World Health Organization

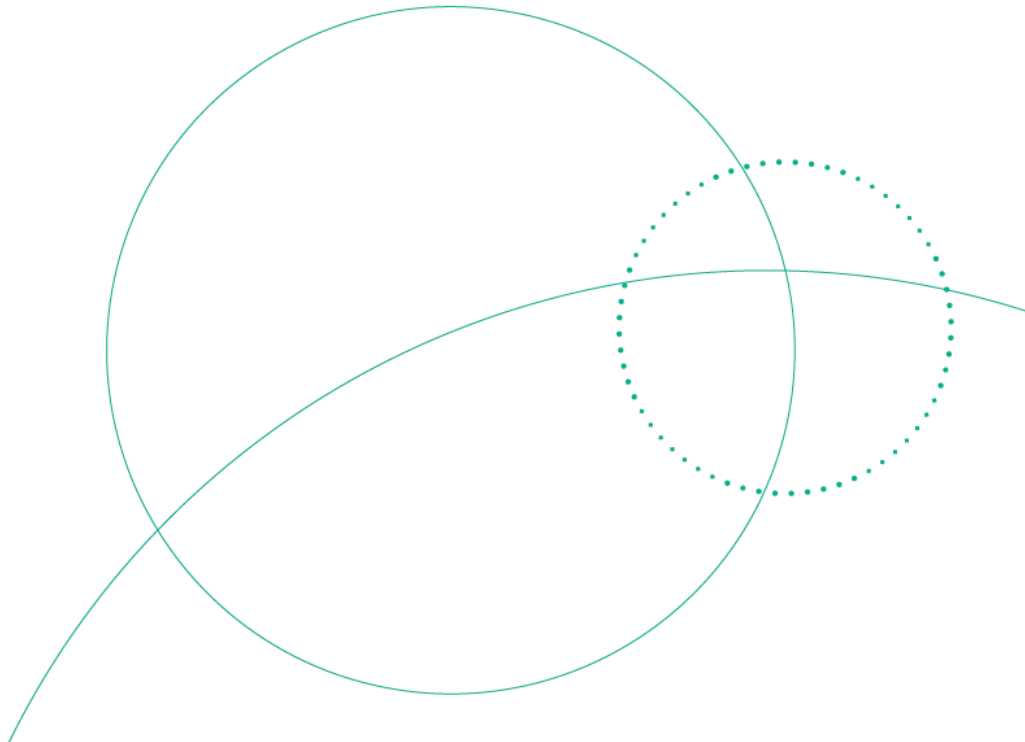
WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 5

Yorkool G1 LN
(Tianjin Yorkool)

P-11664

Efficacy Assessment



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1 Introduction

The primary purpose for the use of a pesticide is the control of a pest, including disease transmitting vectors. Vector control tools, including formulated pesticides, which provide effective management or control of vectors, may be used as part of a resistance management programme. Vector control products for use in public health are a component of Integrated Vector Management (IVM), which is a programme that relies on a suite of diverse interventions and implementations of best practices to manage the vector and chemical/behavioural resistance.

Yorkool G1 LN is a homogenous ITN coated with deltamethrin 1.4 g AI/kg that is intended to provide personal and community protection from Anopheline mosquitoes as part of malaria control programmes.

Semi-field studies to characterize the performance of Yorkool G1 against free-flying mosquitoes with supplementary bioassays to characterize the availability of active ingredients and insecticidal effect of the fabric of the ITN on Anopheline mosquito species were submitted to WHO as part of the prequalification dossier.

2 Semi-field studies

Studies conducted in semi-field settings often include the investigation of endpoints other than mortality, knockdown and blood-feeding inhibition. Examples of these include entry rate, exit rate, and deterrence, as well as analyses for non-standardized calculations of "personal protection". Based on the existing requirements and established decision framework, mosquito mortality and knockdown are considered the primary endpoints for assessment. Therefore, results for these are included within the summaries of these studies. Calculations of blood feeding inhibition were also included for further characterization of the entomological impact of the product.

2.1 Experimental hut trials

Data on the semi-field performance of Yorkool G1 were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP). These summary results are based on ITNs drawn from batches SC200702PK1, SC200704PA1 and SC200803VU1. In these studies, the product is referred to as Yorkool LN.

Two semi-field studies were presented to evaluate the efficacy and wash resistance of Yorkool G1 in Tanzania and in Benin. Both semi-field trials were experimental hut trials (EHT). ITNs used in semi-field studies were prepared using the wash interval determined in previous laboratory studies conducted by WHOPES. The endpoint used to evaluate bioavailability was 24-hour mortality. The negative control used in each study was an untreated net and the positive control was a prequalified ITN product treated with 1.4 g AI/kg deltamethrin, hereafter referred to as PC1.

