Report of the Seventeenth

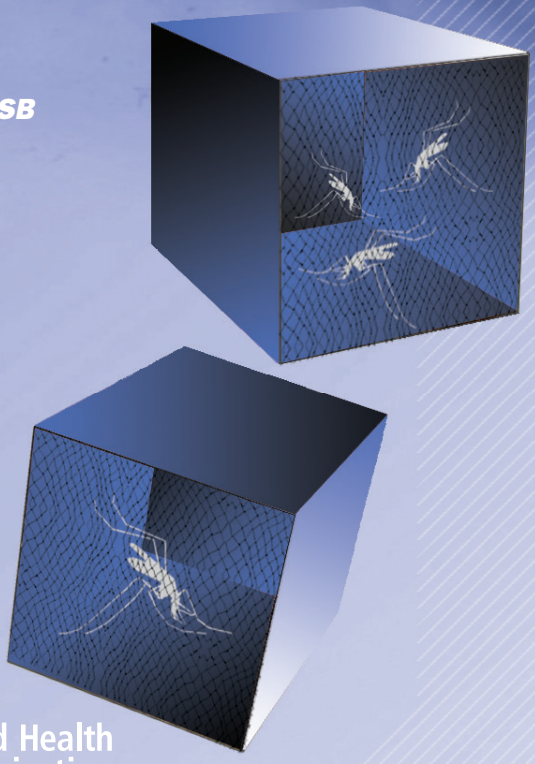
WHOPES

Working Group Meeting

WHO/HQ, GENEVA
15–19 SEPTEMBER 2014

Review of:

ALPHACYPERMETHRIN 250 WG-SB
ICON MAXX
NETPROTECT LN
CHLORFENAPYR 240 SC



World Health Organization

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REVIEW OF:

ALPHACYPERMETHRIN 250 WG-SB
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CONTROL OF NEGLECTED TROPICAL DISEASES
WHO PESTICIDE EVALUATION SCHEME

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The recommendations of the World Health Organization Pesticide Evaluation Scheme (WHOPES) are intended to facilitate the registration and use of the evaluated products by the Member States of the World Health Organization. A recommendation or interim recommendation concerning a specific product means that the World Health Organization has evaluated that product in laboratory and field trials and that the product was found to meet the criteria and requirements of the World Health Organization.

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WHO/HTM/NTD/WHOPES/2014.3

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1. INTRODUCTION

The 17th meeting of the WHOPES Working Group, an advisory group to the World Health Organization (WHO) Pesticide Evaluation Scheme (WHOPES), was held at WHO headquarters in Geneva, Switzerland, from 15 to 19 September 2014.

The Working Group reviewed alphacypermethrin 250 water-dispersible granules packaged in water-soluble bags (WG-SB) for indoor residual spraying (IRS) for control of malaria vectors (Tagros Chemicals India Ltd., India), and ICON MAXX dip-it-yourself kit for long-lasting insecticidal treatment of polyester nets (Syngenta, Switzerland); and re-evaluated submissions on Netprotect long-lasting insecticidal nets (Intelligent Insect Control, France) and Chlorfenapyr 240 suspension concentrate (SC) for IRS (BASF, Germany). The Working Group made recommendations on the use of each of these products.

The Working Group meeting included an open session on 15 September 2014, to which industry representatives were invited, and closed sessions, restricted to the invited experts, on 16–19 September 2014. The meeting was attended by 15 experts (see Annex 1. List of participants).

The meeting was opened by Dr Dirk Engels, Director of the WHO Department of Control of Neglected Tropical Diseases, who welcomed participants, stating that WHOPES is a longstanding WHO programme that supports Member States in vector control efforts, with many in government and industry worldwide using the programme's standards and recommendations. Dr Engels noted that reforms are currently under way in WHO to further standardize WHOPES procedures and to align them with those of WHO's prequalification programme as appropriate. He pointed out the need to encourage enhancement of innovation in vector control to curb the spread of disease vectors, and expressed the hope that discussion on reform would pave the way for transparent procedures and the generation of high-quality data that would align with WHO standards.

