

WHO Prequalification Programme / Vector Control Product Assessment

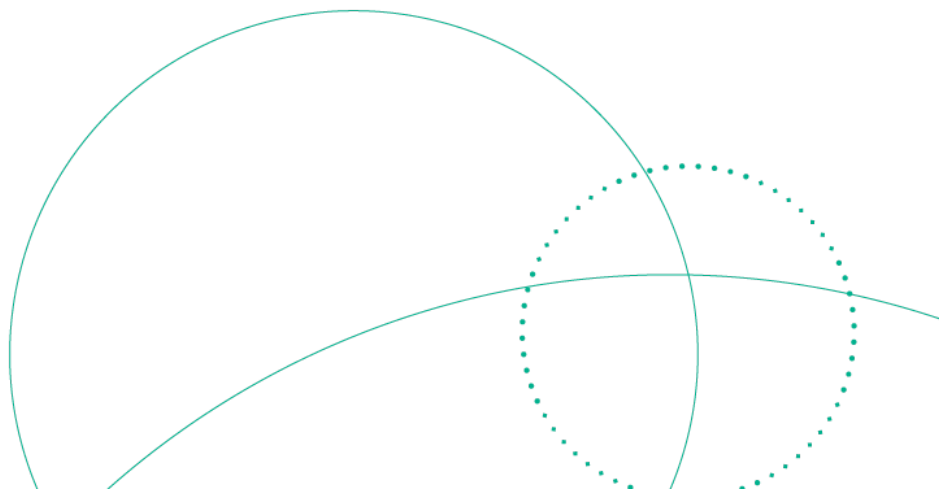
# WHO Public Assessment Report: WHOPAR Part 4

Yahe 4.0

(Fujian Yamei Industry & Trade Co., Ltd)

P-04983

Safety Assessment



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# 1 Risk assessment summary

## 1.1 Introduction

The applicant, Fujian Yamei Industry & Trade Co., Ltd. (Fuzhou, Fujian, China), submitted to the World Health Organization (WHO) Prequalification Unit Vector Control Product Assessment Team (PQT-VCP) a dossier containing supporting data on the product Yahe 4.0 and requested WHO assessment for the purpose of prequalification. Yahe 4.0 is an insecticide treated net (ITN) intended for use in malaria endemic regions. The fabric is made from polyethylene filaments incorporated with Alpha-cypermethrin (CAS No. 67375-30-8) and Piperonyl Butoxide (PBO) (CAS No. 51-03-6).

## 1.2 Active ingredient statement

### 1. Alpha-cypermethrin

Alpha-cypermethrin (CAS No. 67375-30-8) is a broad-spectrum insecticide, effective against target pests through contact and ingestion. Alpha-cypermethrin is a type II synthetic pyrethroid chemical. Pyrethroids disrupt the voltage-gated sodium channels in the nervous system, resulting in neurotoxicity.

### 2. Piperonyl Butoxide

Piperonyl butoxide (CAS No. 51-03-6) is an insecticide synergist. PBO is commonly used in products containing pyrethrins and pyrethroids to increase the efficacy of the actual insecticide in ITNs.

## 1.3 Supporting database

The toxicology databases for alpha-cypermethrin and PBO are adequate to address the health hazards and to assess the risks associated with the proposed uses of Yahe 4.0 as an ITN.

The human health risk assessments, including hazard, exposure, and risk characterization for Alpha-cypermethrin and PBO are presented in the *“Generic Risk Assessment – Human Health – Alpha-cypermethrin (CAS No. 67375-30-8). A long-lasting mosquito net treated with Alpha-cypermethrin”* published by WHO (2021a) and the *“Generic Risk Assessment – Human Health – Piperonyl Butoxide (CAS No. 51-03-6). A synergist in insecticide-treated nets”* published by WHO (2021b). The generic risk assessments (GRA) published by WHO are intended to be used as an example of the implementation of the *“Generic Risk Assessment Model for Insecticide-Treated Nets, 2<sup>nd</sup> edition”* (GRAM)(WHO, 2018) and points of reference for the assessment of new products which are formulated with these active ingredients.

