Default, GRAM
VLS	Volume of liquid on skin	adults 36.7 mL, children 17.6 mL, consisting of hands, fore arms, ½ of lower legs and ½ of feet covered by a liquid film of 0.1 m	Default, GRAM
VolW	Volume of washing water	4000 mL	Default, GRAM
VP	Vapor pressure	2.4 x 10 ⁻⁵ Pa at 25°C	Data derived
WRI	Wash resistance index	97%	Data derived

* Some values identified may not apply to the specific use pattern or scenarios assessed in the present assessment and should only serve as a general list.

2.2.1 Sleeping Under Treated Net

2.2.1.1 Estimated Inhalation Exposure

Inhalation exposure from impregnated materials is expected to be negligible, since many pesticides that are used in impregnated materials have relatively low vapor pressure. As a result, inhalation exposure is not expected to result in appreciable exposure when compared with dermal or non-dietary ingestion exposure (USEPA, 2012; GRAM, 2018).

In order to assess the need to evaluate inhalation exposure, a worst-case scenario (a toddler staying 24 hours/day at a saturated vapor pressure concentration) to the pesticide can be estimated as follows (GRAM, 2018).

$$\begin{aligned}\text{Systemic dose} &= 0.328 \times \text{MM} \times \text{VP} \\ \text{MM} &= \text{molecular mass of the pesticide} = 422.9 \text{ MM of bifenthrin} \\ \text{VP, its vapor pressure at } 25^\circ\text{C (Pa)} &= 2.4 \times 10^{-5} \text{ Pa at } 25^\circ\text{C}\end{aligned}$$

In the case of bifenthrin, the worst-case systemic dose following inhalation exposure is 0.0033 mg/kg bw (0.328 x 422.9 x 0.000024 = 0.0033). This systemic dose is used to calculate the risk ratios for acute and long-term inhalation exposure to bifenthrin.

$$\text{Acute Risk Ratio} = \frac{\text{Systemic dose (0.0033 mg/kg bw)}}{\text{TSD}_{\text{AC}} (0.03 \text{ mg/kg bw})} = 0.11$$

$$\text{Long-term Risk Ratio} = \frac{\text{Systemic dose (0.0033 mg/kg bw/day)}}{\text{TSD (0.01 mg/kg bw/day)}} = 0.33$$

The ratio is less than 1 for both acute and long-term exposure scenarios and therefore, there is no risk of concern via the inhalation route of exposure. Consequently, a more detailed inhalation risk assessment is not necessary.

2.2.1.2 Estimated Dermal Exposure

The estimated systemic dose due to dermal exposure while sleeping under nets is calculated as follows:

$$\text{SysD}_{\text{TWA}} (\text{Dermal}) = \frac{\text{Abs}_D \times \text{Transl} \times \text{ESA} \times \text{SF} \times \text{TC} \times 1000}{\text{BW}}$$

Table 4. Estimated Systemic Dose (TWA) from Dermal Exposure from Sleeping Under Nets

Population	Abs-D (%)	Transl (%)	ESA (m ²)	SF (%)	TC (mg/m ²)	BW (kg)	Systemic dose (µg/kg bw/day)
Guideline scenario							
Adults	26	6	0.408	3	281.8	60	0.897
Children	26	6	0.225	3	281.8	23.9	1.241
Toddlers	26	6	0.115	3	281.8	10.0	1.516
Infants	26	6	0.100	3	281.8	8.0	1.648

2.2.1.3 Estimated Oral Exposure

Oral exposure may occur from hand-to-mouth transfer and from direct mouthing activity such as mouthing, chewing and sucking for the subpopulations of infants and toddlers.

2.2.1.3.1 Indirect Oral Exposure – Hand-to-Mouth Transfer

The estimated systemic dose due to oral exposure via hand-to-mouth transfer is calculated as follows:

$$\text{SysD}_{\text{TWA}} (\text{Indirect Oral}) = \frac{\text{Abs}_O \times \text{SE} \times \text{Transl} \times \text{EHA} \times \text{FHM} \times \text{SF} \times \text{TC} \times 1000}{\text{BW}}$$

Table 5. Estimated Systemic Dose (TWA) from Indirect Oral Exposure – Sleeping and Hand-to-Mouth									
Population	Abs-O (%)	SE (%)	Transl (%)	EHA (m ²)	FHM	SF (%)	TC (mg/m ²)	BW (kg)	Systemic dose (µg/kg bw/day)
Guideline scenario									
Toddlers	100	57	6	0.008	0.164	3	281.8	10.0	0.038
Infants	100	57	6	0.007	0.164	3	281.8	8.0	0.041

2.2.1.3.2 Direct Oral Exposure

The estimated systemic time weighted average (TWA) dose due to oral exposure via mouthing, chewing and sucking is calculated as follows:

$$\text{SysD}_{\text{TWA}} (\text{Direct Oral}) = \frac{\text{Abs}_O \times \text{SE} \times \text{NM} \times \text{SF} \times \text{TC} \times 1000}{\text{BW}}$$

Table 6. Estimated Systemic Dose (TWA) from Direct Oral Exposure – Sleeping and Mouthing, Chewing, Sucking							
Population	Abs-O (%)	SE (%)	NM (m ²)	SF (%)	TC (mg/m ²)	BW (kg)	Systemic dose (µg/kg bw/day)
Guideline scenario							
Toddlers	100	57	0.0014	3	281.8	10.0	0.675
Infants	100	57	0.0014	3	281.8	8.0	0.843

2.2.1.4 Combined Exposure from Sleeping Under Treated Nets

A total daily systemic exposure to bifenthrin while sleeping under a treated net was calculated in as summation of the values for inhalation, dermal and oral routes of exposure given above.

Table 7. Estimated Total Systemic Dose Exposure from Sleeping Under Treated Nets (µg/kg/day)					
Scenario	Inhalation Exposure	Dermal Exposure	Oral Exposure		Total Systemic Dose
			Indirect	Direct	
Adult	Negligible	0.897	-	-	0.897
Children	Negligible	1.241	-	-	1.241
Toddler	Negligible	1.516	0.038	0.675	2.229
Infant	Negligible	1.648	0.041	0.843	2.533

2.2.2 Washing Treated Nets

Exposure due to dermal absorption and oral transfer from hands may occur during washing of nets. This exposure is estimated for adults and children only.