Professor Marc Coosemans was appointed Chair of the open session and Dr Vincent Corbel chaired the closed sessions. Dr John Gimnig was appointed Rapporteur and was asssited by Mr David Bramley from the WHO Secretariat. The meeting held both plenary and group sessions, in which reports of WHOPES-supervised trials, reports submitted by manufacturers, relevant published literature and

unpublished reports were reviewed and discussed (see Annex 2. References).

Declarations of interest

All invited experts completed a declaration of interests for WHO experts prior to the meeting for assessment by the WHO Secretariat. The following interests were declared:

Dr Nicole Achee's university had received repellent products free of charge from SC Johnson & Son, USA, for use in a large-scale intervention trial.

Dr Rajendra Bhatt's institute had received prescribed standard fees from seven manufacturers of pesticide products (BASF, India; Bayer CropScience, Germany; Chemtura, India; Clarke Mosquito Control, USA; Syngenta CropProtection, India; Vestergaard Frandsen, Switzerland; Sumitomo Chemical, Japan) to meet the costs of product evaluation.

Dr Fabrice Chandre's institute had received prescribed standard fees (from Sumitomo Chemical, Japan; Bayer CropScience, Germany; and SPCI, France) to meet the costs of evaluating their respective pesticide products.

Professor Dr Marc Coosemans' institute had received grants from the Bill & Melinda Gates Foundation for evaluating the impact of repellents on malaria in Cambodia. The institute had also received repellents free of charge from SC Johnson & Son, USA, for use in the study.

Dr Vincent Corbel's institute had received prescribed standard fees from Bayer CropScience, Germany, and Sumitomo Chemical, Japan, to meet the costs of evaluating their respective pesticide products.

Dr Olivier Pigeon's research centre had received prescribed standard fees from 14 manufacturers of pesticide products (BASF, Germany; Bayer CropScience, Germany; Gharda Chemicals, India; Intelligent Insect Control, France; Life Ideas Textile Company, China; NRS International, United Arab Emirates; SPCI, France; Sumitomo Chemical, Japan; Syngenta, Switzerland; Tagros, India; Tianjin Yorkool, China; Vector Control Innovations, India; Vestergaard Frandsen, Switzerland; V.K.A. Polymers, India) to meet the costs of

physico-chemical studies of pesticide products manufactured by the respective companies.

Dr Sarah Moore's research unit had received research funding from USAID and the Research Council of Norway for evaluating various long-lasting insecticidal nets. The unit had also received prescribed standard fees from Syngenta, Switzerland, for evaluating its long-lasting insecticidal nets.

Professor Dr Mark Rowland's unit had received funding from IVCC, United Kingdom, for the testing and evaluation of various pesticide products. The unit had also received prescribed standard fees (from Sumitomo Chemical, Japan; BASF, Germany; and Vestergaard Frandsen, Switzerland) to meet the costs of evaluating their respective pesticide products.

Dr Juan Arredondo-Jiménez from Universidad Autónoma de Nuevo León, Mexico, was invited to attend the meeting as an observer and declared no interest.

The interests declared by the experts and the observer were assessed by the WHO Secretariat. The declared interests were not found to be directly related to the topics under discussion at the meeting. It was therefore decided that all the above-mentioned experts could participate in all evaluations, subject to the public disclosure of their interests.

2. REVIEW OF ALPHACYPERMETHRIN 250 WG-SB

Alphacypermethrin WG-SB is a water-dispersible granule formulation packaged in water-soluble bags containing 250 g AI/kg for indoor residual spraying (IRS) for the control of malaria vectors. The product is manufactured by Tagros Chemicals India Ltd., India.