## 1.4 Assessment

### 1.4.1 Product Specific Acute Toxicity Data

Acute 6-pack toxicity data for the proposed ITN was submitted and a summary of these studies is provided in Table 1. The test material in all acute studies was alpha-cypermethrin and PBO extracted from cut filaments of Yahe 4.0 with n-heptane and reconstituted in corn oil to the desired dose level or

concentration. All acute studies were conducted at IIBAT (International Institute of Biotechnology and Toxicology, India) in compliance with Good Laboratory Practices (GLP) and OECD guidelines.

Using the Globally Harmonized System of Classification and Labelling of Chemicals (GHS, 2017), Yahe 4.0 has low acute oral, dermal and inhalation toxicity (Category 5), is not an eye or skin irritant, and is not a skin sensitizer.

Table 1. Acute toxicity of Yahe 4.0				
Route of exposure	Species	Toxicity	GHS category	Reference
Oral	Rat	LD <sub>50</sub> = >2000 mg/kg bw	5	IIBAT, 2021a
Dermal	Rat	LD <sub>50</sub> = >2000 mg/kg bw	5	IIBAT, 2021b
Inhalation (nose only)	Rat	LC <sub>50</sub> = > 5.12 mg/L/4 hrs	5	IIBAT, 2021c
Dermal irritation	Rabbit	Non-irritant	Not classified	IIBAT, 2021d
Eye irritation	Rabbit	Non-irritant	Not classified	IIBAT, 2021e
Dermal sensitization	Guinea pigs	Non-sensitizer	Not classified	IIBAT, 2021f

### 1.4.2 Comparison of the Yahe 4.0 Specifications vs. GRA Values

Table 2: Comparison of the Yahe 4.0 characteristics vs. GRA selected representative values				
Attribute	Alpha-Cypermethrin		Piperonyl Butoxide	
	Yahe 4.0	Alpha-Cypermethrin GRA	Yahe 4.0	PBO GRA
Concentration by weight	6.25 g/kg net	5.8 g/kg net	2.25 g/kg net	25 g/kg net
Fabric weight	38 g/m <sup>2</sup>	35 g/m <sup>2</sup>	38 g/m <sup>2</sup>	40 g/m <sup>2</sup>
Concentration by net area	250 mg/ m <sup>2</sup>	203 mg/m <sup>2</sup>	90 mg/m <sup>2</sup>	1000 g/m <sup>2</sup>
Wash resistance index	95%	90%	92%	90%

The proposed specifications for concentration of Alpha-cypermethrin by net area in the product Yahe 4.0 are slightly higher than the characteristic values in the GRA Alpha-cypermethrin (238 to 250 mg/m<sup>2</sup> vs. 203 mg/m<sup>2</sup>). (WHO, 2021a)

The proposed specifications for PBO in the product YAHE 4.0<sup>®</sup> are less than the characteristic values in the GRA PBO (WHO, 2021b).

## 1.5 Discussion and Conclusion

The risk assessment was conducted according to the guidance provided in the most recent “*Generic Risk Assessment Model for Insecticide-Treated Nets, 2<sup>nd</sup> edition*” (GRAM)(WHO, 2018). In support of new product applications or change applications submitted to the WHO Prequalification Unit – Vector Control Product Assessment Team, applicants may include reference to the GRAs as part of the product dossier.

Although the higher concentrations of Alpha-cypermethrin in Yahe 4.0 result in a total concentration (TC) of 296.87 mg/m<sup>2</sup> net as compared to a TC of 253.75 mg/m<sup>2</sup> in the GRA Alpha-cypermethrin (WHO, 2021a), the risks for all exposure scenarios do not exceed WHO level of concern (risk ratio ≥ 1.0) due to

differences in wash resistance index (WRI) values. The WRI provided by the submitter is 95% (IIBAT, 2021g) as compared to a WRI of 90% applied in the GRA Alpha-cypermethrin (WHO, 2021a).

The proposed specifications for PBO in the product YAHE 4.0<sup>®</sup> are below the characteristic values in the GRA PBO (WHO, 2021b), hence are not of concern.