2.2.2.1 Estimated Dermal Exposure

2.2.2.1.1 Repeated (Long-term) exposure

The estimated time weighted average (TWA) systemic dose from repeated dermal exposure to bifenthrin during washing of ITNs is calculated as follows:

$$\text{SysD}_{\text{TWA}} (\text{Dermal}) = \frac{\text{NoW} \times \text{NoN} \times \text{Abs}_D \times \text{VSL} \times \text{SF} \times \text{TC} \times \text{SN} \times 1000}{\text{VolW} \times \text{BW} \times \text{AT}}$$

Table 8. Estimated Systemic Dose (TWA) from Repeated Dermal Exposure – Washing Nets

Population	Abs-D (%)	NoW (washes)	NoN (Nets)	VLS (mL)	SF (%)	TC (mg/m ²)	SN (m ²)	VolW (mL)	BW (kg)	AT (days)	Systemic dose (µg/kg bw/day)
Guideline scenario											
Adults	26	6.67	5	36.7	3	281.8	15	4000	60	365	0.460
Children	26	6.67	5	17.6	3	281.8	15	4000	23.9	365	0.554

2.2.2.1.2 Acute (Maximum) Exposure

The estimated acute (maximum) systemic dose from bifenthrin due to potential dermal exposure during washing of ITNs is calculated as follows:

$$\text{SysD}_{\text{MAX}} (\text{Dermal}) = \frac{\text{NoN} \times \text{Abs}_D \times \text{VLS} \times \text{SF} \times \text{TC} \times \text{SN} \times 1000}{\text{VolW} \times \text{BW}}$$

Table 9. Estimated Systemic Dose (Maximum) from Dermal Exposure – Washing Nets

Population	Abs-D (%)	NoN (Nets)	VLS (mL)	SF (%)	TC (mg/m ²)	SN (m ²)	VolW (mL)	BW (kg)	Systemic dose (µg/kg bw/day)
Guideline scenario									
Adults	26	5	36.7	3	281.8	15	4000	60	25.2
Children	26	5	17.6	3	281.8	15	4000	23.9	30.3

2.2.2.2 Estimated Oral Exposure – Hand-to-Mouth

2.2.2.2.1 Repeated (Long-term) Exposure

The estimated oral systemic time weighted average (TWA) dose due to oral exposure via hand-to-mouth is calculated as follows:

$$\text{SysD}_{\text{TWA}} (\text{Oral}) = \frac{\text{NoW} \times \text{NoN} \times \text{Abs}_O \times \text{VLH} \times \text{SF} \times \text{TC} \times \text{FHM} \times \text{SN} \times 1000}{\text{VolW} \times \text{BW} \times \text{AT}}$$

Table 10. Estimated Systemic Dose (TWA) from Repeated Oral Exposure – Washing Nets and Hand to Mouth

Population	Abs-O (%)	NoW (washes)	NoN (Nets)	VLH (mL)	SF (%)	TC (mg/m ²)	FHM	SN (m ²)	VolW (mL)	BW (kg)	AT (days)	Systemic dose (µg/kg bw/day)
Guideline scenario												
Adults	100	6.67	5	8.2	3	281.8	0.164	15	4000	60	365	0.065
Children	100	6.67	5	4.3	3	281.8	0.164	15	4000	23.9	365	0.085

2.2.2.2.2 Acute (Maximum) Exposure

The estimated systemic acute oral (maximum) dose due to oral exposure via hand-to-mouth is calculated as follows:

$$\text{SysD}_{\text{MAX}} (\text{Oral}) = \frac{\text{NoN} \times \text{AbsO} \times \text{VLH} \times \text{SF} \times \text{TC} \times \text{FHM} \times \text{SN} \times 1000}{\text{VolW} \times \text{BW}}$$

Table 11. Estimated Systemic Dose (Maximum) from Acute Oral Exposure – Washing Nets and Hand to Mouth

Population	Abs-O (%)	NoN (Nets)	VLH (mL)	SF (%)	TC (mg/m ²)	FHM	SN (m ²)	VolW (mL)	BW (kg)	Systemic dose (µg/kg bw/day)
Guideline scenario										
Adults	100	5	8.2	3	281.8	0.164	15	4000	60	3.552
Children	100	5	4.3	3	281.8	0.164	15	4000	23.9	4.676

2.2.2.3 Combined Exposure from Washing Nets

Estimated total systemic exposure from dermal and inhalation exposure due to washing nets.

Table 12. Estimated Total Exposure from Dermal and Oral Due to Washing Nets (µg/kg/day)

Scenario (Guideline)	Dermal exposure	Oral exposure	Estimated systemic dose (µg/kg/day)
Estimated TWA			
Adults	0.460	0.065	0.525
Children	0.554	0.085	0.640
Estimated maximal			
Adults	25.2	3.552	28.756
Children	30.3	4.676	35.020

2.2.3 Exposure via Breast Milk

Newborns might be exposed to bifenthrin through breast milk of lactating mothers who sleep under the ITN and/or wash the nets. Since data on the actual excretion in milk are not available, an upper bound of the exposure from the mother's milk can be roughly estimated from the physicochemical characteristics and kinetics of the pesticide (WHO, 2018). The estimated systemic dose to the newborn is calculated

based on the estimated systemic dose to the mother. Estimates for systemic maximal and TWA doses from exposure via breast milk are calculated as follows:

$$\text{SysD}_{\text{TWA (Breast milk)}} = \frac{\text{SolC} \times \text{Dose}_{\text{Mbw}} \times T_{1/2} \times \text{IR} \times \text{Abs}_o}{\text{BW}}$$

Since inhalation exposure to the mother sleeping under the net is negligible, the maximum systemic dose and TWA doses are derived from dermal exposure sleeping under the net and oral exposure through washing of nets.

Dose_{Mbw} (Maternal dose) = Total exposure from sleeping under net + Total exposure from washing of net

Dose_{Mbw} (TWA) = 0.897 + 0.525 µg/kg bw/day = 1.422 µg/kg bw/day

Dose_{Mbw} (Maximum) = 0.897 + 28.756 µg/kg bw/day = 29.653 µg/kg bw/day

The estimated maximum systemic dose from exposure via breast milk is shown as follows:

Table 13. Estimated Systemic Dose (TWA and Maximal) from Exposure to Breast Milk							
Population	SolC	Dose (µg/kg bw)	T _{1/2} (days)	IR (kg/day)	Oral absorption (%)	BW (kg)	Systemic dose (µg/kg/day)
TWA							
Newborns	0.361	1.422	2	0.66	100	4.2	0.161
Infants	0.361	1.422	2	0.66	100	8.0	0.085
Maximal daily dose							
Newborns	0.361	29.653	2	0.66	100	4.2	3.364
Infants	0.361	29.653	2	0.66	100	8.0	1.766

2.3 Risk Characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring from the use of the insecticide under defined exposure conditions. Risk characterization consists of comparing the estimate of total exposure (i.e., estimated total systemic dose) with the Tolerable Systemic dose (TSD) established in the hazard assessment. The TSD is the same as the ADI or the cRfD established for the active ingredients (WHO, 2018).

$$\text{Ratio} = \frac{\text{Estimated total systemic dose}}{\text{TSD}}$$

When an insecticide has significant acute toxicity (e.g. aRfD), the risk is also estimated for acute exposure. (WHO, 2018)

$$\text{Ratio} = \frac{\text{Estimated total systemic dose}}{\text{TSD}_{\text{AC}}}$$

When the ratios are less than 1, the health risk is deemed acceptable. Ratios greater than 1 may indicate possible health risks, in which case steps may be taken to reduce the risk, such as changing the

recommended operational conditions or the amount of active ingredient in the technical product. A risk benefit analysis in which the risks of potential toxicity are compared with potential health benefits (disease prevention) may be needed in some cases (WHO, 2018).