The product was tested against pyrethroid resistant natural populations of, in Covè, Benin, *An. coluzzi* and *An. gambiae* s.s, with the relative proportions estimated at 77% and 23%, respectively. The pyrethroid resistance is mediated by *kdr,* with the *An. gambiae* s.l population carrying *kdr* gene

frequencies of >90% L1014F and an intensity of resistance of greater than 200-fold the diagnostic dose, and metabolic resistance through over-expression of CYP6P3 enzymes. In resistance testing conducted during the experimental hut trial, 10.6% and 42.2% mortality were observed following exposure to the diagnostic doses of permethrin and deltamethrin, respectively. In Lupiro, Tanzania, the vector population at the semi-field site was *An. arabiensis* with pyrethroid resistance mediated by the over-expression of cytochrome P450 enzymes and observed mortality to the diagnostic doses of deltamethrin, permethrin and alpha-cypermethrin of 48%, 16% and 22%, respectively, in February 2021.

The results from the free-flying mosquito studies are presented in Table 1. Yorkool G1 ITNs that were washed 20 times using a 1-day wash interval induced 4.9% and 10.6% 24-hour mortality in free-flying *An. gambiae* s.l. mosquitoes in Benin and Tanzania, respectively. Statistical analyses demonstrated that the mortality observed in the 20x Yorkool G1 trial arms was not significantly different to PC1 (Benin: Mortality 4.9% vs 5.8%, P=0.057; Tanzania: OR 1.08, 95% CI 0.85-1.37, p = <0.552).

Supplementary bioassays were used to characterize the bioavailability of the active ingredients on the surface of the ITN pre- and post-hut studies using unwashed and 20x washed nets. WHO cone tests and tunnel tests were the experimental methods used in bioavailability studies. In Benin, the *An. gambiae* s.s. Kisumu strain was used as an insecticide susceptible test system. Susceptibility to the diagnostic doses of permethrin (0.75%) and deltamethrin (0.05%) was confirmed in testing conducted during the experimental period. In Tanzania, the *An. gambiae* s.s. Ifakara strain was used as an insecticide susceptible test system. Susceptibility to the diagnostic doses of permethrin (0.75%), deltamethrin (0.05%), alpha-cypermethrin (0.05%), lambda-cyhalothrin (0.05%), etofenprox (0.5%), bendiocarb (0.1%), and pirimiphos methyl (0.25%) was confirmed in testing conducted February – May 2021. Thresholds of ≥95% knockdown and/or ≥80% mortality in WHO cone tests and ≥80% mortality or ≥90% blood feeding inhibition in tunnel tests were used as the efficacy criteria for bioavailability. The endpoint used to evaluate bioavailability was 24-hour mortality.

The results from supplementary bioassays are presented in Tables 2 and 3. In WHO cone tests using insecticide susceptible test systems, 60-minute KD greater than 95% and 24-hour mortality greater than 80% was not observed using unwashed and 20x washed nets, before and after the EHT in Benin. In Tanzania, in WHO cone tests using insecticide susceptible test systems, 60-minute KD greater than 95% and 24-hour mortality greater than 80% were observed using unwashed and 20x washed nets, before and after the EHT.

In tunnel tests using insecticide susceptible test systems in Benin, 24-mortality greater than 80% and blood feeding inhibition greater than 90% were observed against unwashed and 20x nets.

Table 1. Mortality and Blood Feeding Inhibition of Free-Flying Pyrethroid Resistant *An. gambiae* s.l. in two Experimental Hut Trials				
Product	**Washing condition**	**% M24 (95% CI)**	**% Feeding inhibition (95% CI)**	**Sample Size**
Benin (*An.gambiae* s.l)				
Total number of mosquitoes collected =3,222			Compliant with power calculation? Yes	
Control	Unwashed	0.9 (0-2)	-	437
Yorkool G1	Unwashed	7.5 (3.3-11.8)	4.7	146
	20x washed	4.9 (3.6-6.1)	0.8	1,113
PC1	Unwashed	5 (3-7)	0	497
	20x washed	5.8 (4.4-7.3)	-15	1,029
Tanzania (*An.gambiae* s.l.)				
Total number of mosquitoes collected = 7,087			Compliant with power calculation? Yes	
Control	Unwashed	4.4 (2.0-6.9)	-	881
Yorkool G1	Unwashed	8.4 (4.6-12.10)	90.3 (86.9-93.7)	1,099
	20x washed	10.6 (6.0-14.0)	91.8 (89.2-94.3)	1,958
PC1	Unwashed	13.8 (8.9-18.7)	93.5 (91.3-95.7)	1,572
	20x washed	10.2 (7.0-13.4)	92.6 (90.7-94.6)	1,577