Alphacypermethrin wettable powder (WP) (50 g AI/kg) was previously evaluated by WHO and recommended for IRS for malaria vector control at the dosage of 25–30 mg/m^2 with expected residual activity of 4–6 months.[1]

WHO specifications for alphacypermethrin technical material and WP, SC, EC and UL formulations, developed under the new procedure using the data package of Tagros Chemicals India Ltd., have been published on the WHOPES website.[2]

The present review of the efficacy of alphacypermethrin 250 WG-SB (Tagros Chemicals India Ltd., India) for IRS against malaria vectors is based on a study comparing the product with the efficacy of the alphacypermethrin WP formulation (50 g AI/kg) as a positive control.

The following are extracts from the material safety data sheet of the manufacturer for alphacypermethrin 250 WG:

Acute oral LD_{50} (rat)	>50 mg AI/kg
Acute dermal (rat)	>2000 mg AI/kg
Skin irritation (rabbit)	Slightly irritating
Eye irritation (rabbit)	Minimally irritating
Skin sensitization (guinea pig)	Not a skin sensitizer

2.1 Safety assessment

The human risk assessment of alphacypermethrin 250 WG-SB for IRS, as provided by the manufacturer, was reviwed by WHO (Aitio, 2014). The product is a water-dispersible granule formulation in water-soluble bags containing 250 g AI/kg alphacypermethrin. WHO's

[1] Report of the Second WHOPES Working Group Meeting, 22–23 June 1998. Geneva: World Health Organization; 1998 (http://whqlibdoc.who.int/hq/1998/CTD_WHOPES_98.10.pdf, accessed 29 October 2014).

[2] See: http://who.int/whopes/quality/newspecif/en/ (accessed 29 October 2014).

Generic risk assessment model for indoor residual spraying of insecticides – first revision[1] was used as a guidance document in conducting the safety assessment of this formulation. In the assessment, assumptions were made that:

- the technical material used in manufacture of alphacypermethrin 250 WG-SB complies with the WHO specification;
- dermal absorption of alphacypermethrin from the formulation, from the diluted solution and from the product dried on the surfaces is 1% and that of the oral absorption is 60%;[2]
- inhalation exposure to gaseous alphacypermethrin of the operator and residents is negligible due to low vapour pressure (3.4×10^{-7} Pa at 25^{o});[3]
- spraying represents moderate physical activity and thus the breathing volume of an adult per hour is 1.9 m^3;[1]
- the translodgeable part from the walls and floors onto the skin is 11%, which is line with the United States Environmental Protection Agency estimate for hard surfaces;[1]
- the representative biological half-time (in mother's milk) of alphacypermethrin is 25 days;[2]
- the half-time of alphacypermethrin on the walls does not exceed 6 months, which is taken as the interval between successive sprayings. This seems to be a "worst case" scenario as the soil photolysis half-time for alphacypermethrin was estimated to be 31 days in light and 193 days in darkness.[3]

Alphacypermethrin is very toxic to aquatic organisms. However, the exposure of aquatic organisms to alphacypermethrin from IRS should

[1] Generic risk assessment model for indoor residual spraying of insecticides, first revision. Geneva: World Health Organization; 2011 (http://whqlibdoc.who.int/publications/2011/9789241502177_eng.pdf, accessed 29 October 2014).

[2] Cypermethrin (including alpha- and zetacypermethrin). In: Pesticide residues in food – 2006. Joint FAO/WHO meeting on pesticide residues. Evaluations 2006. Part II Toxicological Geneva: World Health Organization; 2008:157–225 (http://www.inchem.org/documents/jmpr/jmpmono/v2006pr01.pdf, accessed 29 October 2014).

[3] Alpha-Cypermethrin. SANCO/4335/2000 final. 13 February 2004. European Commission Health & Consumer Protection Directorate-General. Directorate E – Food Safety: plant health, animal health and welfare, international questions. E1 - Plant health (http://ec.europa.eu/food/plant/protection/evaluation/existactive/list_alpha_cypermethrin.pdf, accessed 29 October 2014).

be negligible. User training should emphasize the importance of prevention of spills into aquatic environments.