The ratios for all populations (adults, children, toddlers and infants) sleeping under the net, for adults and children washing the net, and for newborn/infants exposed via breast milk to bifenthrin are presented.

Table 14. Exposure Estimates and Risk Ratios for Sleeping Under Treated Nets
(µg/kg bw/day)

Population	Dermal Exposure	Indirect Oral Exposure	Direct Oral Exposure	Total Exposure	TSD* (µg/kg bw/day)	Risk ratio
Adults	0.897	-	-	0.897	10	0.09
Children	1.241	-	-	1.241	10	0.12
Toddler	1.516	0.038	0.675	2.229	10	0.22
Infant	1.648	0.041	0.843	2.533	10	0.25

*TSD = 0.01 mg/kg bw/day

Table 15. Exposure Estimates and Risk Ratios for Washing Treated Nets
(µg/kg bw/day)

Population	Dermal Exposure	Oral Exposure	Total Exposure	TSD _{AC} *	TSD*	Risk ratio
Repeat Exposure (TWA)						
Adults	0.460	0.065	0.525	N/A	10	0.05
Children	0.554	0.085	0.640	N/A	10	0.06
Acute Exposure (Maximum)						
Adults	25.2	3.552	28.756	30	N/A	0.96
Children	30.3	4.676	35.020	30	N/A	1.17

*TSD_{AC} = 0.03 mg/kg bw

*TSD = 0.01 mg/kg bw/day

Table 16. Exposure Estimates and Risk Ratios for All Populations Sleeping Under and Washing Treated Nets
(µg/kg bw/day)

Population	Sleeping Under Nets (Combined)	Washing of Nets (Combined)	Total Exposure	TSD _{AC} *	TSD*	Risk ratio
Repeat Exposure (TWA)						
Adults	0.897	0.525	1.422	N/A	10	0.14
Children	1.241	0.640	1.881	N/A	10	0.19
Acute Exposure (Maximum)						
Adults	0.897	28.756	29.653	30	N/A	0.99
Children	1.241	35.020	36.261	30	N/A	1.21

*TSD_{AC} = 0.03 mg/kg bw

*TSD = 0.01 mg/kg bw/day

Table 17. Exposure Estimates and Risk Ratios for Populations Sleeping Under Treated Nets and Consuming Breast Milk ($\mu\text{g}/\text{kg bw}/\text{day}$)

Population	Total Exposure Sleeping Under Nets (oral direct + oral indirect + dermal)	Breast Milk Exposure	Total Exposure	TSD _{AC} *	TSD*	Risk ratio
Repeat Exposure (TWA)						
Newborn	N/A	0.161	0.161	N/A	10	0.02
Infant	2.533	0.085	2.618	N/A	10	0.26
Acute Exposure (Maximum)						
Newborn	N/A	3.364	3.364	30	N/A	0.11
Infant	2.533	1.766	4.299	30	N/A	0.14

*TSD_{AC} = 0.03 mg/kg bw

*TSD = 0.01 mg/kg bw/day

For all subpopulations of users sleeping under ITNs assessed in this risk assessment, the risk ratios are all below 1.

For all relevant subpopulations of users washing nets the risk ratios are all below 1 with the exception of acute exposure of that for children, which resulted in a ratio slightly above 1.

For all relevant subpopulations, combining sleeping and washing nets, estimates of the risk ratios are below 1 with the exception of that for acute exposure, again, for children, which resulted in a ratio slightly above 1.

Furthermore, all relevant subpopulations sleeping under nets and consuming breast milk risk resulted in ratios that are well below 1.

2.4 Conclusions

Based on the selected inputs and the calculations of risk ratios as per the GRAM (2018) it was concluded that there were no unacceptable risks identified for all users sleeping under the ITN. Furthermore, there were no unacceptable risks identified for newborns nor infants exposed through the consumption of breast milk.

The exposure scenarios for washing ITNs and aggregation of washing and sleeping under ITNs leads to the characterization of risk in two ways:

1. The time-weighted average risk ratio is based on the chronic exposure and chronic TSD. In this case, for ProNet Duo, there are no identified risks of concern.
2. The maximal acute risk ratio is based on the highest value measured during a single exposure event. In this case, for ProNet Duo, there was a slight exceedance of the risk ratio for children's dermal exposure related to the washing of ITNs, not from sleeping under ITNs.

Given the driver of exposure concern for ProNet Duo (bifenthrin) is dermal exposure, the highest maximal acute dermal exposure risk comes from the assumptions set forth in the GRAM (2018) that 5

nets are washed at a time, the volume of water used for washing is 4L, gloves are not worn, and that contaminated skin is not rinsed immediately after the washing of the net. Furthermore, it is assumed that the concentration of bifenthrin in all ITNs washed is at the highest allowable concentration of the manufacturing release specification. Given the conservative nature of these assumptions, a positive prequalification decision could be made for PRONet Duo.

All risk ratios for adults washing nets and combined washing and sleeping under ITNs for repeated exposure, and adults for acute exposure, resulted in acceptable risk ratios.

No risks were estimated for infants and newborns sleeping under the treated nets and exposed through breast milk for both repeated and acute exposure.

The use of PRONet Duo ITN used in the course of vector control, presents acceptable risk ratios for adults, children, toddlers, and infants sleeping under the treated nets for both repeated and acute exposure.

The assessment of the submitted information on safety supports prequalification of the ITN product, PRONet Duo containing bifenthrin at 245 mg/m² and chlorfenapyr at 280 mg/m².

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4 Appendices

Appendix A. Toxicity Profile: Bifenthrin Technical

Table A1. Acute Toxicity of Bifenthrin Technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD ₅₀ > 50 ≤ 300 mg/kg bw	3	JMPR, 2009
Acute dermal toxicity	Rabbit and Rat	LD ₅₀ > 2000 mg/kg	4	JMPR, 2009
Acute Inhalation (nose only)	Rat	LC ₅₀ > 0.5 ≤ 1.0 mg/L	3	JMPR, 2009
Dermal irritation	Rabbit	Non-irritant	Not classified	JMPR, 2009
Eye irritation	Rabbit (female)	Non-irritant	Not classified	JMPR, 2009
Skin sensitization, Buehler	Guinea pigs (male)	Non-sensitizer	Not classified	JMPR, 2009
Skin sensitization, maximization test	Guinea pigs (female)	Positive		JMPR, 2009

Table A2. Summary of Subchronic, Chronic, and Carcinogenicity Studies with Bifenthrin