Table 2. Knockdown and mortality results for insecticide susceptible laboratory strains using WHO cone bioassays						
	Benin			**Tanzania**		
	An. gambiae Kisumu			*An. gambiae* Ifakara		
	n	%KD60 (95% CI)	%M24 (95% CI)	n	%KD60 (95% CI)	%M24 (95% CI)
Before hut trial						
UW	52	73.1 (61-85.2)	71.2 (58.9-83.5)	300	100	97.7 (99.0-100)
20x washed	53	66 (55.3-78.6)	69.8 (57.4-82.2)	300	98.7	52.7 (47.3-58.1)
After hut trial						
UW	45	71.1 (57.9-84.3)	31.1 (17.6-44.6)	200	100	99 (97.6-100)
20x washed	50	50 (36.1-63.9)	16 (5.8-26.2)	200	100	66 (58.1-73.9)

Table 3. Mortality and blood feeding inhibition results for an insecticide susceptible laboratory strain using tunnel tests			
	Benin		
	An. gambiae Kisumu		
	n	%BFI	%M24 (95% CI)
UW	223	97.6 (95.6-99.6)	99.1 (97.9-100)
20x washed	218	97.6 (95.6-99.6)	99.5 (98.6-100)

2.2 Chemical characterization

Data on the deltamethrin content of sampled pieces of the Yorkool G1 product (100D) used in the semi-field studies were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP). These summary results are based on ITNs drawn from batches SC200702PK1, SC200704PA1, and SC200803VU1. The results are summarized in Table 4.

Table 4. AI content and retention of sampled pieces of Yorkool G1 (100D) used in the semi-field studies in Tanzania and Benin (batch numbers SC200702PK1, SC200704PA1, and SC200803VU1 - used in both locations)				
	Tanzania		Benin	
	Mean deltamethrin content (g/kg)	Deltamethrin retention (per wash)	Mean deltamethrin content (g/kg)	Deltamethrin retention (per wash)
Before hut trial				
UW	1.49	-	1.59	-
20x washed	0.23	15.44% (91.08%)	0.60	37.74% (95.24%)
After hut trial				
UW	1.40	-	1.44	-
20x washed	0.29	20.71% (92.43%)	0.57	39.58% (95.47%)

The mean AI content presented in Table 4 was determined based on 15 net samples belonging to 3 batches for unwashed (UW) product and after 20 washes before hut trial and after hut trial.

AI retention per wash in Table 4 is calculated as:

- AI retention per wash = 100 x $\sqrt[n]{(t_n/t_0)}$ where:
  - t_n = total active ingredient content after n washing cycles
  - t_0 = total active ingredient content before washing
  - n = number of washes.

The chemical analysis performed on samples of ITNs used in the semi-field studies confirmed that the test samples conformed with the batch analysis data presented in Module 3 and that the test samples were appropriate for use in the study.

The AI content for the unwashed product complied with the target dose interval limits in the specification (i.e., 1.4 ± 25% g/kg for deltamethrin).

2.3 Semi-field studies conclusions

The submitted semi-field studies demonstrate the impact of Yorkool G1 on free-flying mosquitoes and the bioavailability of the treatments on the ITN fabric using WHO cone bioassays and tunnel tests. Based on the submitted studies, the impact of Yorkool G1 ITNs that have been prepared using a one-day wash interval can be sustained against pyrethroid resistant free-flying mosquitoes up to 20 washes. The bioavailability of the treatments on the Yorkool G1 fabric was sustained up to 20 washes against insecticide susceptible test systems of the *An. gambiae* complex.

3 Efficacy conclusions

Based on the studies and information provided, all data requirements for the prequalification assessment of product efficacy have been satisfied. These data have been relied upon to assess the bioavailability and the impact on free-flying mosquitoes of the proposed product for the purpose of characterising the fabric of the product and establishing the duration of biological impact using products prepared with a defined wash interval.

The efficacy component of the dossier is considered complete, and the assessment of the submitted information on efficacy supports prequalification of the product.

Table 5. List of efficacy studies submitted to WHO as part of the prequalification dossier

Studies that were relied upon for decision making	
Study number	Study title
20-10	Experimental hut evaluation of the efficacy and wash resistance of Yorkool LN (a deltamethrin only net) by Tianjin Yorkool International Trading Co., Ltd against pyrethroid resistant *Anopheles gambiae* sl in Cove, Southern Benin
BIT073 WP5	An experimental hut evaluation of Yorkool long lasting insecticidal nets (LN) in comparison to PermaNet 2.0 LNs against wild mosquitoes in Tanzania
21193	Active ingredient analysis of different nets collected from the Yorkool LN Phase II Semi filed hut study before and after subjecting to different washes – Determination of Deltamethrin content
TE2021-007	Chemical analysis of Yorkool LN Phase II semi field hut study
Studies that were not used to inform decision making	
	None