The hazard assessment conclusion based on the generic model is that, when used for IRS as instructed, alphacypermethrin 250 WG-SB does not pose undue hazards to the spray operators or residents of the treated dwellings or to wildlife.

2.2 Efficacy – WHOPES supervised trials

2.2.1 Karnataka, India

A small-scale study was conducted in India to compare the initial efficacy and residual activity of alphacypermethrin WG-SB at 20 and 30 mg AI/m² and alphacypermethrin WP at 20 and 30 mg AI/m² on different wall surfaces (Sreehari et al., 2014). The study was conducted in the village of Balepura where 61 houses were assigned to the four treatment arms and 8 to the unsprayed control arm. The insecticides were applied using a hand-operated compression sprayer fitted with a pressure gauge, a control flow valve set at 1.5 bar and a flat fan nozzle (8002) according to the WHO guidelines.[1]

Treatments were applied in houses with four types of wall surfaces: cement walls with distemper coating (a paint containing water, chalk and glue/resin), cement walls with lime coating, mud walls with lime coating and brick walls unpainted. To assess the quality of the spray application, the chemical content of 97 filter-papers fixed to the sprayed walls was analysed using a method based on CIPAC.

Cone bioassays were performed using a colony of *Anopheles stephensi* (established from field-collected larvae), which was susceptible to alphacypermethrin 0.1%. Between 3 and 6 replicates of 10 mosquitoes were exposed for 30 minutes in the cones (10 mosquitoes per cone) per treatment in different houses. Bioassays were carried out one week after treatment until week 22. Residual efficacy in months was set at a threshold value of <80% mortality for two consecutive bioassays.

[1] Manual for indoor residual spraying: application of residual sprays for vector control, third edition. Geneva: World Health Organization; 2007 (http://whqlibdoc.who.int/hq/2007/WHO_CDS_NTD_WHOPES_GCDPP_2007.3_eng.pdf, accessed 29 October 2014).

The average of the applied to target dose ratio was 0.89–1.17 for alpha-cypermethrin WG-SB at 20 mg AI/m², 0.83–1.80 for the WG-SB at 30 mg AI/m², 0.87–1.66 for alpha-cypermethrin WP at 20 mg AI/m² and 0.68–1.06 for WP at 30 mg AI/m². The AI content variation between filter-papers, as expressed as relative standard deviation (RSD), ranged from 16.1% to 85.3% (Table 2.1) (Pigeon, 2014a).

The average applied to target dose ratio was within the expected range of the target dose ±25% for the WG-SB treatment with the exception of 30 mg/m^2 treatment on one surface (mud wall with lime coating), which was higher than expectation (Table 2.1). The average applied/target dose ratio ±25% for the WP treatment was higher than expectation for three of the four surfaces at 20 mg/m^2 and below expectation for one of the surfaces at 30 mg/m^2.

A decrease in residual activity with time was observed by cone bioassay on the sprayed surfaces. Alphacypermethrin WG-SB showed residual efficacy for 13–15 weeks for the 20 mg/m^2 and 13–16 weeks for the 30 mg/m^2 application rates (Figure 2.1). Alphacypermethrin WP showed residual efficacy for 11–15 weeks for the 20 mg/m^2 target application rate and 11–14 weeks for the 30 mg/m^2 rate. Noting that the actual rate deviated from the target for the WP treatment, the residual efficacy for the treatment close to the 20 mg/m^2 actual dosage was 11–14 weeks and for the treatments close to the 30 mg/m^2 actual dosage the residual efficacy was 11–15 weeks (Table 2.1). Residual efficacy was lowest for the brick wall unpainted surface, highest on the cement wall with distemper coating and intermediate for the lime-coated surfaces regardless of the underlying (mud or cement) substrate (Figure 2.1).

After spraying, no significant adverse events were reported by the spraymen or inhabitants.