Study dose levels	Results (mg/kg bw/day)	Reference
21-day dermal study, rats 6 hours/day 5 days/week 0, 25, 50, 100, 1000 mg/kg/day Purity: 93.2%	NOAEL = 47 mg/kg/day BMDL ₁₀ = 96.3 mg/kg/day LOAEL = 93 mg/kg/day based on staggered gait (males) and exaggerated hind limb flexion (females) BMD ₁₀ = 187.0 mg/kg/day based on exaggerated hind limb flexion	JMPR, 2009; USEPA, 2020
21/28-day Dermal toxicity - rabbits 6 hours/day 0, 25, 50, 100, 500 mg/kg/day Purity: 88.35%	NOAEL = 88 mg/kg bw/day LOAEL = 442 mg/kg bw/day based on loss of muscle coordination and increased incidence of tremors.	JMPR, 2009; USEPA, 2020
90-day Oral Toxicity, rats Dietary 0, 12, 50, 100 and 200 ppm (equivalent to 0, 0.88, 3.8, 7.5 and 15 mg/kg bw/day in males and 0, 1.04, 4.3, 8.5 and 17.2 mg/kg bw/day in females, respectively) Purity: 91.4%	NOAEL = 3.8 mg/kg/day (males); 4.3 mg/kg/day (females) LOAEL = 7.5 mg/kg/day (males); 8.5 mg/kg/day (females) based on increased incidence of tremors.	JMPR, 2009; USEPA, 2020

Table A2. Summary of Subchronic, Chronic, and Carcinogenicity Studies with Bifenthrin

Study dose levels	Results (mg/kg bw/day)	Reference
90-day Oral Toxicity, beagle dogs Gelatin capsules 0, 2.5, 5.0, 10.0 and 20.0 mg/kg bodyweight/day Purity: 88.35%	NOAEL = 2.21 mg/kg/day LOAEL = 4.42 mg/kg/day based on increased incidence of tremors.	USEPA, 2020
Carcinogenicity, mice 18-month dietary 0, 50, 200, 500 and 600 ppm (equivalent 0, 76, 29, 74 and 92 mg/kg bw/day in males and 0, 10, 37, 93 and 110 mg/kg bw/day in females, respectively) Purity: 88.35%	NOAEL = 6.7/8.8 mg/kg/day (m/f) LOAEL = 25.6/32.7 mg/kg/day (m/f) based on increased incidence of tremors. There was evidence of carcinogenicity.	JMPR, 2009; USEPA, 2020
Chronic/carcinogenicity -rats Dietary 0, 12, 50, 100 and 200 ppm Purity: 88.35%	NOAEL = 4.7/3.0 mg/kg/day (m/f) mg/kg bw/day LOAEL = 9.7/6.1 mg/kg/day (m/f) based on increased incidence of tremors. No conclusive evidence of carcinogenic potential.	USEPA, 2020
1-year dog study Gelatin capsule 0, 0.75, 1.50, 3.00 and 5.00 mg/kg/day Purity: 88.35%	NOAEL = 1.3 mg/kg bw/day LOAEL = 2.7 mg/kg bw/day based on increased incidence of tremors.	JMPR, 2009; USEPA, 2020

Table A3. Summary of Developmental Toxicity and Reproduction Studies with Bifenthrin

Study dose levels	Results (mg/kg bw/day)	Reference
Developmental toxicity, rats Gavage Days 6-15 of gestation 0 (vehicle), 0.50, 1.0 and 2.0 mg/kg/day Vehicle: corn oil Purity: 88.35%	Maternal NOAEL = 0.88 mg/kg bw/day Maternal LOAEL = 1.77 mg/kg bw/day based on tremors during gestation Dev. Tox NOAEL = 1.77 mg/kg bw/day Dev. Tox LOAEL = Not determined	USEPA, 2020
Developmental toxicity, rats Dietary Dietary 0, 30, 60, 90, or 200 ppm (equivalent to 0, 2.5, 5.0, 7.4, and 16.3 mg/kg bw/day) Purity: 95.3%	Maternal NOAEL = 7.4 mg/kg bw/day Maternal LOAEL = 16.3 mg/kg bw/day based on clinical signs and decreased food consumption, body weight gains, and body weight gains adjusted for gravid uterine weight. Dev. Tox NOAEL = 16.3 mg/kg bw/day Dev. Tox LOAEL = Not determined	JMPR, 2009
Developmental toxicity, rabbits Days 7-19 of gestation 0 (vehicle), 2.67, 4.0 and 8.0 mg/kg/day. Individual doses were adjusted daily in order to compensate for changes in maternal body weights.	Maternal NOAEL = 2.67 mg/kg bw/day Maternal LOAEL = 4.0 mg/kg bw/day based on treatment-related head and forelimb twitching.	JMPR, 2009

Vehicle: corn oil Purity: 88.35%	Dev. Tox NOAEL = greater than 8.0mg/kg bw/day Dev. Tox LOAEL = Not determined	
Reproduction Toxicity, rats Dietary 0, 30, 60, or 100 ppm (approximately equivalent to 0, 1.5, 3.0 and 5.0 mg/kg/day Purity: 88.35%	Parental systemic NOAEL = 3.0 mg/kg bw/day Parental systemic LOAEL = 5.0 mg/kg bw/day based on tremors and decreased body weight; not observed for males. Reproductive NOAEL = 5.0 mg/kg bw/day LOAEL = not observed	USEPA, 2020

Table A4. Summary of Genotoxicity Studies with Bifenthrin

Study dose levels	Results	Reference
Bacterial reverse mutation assay (Ames assay) - <i>Salmonella typhimurium</i> Dose level: 0, 10, 33, 67, 100, 33, 667, 1000, 3.333, 6.667, 10.000 µg/plate in mutation test 1 0, 375, 1.875, 3.750 and 7.500 µg/plate in mutation test 2 (in both the presence and absence of S-9 mix) 5 Strains with and without metabolic activation. Microsomes from male and female Swiss Webster mice and male Sprague Dawley rats Purity: 91.4%	Not mutagenic in all <i>Salmonella typhimurium</i> tested in both presence and absence of metabolic activation (S9-mix)	JMPR, 2009
Mouse Lymphoma Mutagenesis Assay - Mouse Lymphoma Cells Dose level: 0.24, 0.18, 0.13, 0.10, 0.075, 0.056, 0.042, 0.032, 0.024, 0.018 µg/ml without metabolic activation. 0.10, 0.075, 0.056, 0.042, 0.032, 0.024, 0.018, 0.03, 0.010, 0.0075 µg/ml with metabolic activation L5178Y TK+/- Rat liver S-9 Purity: 88.35%	Weak positive results with and without metabolic activation	JMPR, 2009
<i>In vivo</i> Cytogenetics – rats Dose level: 30, 10 and 3 mg/kg/day for five consecutive days. 5-day exposure oral by gavage Purity: 88.35%	Negative	JMPR, 2009
<i>In vitro</i> Chromosome Aberration - Chinese Hamster Ovary (CHO) Dose level: 10.00, 30.00, 60.00 and 100.00 µg/mL in DMSO. Tested to 10,000 µg/mL with and without activation.	Negative	JMPR, 2009