Based on the proposed product characteristics and the use pattern, it was determined that the risk ratios for Yahe 4.0 are acceptable (i.e., less than 1) for all population subgroups (adults, children, toddler, infants and newborn), for all exposure scenarios (sleeping under the net, washing the net, sleeping under and washing the net) and the exposure routes (oral, dermal and inhalation) are similar to those obtained for Alpha-cypermethrin and PBO in their respective GRAs (WHO, 2021a,b).

Therefore, it can be concluded that the ITN proposed product Yahe 4.0 can be used safely for its intended purpose. Assessment of the submitted information supports the prequalification of the product Yahe 4.0.

## 2 References

- IIBAT (International Institute of Biotechnology and Toxicology), 2021a. YAHE 4.0 LLIN – Alpha-cypermethrin 250 mg/m<sup>2</sup> ± 25% and Piperonyl butoxide 90 mg/m<sup>2</sup> ± 25% incorporated in polyethylene filaments: Acute oral toxicity study in Wistar rats. Study No. 20262, 25 January 2021.
- IIBAT, 2021b. YAHE 4.0 LLIN – Alpha-cypermethrin 250 mg/m<sup>2</sup> ± 25% and Piperonyl butoxide 90 mg/m<sup>2</sup> ± 25% incorporated in polyethylene filaments: Acute dermal toxicity study in Wistar rats. Study No. 20263, 23 January 2021.
- IIBAT, 2021c. YAHE 4.0 LLIN – Alpha-cypermethrin 250 mg/m<sup>2</sup> ± 25% and Piperonyl butoxide 90 mg/m<sup>2</sup> ± 25% incorporated in polyethylene filaments: Acute inhalation toxicity study in Wistar rats. Study No. 20264, 22 January 2021.
- IIBAT, 2021d. YAHE 4.0 LLIN – Alpha-cypermethrin 250 mg/m<sup>2</sup> ± 25% and Piperonyl butoxide 90 mg/m<sup>2</sup> ± 25% incorporated in polyethylene filaments: Acute dermal irritation/corrosion study in New Zealand White rabbits. Study No. 20265, 23 January 2021.
- IIBAT, 2021e. YAHE 4.0 LLIN – Alpha-cypermethrin 250 mg/m<sup>2</sup> ± 25% and Piperonyl butoxide 90 mg/m<sup>2</sup> ± 25% incorporated in polyethylene filaments: Acute eye irritation/corrosion study in New Zealand White rabbits. Study No. 20266, 23 January 2021.
- IIBAT, 2021f. YAHE 4.0 LLIN – Alpha-cypermethrin 250 mg/m<sup>2</sup> ± 25% and Piperonyl butoxide 90 mg/m<sup>2</sup> ± 25% incorporated in polyethylene filaments: Skin sensitization study in Guinea Pigs. Study No. 20267, 22 January 2021.
- IIBAT, 2021g. Regeneration, wash resistance and efficacy of YAHE 4.0 LLIN - Alpha-cypermethrin 250mg/m<sup>2</sup> ± 25% + Piperonyl butoxide 90mg/m<sup>2</sup> ± 25% incorporated in polyethylene filaments against susceptible and pyrethroid-resistant mosquito strains of *Anopheles stephens*. Report No. 20261, 2021.
- WHO (World Health Organization), 2018. A Generic Risk Assessment Model for Insecticide-treated Nets, 2<sup>nd</sup> Edition. Available at: <http://www.who.int/whopes/resources/9789241513586>.

- WHO, 2021a. Generic Risk Assessment – Human Health, Alpha-cypermethrin (CAS No. 67375-30-80). A long-lasting mosquito net treated with Alpha-cypermethrin. 16 June 2021. Available at: <https://extranet.who.int/pqweb/key-resources/documents/generic-risk-assessment-human-health-itns-formulated-alpha-cypermethrin>.
- WHO, 2021b. Generic Risk Assessment – Human Health, Piperonyl Butoxide (CAS No. 51-03-6). A synergist in insecticide-treated nets. 8 June 2021. Available at: <https://extranet.who.int/pqweb/key-resources/documents/generic-risk-assessment-human-health-itns-formulated-piperonyl-butoxide>.