2.2.2 Ouidah, Benin

A similar small-scale study was conducted in Ouidah, Benin, to compare the initial efficacy and residual activity of alphacypermethrin WG-SB at 20 and 30 mg AI/m² and alphacypermethrin WP at 20 and 30 mg AI/m² on different wall surfaces (Djenontin et al., 2014). The study was conducted in Tokoli village where 40 houses were assigned to the four treatment arms (5 houses per treatment) and 10 to the untreated control arm. The insecticides were applied using a

hand-operated compression sprayer fitted with a pressure gauge, a control flow valve (1.5 bar) and a flat fan nozzle (8002).

The treatments were sprayed in houses with two types of wall surface: cement/sand and mud plaster. To assess the quality of the spray application, the chemical content of a total of 200 filter-papers (40 control; 160 treated) fixed to the walls was analysed using a method based on CIPAC.

Cone bioassays were performed using a colony of *An. gambiae* Kisumu, which was susceptible to pyrethroids. Four replicates of 10 mosquitoes were exposed for 30 minutes in the cones in five houses per treatment at each interval, with bioassays conducted one week after treatment, then fortnightly for two months and then monthly.

The applied to target dose ratio exceeded expectation by a factor of 1.42–1.92 across the range of treatments and target application rates (Table 2.2) (Pigeon, 2014b). The AI content variation between filter-papers, expressed as RSD, ranged from 26.9% to 38.7%. The applied dosage was on average 10 mg/m^2 higher than the target dosage ±25% for all treatments.

Residual activity decreased with time on the sprayed surfaces. Alphacypermethrin WG-SB showed two weeks' residual efficacy at 20 and 30 mg/m^2 on mud, four weeks at 20 mg/m^2 on cement and six weeks at 30mg/m^2 on cement. Alphacypermethrin WP showed longer residual efficacy than WG-SB across all treatments: two weeks at 20 mg/m^2 on mud, eight weeks at 30 mg/m^2 on mud, and 12 weeks on cement at both 20 and 30 mg/m^2.

After spraying, no significant adverse events were reported by the spraymen or inhabitants.

2.3 Conclusions and recommendations

Alphacypermethrin 250 WG-SB (Tagros Chemicals India. Ltd., Chennai, India) is a water-dispersible granule formulation containing 250 g of active ingredient per kg, packaged in water-soluble bags, intended for IRS for malaria vector control.

The present review assesses the efficacy and residual activity of alphacypermethrin 250 WG-SB in comparison with the WHO recommended alphacypermethrin 50 WP (wettable powder formulation containing 50 g of AI per kg) as a positive control against malaria vectors from WHOPES-supervised small-scale field studies in

Benin and India. Two application rates (20 and 30 mg/m^2) were compared on cement and mud-plastered walls.

In India, alphacypermethrin WG-SB showed residual efficacy for 13–15 weeks for the 20 mg/m^2 application rate and 13–16 weeks for the 30 mg/m^2 rate. Alphacypermethrin WP showed up to 14 weeks of residual efficacy for the 20 mg/m^2 application rate and 15 weeks for the 30 mg/m^2 rate based on the actual dosage applied, though the difference from the WG-SB was not significant.

In Benin, alphacypermethrin WG showed consistently shorter residual efficacy than WP across all treatments. The duration of residual activity ranged from two to 12 weeks and was consistently shorter than in India.

Noting the above, the Working Group concluded:

- that there was no clear evidence that the residual efficacy of alphacypermethrin 250 WG-SB differed from alphacypermethrin 50 WP when applied at 20 and 30 mg/m^2 for IRS against malaria vectors.

The Working Group recommended:

- the use of alphacypermethrin 250 WG-SB at 20–30 mg/m^2 with residual efficacy of up to four months.

Note: WHO recommendations on the use of pesticides in public health are valid ONLY if linked to WHO specifications for their quality control.