Purity: 88.35%		
HGPRT Assay – CHO Test 1: 2.5, 5.0, 10, 25, 50, 100, 250, 500, 1000 µg/mL Test 2: 250, 500, 750, 1000 µg/mL (without S9), 20, 30, 40, 50 µg/mL (with S9) With and without metabolic activation Purity: 88.35%	Inconclusive w/ metabolic activation	JMPR, 2009
In vitro Gene Mutation Preliminary cytotoxicity test – CHO Dose levels: range of 0.10 to 10.000 µg/ml Main study: 100, 500, 1.000, 2.500, 5.000, 10.000 µg/ml in acetone Tested to 10,000 µg/mL with and without activation. Purity: 88.35%	Not mutagenic	JMPR, 2009
HGPRT Gene Mutation Preliminary cytotoxicity test - Mouse Lymphoma Cells Dose levels: 1, 5, 10, 30, 100 µg/ml Main study: 1.0, 30.0, and 60.00 µg/mL in acetone. L5178Y Dosed to the limit of solubility (500 µg/mL) Purity: 88.35%	Not mutagenic	JMPR, 2009
Unscheduled DNA Synthesis Initial cytotoxicity test – rat hepatocytes Ten treatments ranging from 100 to 0.005 µg/ml UDS assay: 0.01, 0.05, 0.1, 0.5, 1.0, 2.0 µg/ml in acetone. Tested at levels up to 100 µg/mL in DMSO. Purity: 88.35%	Marginally positive at one highly toxic dose. Two repeat assays yielded negative responses	JMPR, 2009
Cell Transformation - Mouse Embryo Cells (BALB/3T3) No metabolic activation 3 - 100 µg/mL in DMSO Purity: 88.35%	Negative	JMPR, 2009
Sex Linked Recessive Lethal – Genotoxicity Drosophila Concentrations of 50 and 100 µg/mL Purity: 88.35%	Negative	JMPR, 2009
In vitro Sister Chromatid Exchange – CHO With and without metabolic activation up to 60 µg/mL in DMSO Purity: 88.35%	Negative	JMPR, 2009

Table A5. Summary of Neurotoxicity Studies with Bifenthrin

Study dose levels	Results (mg/kg bw/day)	Reference
Acute neurotoxicity study - Rat Undiluted (gavage) 14-day observation Single oral dose: 0, 10, 35, 75 mg/kg Purity: 93.7%	NOAEL = 35 mg/kg (32.8 mg ai/kg) LOAEL = 75 mg/kg (70.3 mg ai/kg) based on mortality (females only), clinical and FOB findings and differences in motor activity. No vehicles utilized and heated to 80°C to liquefy.	USEPA, 2020
Subchronic Neurotoxicity – rats 13 weeks, dietary 0 or 50 ppm (10 animals/sex/group) or 100, 200, or 300 ppm (5 animals/sex/group) Purity: 93.7%	NOAEL = (50 ppm) 2.9/3.7 mg/kg/day (m/f) LOAEL = 6.0/7.2 mg/kg/day based on neuromuscular findings (tremors, changes in grip strength and landing foot-splay).	USEPA, 2020
Developmental Neurotoxicity - rats	Maternal NOAEL = 3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation. LOAEL = 7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation based on clinical signs of neurotoxicity (tremors, clonic convulsions, and increased grooming counts.) Offspring NOAEL = 3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation. Offspring LOAEL = 7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation based on clinical signs of neurotoxicity (increased grooming counts).	USEPA, 2020

Table A6. Summary of Dermal Absorption Studies with Bifenthrin

Study dose levels	Results (mg/kg bw/day)	Reference
Dermal penetration – rats Applied as a dilution of a liquid formulation. Achieved average dose (mg/kg bw) Group I: 0.18; Group II: 1.96; Group III: 19.38 Purity: 95.49%	Dermal absorption 10-hours after administration of test material was 55.4% of the applied dose in animals dosed w/49.2 ug/10.8 sq. cm (4.6 ug/sq. cm))	USEPA, 2020
Dermal penetration – rats Recover times: 0, 4, 10, and 24h post-dosing	Group A: Means of 4.6, 14.2, 12.8, and 14.7% total dose, respective to the time course were recovered from the skin. Corresponding percentages in the wash were 45, 81, 79, 70%, respectively. Group B: Means of 20, 38, 42, and 41% recovered from skin, respective, to the time course. Corresponding percentages in the wash were 74, 51, 41, and 38%, respectively.	USEPA, 2020
<i>In vitro</i> dermal absorption Applied to human and rat epidermal membranes in static diffusion cells.	(Hughes and Edwards, 2010) For rat: receptor fluid 2% at 48h, skin 33-43%, tape stripping 24%, 20% remaining on skin, skin wash removed 59-	USEPA, 2020

Study groups: Time course for 24h and 48h, tape strip study, skin metabolism study	69% of applied doses. Only parent bifenthrin was detected in skin. Human: receptor fluid 1-2% at 48h, skin retained 14-21%, tape stripping 20% with 5% remaining on skin, skin wash removed 75-83% of applied doses. Rat absorption: 45.5% Human absorption: 26.2%	
Dermal Penetration - rats	Small amounts of radioactivity were present in blood, excrement, and carcasses, with almost all of the absorbed radioactivity localized in skin at the application site, and in the skin adjacent to the application site. Average percentages of FMC 54800 (bifenthrin) dosages absorbed at 10 hours were 55.8%, 54.1%, and 37.5% for the 49.2, 514 and 5253 ug/rat groups, respectively. Corresponding percentages for the 3 groups at the 0.5 hour sacrifice were 54.6%, 56.4% and 52.5%, so the percentage absorption did not seem to depend on duration. At 10 hours and the lowest dose level, the percentages present were as follows: excreta < 0.44%, carcass < 1.8%, skin at application site 5.5%.	USEPA, 2020

Table A7. Summary of Special Studies with Bifenthrin

Study dose levels	Results (mg/kg bw/day)	Reference
Wolansky <i>et al.</i> (2006) Acute motor activity assessment – male rats	Threshold dose*, 1.25 ±0.31 mg/kg bw ED ₃₀ [^] = 3.21 ±0.32 mg/kg bw BMDL1SD is 3.1 mg/kg and the BMD1SD is 4.1mg/kg bw based on reductions in locomotor activity	JMPR, 2009; USEPA, 2016
Acute oral toxicity (Weiner <i>et al.</i> , 2009)	The BMDL ₂₀ was 0.4 mg/kg bw and the BMD ₂₀ was 14.3 mg/kg bw based on multiple alterations in FOB parameters	USEPA (2020)

*The threshold dose is defined as an estimate of the highest no-effect dose level at which treated rats did not display any decreases in motor activity.

[^]ED₃₀ is defined as the dose associated with a 30% decrease in motor activity. From: Wolansky MJ, Gennings C, Crofton, KM (2006) Relative potencies for acute effects of pyrethroids on motor function in rats. *Toxicol Sci* 89: 271–277.

Appendix B. Hazard Assessment

WHO Prequalification Programme / Vector Control Product Assessment

WHO

Hazard Assessment:

Bifenthrin

(CAS No. 82657-04-3)

1 Introduction to Bifenthrin

The use of vector control products (VCPs) is critical in the protection of global human health by combatting and preventing the transmission of major vector-borne diseases. Through the procedures of Prequalification Unit Vector Control Product Assessment Team (PQT/VCP), VCPs and public health pesticide active ingredients are assessed to determine that they can be used safely and effectively and are manufactured to a high-quality standard. The intent of the hazard assessment of each active ingredient (AI) is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. PQT/VCP relies on these authoritative evaluations, focusing on the studies and endpoints applicable to the risk assessment of the use patterns of VCPs. As such, this hazard assessment is not exhaustive in its summary or assessment of publicly available information characterizing the hazard of the AI.

Bifenthrin [2-methylbiphenyl-3-ylmethyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)- 2,2-dimethylcyclopropanecarboxylate], is a pyrethroid, and like other pyrethroids, causes neurotoxicity from interaction with sodium channels. Bifenthrin is registered for use on crops, ornamentals, and outdoor commercial and residential settings. Several formulations of bifenthrin are also approved for use in commercial and residential outdoor and indoor sites as well as in treated nets. Pyrethroids act through disruption of the voltage-gated sodium channels in the nervous system, resulting in neurotoxicity.

Pyrethroids disrupt the voltage-gated sodium channels in the nervous system, resulting in neurotoxicity and have historically been classified into two groups based on chemical structure and toxicological effects: type I and type II. Bifenthrin lacks an alpha-cyano moiety and is classified as a type I pyrethroid. Clinical signs characteristic of type I involves the nervous system characterized by tremors, hyperactivity, elevated body temperature and altered FOB observations. The term T-syndrome (from tremor) has been applied to type I responses.

A human health hazard assessment on bifenthrin and an annual summary report is available from the US Environmental Protection Agency (USEPA, 2020) and the Joint Meeting on Pesticide Residues (JMPR, 2009). The bifenthrin toxicity database contains a complement of toxicity studies used to develop the hazard characterization and were considered in designating the points of departure (PODs).

2 Hazard Characterization

Only studies relevant to the hazard evaluation are discussed, for a full description of all toxicology studies related to the active ingredient, the reader is referred to the references cited. There is sufficient information on the toxicity of the active ingredient, bifenthrin technical, to conduct a human health hazard assessment. Administration of bifenthrin to rats, mice, and dogs by the oral route resulted in characteristic type-I pyrethroid neurotoxicity: tremors, staggered gait, loss of muscle coordination, twitching, and changes in motor activity and functional observation battery (FOB) as the most common adverse effects. No reports of histopathological observation were noted in the nervous system. There was no evidence of gender-related differences in the effects of bifenthrin exposure in the database. The principal target organ in all studies and in all species was the nervous system with the rat being the most sensitive species.

Bifenthrin did not cause developmental or reproductive toxicity. There is weak evidence for mutagenicity. The USEPA has classified bifenthrin as a Group C “Possible human carcinogen” based on an increased incidence of urinary bladder tumors in mice (2020).

2.1 Acute Toxicity

Bifenthrin has moderate acute toxicity via the oral and inhalation route of exposure (GHS Category 3) and low toxicity (GHS Category 4) via the dermal route of exposure. It is not irritating to the eye and non-irritating to the skin. It resulted as a skin sensitizer in one dermal sensitization assay and not a sensitizer in another dermal sensitization assay (Appendix 5.1).

2.2 Subchronic Toxicity

In an oral toxicity study, male and female Sprague Dawley rats (15/sex/dose) were administered bifenthrin (91.4% purity) in their diet at doses of 0, 12, 50, 100, and 200 ppm (equivalent to 0, 0.88, 3.8, 7.5 and 15 mg/kg/day for males and 0, 1.04, 4.3, 8.5, and 17.2 mg/kg/day for females) for 90-days. The NOAEL was 3.8 mg/kg bw/day in males and 4.3 mg/kg bw/day in females and the LOAEL was 7.5 mg/kg bw/day in males and 8.5 mg/kg bw/day in females based on increased incidence of tremors in both sexes (JMPR, 2009; USEPA, 2020).

Another 90-day oral study was conducted where beagle dogs were fed gelatine capsules of bifenthrin (purity 88.35%) at doses of 0, 2.5, 5.0, 10, and 20 mg/kg bw/day. The NOAEL of 2.21 mg/kg bw/day was established based on increased incidence of tremors at the LOAEL of 4.42 mg/kg bw/day (JMPR, 2009; USEPA, 2020).

In a 21-day dermal toxicity study with male and female Sprague-Dawley rats, the test substance, bifenthrin (purity 93.2%), was applied to the skin of rats for 6 hours/day, 5 days/week for 21 days at doses of 0, 25, 50, 100, 1000 mg/kg/day. A NOAEL was established at 47 mg/kg bw/day based on staggered gait (males) and exaggerated hind limb flexion (females) at the LOAEL of 93 mg/kg bw/day (JMPR, 2009; USEPA, 2020).

In a 21-day dermal toxicity study with male and female New Zealand White rabbits, bifenthrin (purity 88.5%) was applied daily to the skin of rabbits for 6 hours/day at doses 0, 25, 50, 100, 500 mg/kg bw/day for 21 consecutive days. A NOAEL of 88 mg/kg bw/day was selected based on loss of muscle

coordination and increased incidence of tremors at the LOAEL of 442 mg/kg bw/day (JMPR, 2009; USEPA, 2020).

In a 28-day inhalation toxicity study with rats, the NOAEC was 0.0059 mg/L/day and the LOAEC was 0.0196 mg/L/day based on tremors and increased respiration rate (USEPA, 2020).

2.3 Chronic Toxicity and Carcinogenicity

A carcinogenicity study was conducted with male and female Swiss-Webster mice where doses of 0, 50, 200, 500, and 600 ppm of bifenthrin (purity 88.35%) were administered for 18 months via diet. (equivalent to 0, 6.7, 25.6, 65.4, and 81.3 mg/kg bw/day for males and 0, 8.8, 32.7, 82.2, and 97.2 mg/kg bw/day for females) for 87 weeks (males) or 92 weeks (females). A NOAEL of 6.7/8.8 mg/kg bw/day (male/female) was established based on increased incidence of tremors observed at the LOAEL of 25.6/32.7 mg/kg bw/day. There was evidence for carcinogenicity in male mice (USEPA, 2020).