Table 2.1 Cone bioassay results in WHOPES small-scale evaluation in India against *Anopheles stephensi*

Formulation	Target dose (mg AI/ m^2)	Actual dose (mg AI/ m^2)	Actual/ target dose ratio	N papers analysed[a]	RSD[b]	Surface type	Efficacy (months ≥80%)
Alpha-cypermethrin 250 WG-SB	20	17.7	0.89	6	47.5	Cement wall + distemper coating	3
	20	23.3	1.17	6	24.7	Cement wall + lime coating	3
	20	22.8	0.90	6	85.3	Mud wall + lime coating	3
	20	21.7	1.11	7	16.9	Brick wall unpainted	3
Alpha-cypermethrin 250 WG-SB	30	26.5	0.83	6	44.0	Cement wall + distemper coating	3
	30	30.8	1.03	6	38.7	Cement wall + lime coating	3
	30	53.9	1.80	6	20.3	Mud wall + lime coating	3
	30	26.4	0.88	6	57.4	Brick wall unpainted	3

Table 2.1 (cont.) Cone bioassay results in WHOPES small-scale evaluation in India against *Anopheles stephensi*

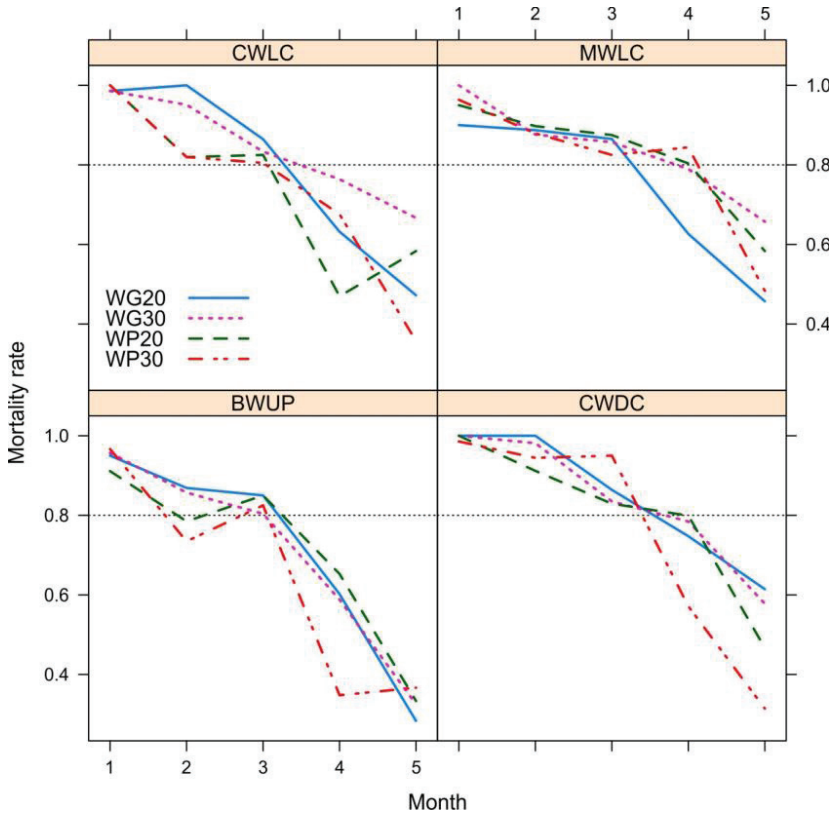
Formulation	Target dose (mg AI/ m^2)	Actual dose (mg AI/ m^2)	Actual/ target dose ratio	N papers analysed[a]	RSD[b]	Surface type	Efficacy (months ≥80%)
Alpha-cypermethrin 50 WP	20	30.5	1.53	6	19.3	Cement wall + distemper coating	3
	20	17.3	0.87	6	35.6	Cement wall + lime coating	3
	20	29.8	1.50	6	16.1	Mud wall + lime coating	4
	20	33.1	1.66	6	22.4	Brick wall unpainted	3
Alpha-cypermethrin 50 WP	30	20.6	0.68	6	36.7	Cement wall + distemper coating	3
	30	26.6	0.88	6	43.8	Cement wall + lime coating	3
	30	22.8	0.76	6	53.6	Mud wall + lime coating	4
	30	31.7	1.06	6	42.5	Brick wall unpainted	3

The residual activity of the IRS applications was measured by standard WHO plastic cones placed on treated wall surfaces. Tests were performed biweekly on susceptible *Anopheles stephensi* laboratory colonies until the end of the trial.

[a] Total number of filter-papers analysed, 6 houses per arm and surface type.

[b] RSD = Relative standard deviation of the AI content between filter-papers.

Figure 2.1 Mortality rates in cone bioassays as function of months after spray application in Balepura village, Karnataka, India (the dotted line represents the 80% cut-off value)



CWLC: cement wall with lime coating. MWLC: mud wall with lime coating. BWUP: brick wall, unpainted. CWDC: cement wall with distemper coating.

Table 2.2 Cone bioassay results in WHOPES small-scale evaluation in Benin against *Anopheles gambiae s.s.* Kisumu strain

Formulation	Target dose (mg AI/ m^2)	Actual dose (mg AI/ m^2)	Actual/target dose ratio	N papers analysed[a]	RSD[b] (%)	Surface type	Efficacy (months ≥80%)
Alpha-cypermethrin 250 WG	20	38.4	1.92	20	38.7	Cement wall	1
	20	34.8	1.74	20	36.0	Mud-plastered wall	1
Alpha-cypermethrin 250 WG	30	53.4	1.78	20	35.7	Cement wall	2
	30	42.6	1.42	20	34.4	Mud-plastered wall	1
Alpha-cypermethrin 50 WP	20	32.6	1.63	20	34.1	Cement wall	3
	20	35.0	1.75	20	36.5	Mud-plastered wall	1
Alpha-cypermethrin 50 WP	30	43.8	1.46	20	35.5	Cement wall	3
	30	42.6	1.43	20	26.9	Mud-plastered wall	2

[a] Total number of filter-papers analysed, 5 houses per arm and surface type and 4 filter-papers per room.

[b] RSD = Relative standard deviation of the AI content between filter-papers.

3. REVIEW OF ICON MAXX LONG-LASTING NET TREATMENT

ICON® MAXX is manufactured by Syngenta, Switzerland, as a "dip-it-yourself" kit for long-lasting insecticidal treatment of polyester nets. The kit is based on the slow-release capsule suspension (CS) of lambda-cyhalothrin that was previously evaluated by WHOPES and was recommended for treatment of mosquito nets by the 11th meeting of the WHOPES Working Group.[1] The manufacturer designed ICON MAXX as a long-lasting insecticide treatment for polyester mosquito nets able to withstand multiple washes. WHO specifications for lambda-cyhalothrin CS have been published and are available on the WHOPES website.[2]

ICON MAXX is supplied as a twin-sachet pack, containing 7.3 ml of lambda-cyhalothrin 10% CS and 7.7 ml of binding agent, sufficient for the treatment of an individual polyester mosquito net.[3] The target dose of ICON MAXX on a family-size (130 x 180 x 150 cm) polyester mosquito net is 62 mg AI/m^2 (corresponding to 1.55 g AI/kg for a 100-denier fabric net). The target dose depends on the net size and can range from 50 mg AI/m² (for a large family-size net) to 83 mg AI/m² (for a single-size net).

A safety assessment of ICON MAXX treatment and subsequent use of treated nets was carried out by the 11th WHOPES Working Group meeting.[1] Considering the safety, efficacy and resistance to washing of nets treated with ICON MAXX in laboratory and small-scale field studies, the Working Group recommended that a time-limited interim recommendation be given to ICON MAXX, that WHOPES should coordinate large-scale (Phase III) field studies to confirm the long-lasting efficacy of the treatment as a requirement for developing full recommendations on the use of the product and that, given the heterogeneity in AI concentration observed on nets during trials, nets treated with ICON MAXX could not be recognized as equivalent to WHOPES-recommended, factory-produced long-lasting insecticidal nets (LNs).