A chronic/carcinogenicity study with male and female Sprague Dawley rat was run where bifenthrin at a purity of 88.35%. Doses of 0, 12, 50, 100, and 200 ppm were administered in diet. (equivalent to 0, 0.6, 2.3, 4.7, and 9.7 mg/kg bw/day for males and 0, 0.7, 3.0, 6.1, and 12.7 mg/kg bw/day for females) A NOAEL of 4.7/3.0 mg/kg bw/day (male/female) was established based on increased incidence of tremors at the LOAEL of 9.7/6.1 mg/kg bw/day (male/female). There was no evidence of carcinogenicity (USEPA, 2020).

Bifenthrin (purity 88.35%) was administered to beagle dogs in a one-year oral toxicity study. Dose levels of 0, 0.75, 1.50, 3.00, and 5.00 mg/kg bw day resulted in the NOAEL of 1.3 mg/kg bw/day based on increased incidence of tremors at the LOAEL of 2.7 mg/kg bw/day (USEPA, 2020).

2.4 Developmental Toxicity

A prenatal developmental toxicity study was conducted with Sprague-Dawley rat. Bifenthrin (purity 88.35%) in the vehicle corn oil was administered to rats via gavage at doses of 0, 0.50, 1.0, and 2.0 mg/kg bw/day. The maternal NOAEL was set at 0.88 mg/kg bw/day based on tremors during gestation at the LOAEL of 1.77 mg/kg bw/day. A developmental NOAEL was established at 1.77 mg/kg bw/day (the highest dose tested) because a LOAEL was not established.

Another prenatal developmental toxicity study in pregnant Sprague Dawley rats was conducted with bifenthrin (purity 95.3%) administered via diet at doses of 0, 30, 60, 90, 200 ppm (equivalent to 0, 2.5, 5.0, 7.4, and 16.3 mg/kg bw/day). The maternal NOAEL was established at 7.4 mg/kg bw/day based on clinical signs and decreased food consumption, body weight gains, and body weight gains adjusted for gravid uterine weight at the LOAEL of 16.3 mg/kg bw/day. A developmental NOAEL was set at 16.3 mg/kg bw/day; the highest dose tested. A developmental LOAEL was not established (JMPR, 2009).

In a prenatal developmental toxicity study with New Zealand rabbits bifenthrin (purity 88.35%) was administered via gavage at doses of 0, 2.67, 4.0, and 8.0 mg/kg bw/day. A maternal NOAEL was selected at 2.67 mg/kg bw/day based on treatment-related head and forelimb twitching at the LOAEL of 4.0 mg/kg bw/day. A developmental NOAEL was greater than 8 mg/kg bw/; a LOAEL was not determined (JMPR, 2009).

2.5 Reproduction Toxicity

In a two-generation reproduction toxicity study, Sprague-Dawley rats were administered bifenthrin (88.35% purity) at doses of 0, 30, 60, or 100 ppm (equivalent to 0, 1.5, 3.0, or 5.0 mg/kg bw/day) for two generations. A parental systemic NOAEL of 3.0 mg/kg bw/day was set based on tremors and decreased body weight in females at the LOAEL of 5.0 mg/kg bw/day. A reproduction NOAEL of 5.0 mg/kg bw/day, the highest dose tested, was indicated based on no LOAEL being established (JMPR, 2009; USEPA, 2020).

2.6 Genotoxicity

In an Ames assay, bifenthrin was negative both with and without S9 activation in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1538 (USEPA, 1992).

In an in vitro chromosomal aberration assay with Chinese Hamster Ovary cells, bifenthrin at doses ranging from 100 to 1000 µg/mL with and without metabolic activation did not cause an increased incidence of chromosomal aberrations (USEPA, 1992).

In an in vivo chromosomal aberration assay with rat bone marrow cells, bifenthrin was administered orally to rats at 3, 10 or 30 mg/kg bw for 5 days. There was no severity or increased incidence of chromosomal aberrations (USEPA, 1992).

In a forward mutation assay at the TK Locus in mouse lymphoma cells, bifenthrin was shown to be mutagenic both with and without metabolic activation. Doses of 0.42 to 0.24 µg/mL without S9 activation resulted in a 1.8 to 4.2-fold, dose-dependent increase in mutation frequency at the TK locus. Doses of 0.024 to 0.1 µg/mL resulted in a 1.3 to 2.0-fold dose-dependent increase in mutation frequency (1992).

Conflicting evidence for mutagenicity was seen for unscheduled DNA synthesis in rat hepatocytes. In the first study, bifenthrin was mutagenic at 2 µl/mL as there was an average net grain count of 9.3/nucleus as compared with 2.5-3.8 for different controls. In the second study, there was no evidence of UDS at doses ranging from 1.0 to 2.0 µl/mL using several criteria for evaluation such as increase in average net nuclear grain/nucleus, number of nuclei/exposure level with 5 and/or 20 or more net nuclear grains (USEPA, 1992).

2.7 Neurotoxicity

An acute neurotoxicity study was conducted in rats via a single oral gavage administration followed by 14 days of observation. The doses levels of bifenthrin (purity 93.7%) selected were 0, 10, 35, 75 mg/kg bw. A NOAEL of 35 mg/kg bw was established based on mortality (females only), clinical and FOB findings and differences in motor activity at the LOAEL of 75 mg/kg bw (USEPA, 2020).

A subchronic neurotoxicity study in rats dosed 0 or 50 ppm to 10 animals/sex/group or 100, 200, 300 ppm to 5 animals/sex/group of bifenthrin (purity 93.7%) for 13 weeks. A NOAEL of 50 ppm (2.9/3.7 mg/kg bw/day (male/female) was selected based on neuromuscular findings (tremors, changes in grip strength and landing foot-splay) at the LOAEL of 6.0/7.2 mg/kg bw/day (male/female) (USEPA, 2020).

In a developmental neurotoxicity study, bifenthrin (94.8% purity) was administered in the diet to female Crl:CD (SD) rats (25/dose group) at doses of 0, 50, 100 and 125 ppm (mean-measured concentrations of

0, 3.6, 7.2 and 9.0 mg/kg/day, respectively, during gestation and 0, 8.3, 16.2 and 20.7 mg/kg/day, respectively, during lactation) from GD 6 through LD 21. The maternal LOAEL for bifenthrin in rats was 100 ppm (7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation) based on clinical signs of neurotoxicity (tremors, clonic convulsions, and increased grooming counts). The maternal NOAEL is 50 ppm (3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation). The offspring LOAEL for bifenthrin in rats is 100 ppm (7.2 mg/kg/day during gestation and 16.2 mg/kg/day during lactation; maternal dose) based on clinical signs of neurotoxicity (increased grooming counts). The offspring NOAEL is 50 ppm (3.6 mg/kg/day during gestation and 8.3 mg/kg/day during lactation; maternal dose (USEPA, 2016)).

In an acute oral toxicity study, Weiner et al. (2009) gave a single gavage dose of bifenthrin in corn oil at 0, 40 or 55 mg/kg bw. The BMDL20 was 0.4 mg/kg bw and the BMD20 was 14.3 mg/kg bw based on multiple alterations in FOB parameters (USEPA, 2020).

Wolansky, et al. 2006 measured motor activity at the time of peak effect after exposure to 11 pyrethroids, including Bifenthrin. Male adult Long-Evans rats were given a single oral gavage dose of bifenthrin at 0, 0.03, 0.1, 1.0, 4.0, 8.0, 12.0, 16.0, 24.0 and 28.0 mg/kg bw and there were 4-12 rats/group used for bifenthrin minimizing variability and increasing the confidence in the BMD estimates determined from this study. Moreover, each pyrethroid was evaluated by the same scientist, thus decreasing some of the variability associated with neurobehavioral measures. Because of the high confidence and the robustness of the data, this study was used in establishing the Point of departure (POD) for risk assessment. The EPA conducted a benchmark dose (BMD) analysis for all the pyrethroids included in the Wolansky et al. In performing BMD analysis, a benchmark response (BMR) must be selected. As a general approach, it is preferable to use a combination of biological and statistical factors in the BMR selection. In the case of motor activity data, the scientific community has not established a specific level of change that would be considered to be adverse. Therefore, EPA has elected to use one standard deviation (1SD) from the control group, as suggested for continuous endpoints in the Agency's BMD guidance (USEPA, 2012) as the BMR. EPA uses the BMDL, not the BMD, for deriving PODs. USEPA has estimated the BMD1SD and the BMDL1SD (the lower 95% confidence limit of the BMD1SD). For bifenthrin the BMDL1SD is 3.1 mg/kg and the BMD1SD is 4.1 mg/kg bw based on reductions in locomotor activity (USEPA, 2016 and 2020).

2.8 Absorption, Distribution, Metabolism, and Excretion (ADME)

Absorption, distribution, metabolism and elimination (ADME) studies on the product are not required by PQT/VCP, however ADME on the AI are considered and integrated into the hazard assessment.

2.8.1 Oral route studies

Bifenthrin, as with the metabolic profiles of pyrethroids in general, is rapidly absorbed and metabolized, and quickly reaches its time-to-peak effect following an oral dose. Time-to-peak in plasma was observed at 4 or 6 hours from a low to high dose administration, respectively. The highest distribution location after 7 days was in the fat of rats. Feces were the main route of excreta at 48 hours (73-80% in the feces compared with 6-9% in the urine, depending on whether it was alcohol-labelled or the acid-labelled bifenthrin). Approximately 70% of the administered radioactive dose was found in feces and about 20% in urine. Around 91% of the administered dose of the alcohol-labelled bifenthrin was recovered in the excreta after 7 days and about 86% total administered dose was recovered in the excreta of rats at 7

days for the acid-labelled bifenthrin. The major metabolic route observed was hydrolysis of the ester linkage with oxidation. However, unmetabolized parent bifenthrin was predominant. There were no significant differences noted between male and female rats (USEPA, 2020 and JMPR, 2009). According to a study reviewed by EFSA, 50% of administered bifenthrin was bioavailable based on bile cannulated rats showing 50% of compound excreted via the feces. Furthermore, elimination of the radioactivity was complete by 48 hours following administration (EFSA, 2011).

2.8.2 Dermal route studies

A 2010 *in vitro* rat and human dermal penetration study was conducted by Hughes and Edwards which resulted in 45.5% absorption in rats and 26.2% absorption in humans (US EPA, 2020). In addition, there is an *in vivo* rat dermal absorption study identified by JMPR (2009) and resulted in their conclusion that there is moderate dermal absorption at 50%. However, this study and others were reviewed by the USEPA and found to only be of supportive value. Since several pyrethroids have demonstrated that dermal penetration for this class of chemicals is typically low, a 10% default is often applied in cases of uncertainty. Given the robustness and conclusions from the 2010 *in vitro* human and rat study, however, a 10% default may not suffice in the case of bifenthrin. Therefore, a dermal absorption value of 26% is used for risk assessment purposes.

2.8.3 Inhalation route studies

Absorption via the inhalation route is assumed to be 100% that via the oral route. Due to the lack of a long-term inhalation study, oral exposure is used for risk assessment purposes.

3 Points of Departure (POD), Reference Doses (RfD), and Cancer Classification

3.1 Points of Departure

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Lowest Observed Adverse Effect Level (LOAEL); Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

3.2 Reference Doses

3.2.1 Acute Reference Dose (aRfD)

Bifenthrin was evaluated by the JMPR in 2009, at which time an aRfD of 0.01 mg/kg bw was established from a NOAEL of 1.3 mg/kg bw in an acute oral motor activity assessment study in rat (Wolansky, 2006). The NOAEL of 1.3 mg/kg bw is based on motor activity. An uncertainty factor of 100 to account for interspecies extrapolation (10) and intraspecies variabilities (10) is applied.

The USEPA (2020) used the BMDL1SD of 3.1 mg/kg bw based on the decreased locomotor activity observed at BMD1SD of 4.1 mg/kg bw in the acute neurotoxicity study by Wolansky et al., 2006. This study/endpoint/dose was selected because it utilized a rat strain (Long-Evans) sensitive to neurotoxicity and measured an objective apical endpoint (locomotor activity) as the toxicity endpoint of concern. The BMD data analysis was utilized as a standardized method to address concerns of dose selection and dose spacing. An uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variation) was used to derive the aRfD.

$$\text{aRfD} = 3.1 \text{ mg/kg bw} \div 100 = 0.031 \text{ mg/kg bw}$$

3.2.2 Chronic Reference Dose (cRfD)

The USEPA (2020) did not establish a cRfD since the single-dose and repeated-dose studies with bifenthrin showed that repeat exposures did not result in lower PODs, i.e., there is no evidence of increasing toxicity with an increased duration of exposure. Therefore, the exposure assessments are conducted as a series of acute exposures, and these are protective scenarios in which exposure occurs for multiple days. Therefore, a cRfD was not established (USEPA, 2020).

cRfD = Not Established

3.2.3 Acceptable Daily Intake (ADI)

JMPR (2009) established an ADI of 0.01 mg/kg bw/day based on the NOAEL of 1.0 mg/kg bw/day established in the prenatal developmental toxicity study in rats based on maternal toxicity (increased incidence of tremors) and developmental toxicity (increased incidence of hydronephrosis without hydronephrosis in fetuses) at 2.0 mg/kg bw/day and the application of a 100-fold uncertainty factor.

$$ADI = 1.0 \text{ mg/kg bw/day} \div 100 = 0.01 \text{ mg/kg bw/day}$$

3.3 Cancer Classification

The USEPA, in accordance with the 1986 Guidelines for Cancer Risk Assessment has placed bifenthrin as a Group C Chemical; Possible Human Carcinogen based on the presence of urinary bladder tumors in one sex (males) in one species (rats) observed only at the high dose. The Agency has determined that quantification of risk using a non-linear approach (i.e., reference dose, RfD) will adequately account for all chronic toxicity, including carcinogenicity that could result from exposure to bifenthrin (USEPA, 2020).

4 References

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