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[1] Report of the Eleventh WHOPES Working Group meeting, Geneva 10–13 December 2007. Geneva: World Health Organization; 2008 (http://whqlibdoc.who.int/hq/2008/WHO_HTM_NTD_WHOPES_2008.1_eng.pdf?ua=1, accessed 29 October 2014).

[2] See: http://www.who.int/whopes/quality/newspecif/en/ (accessed 29 October 2014).

[3] Syngenta clarified to WHO on 6 October 2014 that ICON MAXX is supplied as twin sachets containing 7.3 ml of lambda-cyhalothrin 10% CS and 7.7 ml of binder.

Subsequent to the above recommendations, WHO carried out two Phase III trials of polyester nets manually treated at the recommended dose of lambda-cyhalothrin using the ICON MAXX kit in India and the United Republic of Tanzania to determine the duration of effective life up to 36 months. Additional background information was sought from the manufacturer and from a literature review. Only one background document was found from Côte d'Ivoire (Winkler et al., 2012).[1] This manuscript reported on a Phase I laboratory study and a Phase II experimental hut study. The information was not considered relevant to Phase III field studies that are needed for full recommendation, and therefore the present assessment includes only two WHOPES-supervised trials.

3.1 Efficacy – WHOPES-supervised Phase III trials

Odisha, India. A Phase III field trial was conducted in five villages in Koraput District in Odisha State of India (Sahu et al., 2014). A census was carried out in all villages prior to the start of the study. Each house was geo-coded using a hand-held GPS, and information on the name, age and gender of every resident was obtained along with the type of house, the availability of nets/ITNs, their frequency of use and washing, and information on the occupation and household income of all residents.

Before distribution, polyester nets of size 120 x 200 x 180 cm were treated with ICON MAXX according to the manufacturer's instructions, using 7.3 ml of lambda-cyhalothrin 10% CS and 7.7 ml of binder mixed in an appropriate amount of water. The target dose of these nets was 62 mg AI/m^2. Other polyester nets were treated with lambda-cyhalothrin 10% CS (ICONET) to a target dose of 15 mg AI/m^2. Following community sensitization activities, 440 households consented and were enrolled in the study. Of these, 300 were randomly selected to receive one coded polyester net with ICON MAXX long-lasting treatment while 140 were randomly selected to receive one coded conventionally treated net (CTN) treated with lambda-cyhalothrin at a target dose of 15 mg AI/m^2 without the binder. All coded nets were marked with polyester bands fixed to each net and a water-soluble ink to assist in the assessment of washing. An additional 395 non-coded nets were provided to other residents of

[1] Winkler MS, Tchicaya E, Koudou BG, Donzé J, Nsanzabana C, Müller P et al. Efficacy of ICON® Maxx in the laboratory and against insecticide-resistant *Anopheles gambiae* in central Côte d'Ivoire. Malar J. 2012;11:167.

these households. All nets were treated by dipping them in aluminium basins where they were turned in the insecticide solution for at least 2 minutes, allowed to drip over the basin to remove excess water and then dried horizontally in the shade. The dipping was done by a team of volunteer adult males who were provided with training and personal protective equipment.

To determine the initial dose, 30 nets from each arm were destructively sampled before distribution. Four pieces (25 x 25 cm) were removed from each net, in accordance with WHOPES guidelines, with position 1 excluded, pooled together and subjected to chemical analysis using the CIPAC method 463/LN/M/3. Lambda-cyhalothrin was extracted by ultra-sonication for 30 minutes in acetone-containing glacial acetic acid and dicyclohexyl phthalate as internal standard. The lambda-cyhalothrin content was measured by gas chromatography with flame ionization detection (GC-FID). Chemical analysis was also performed on 30 nets from each arm that were removed from the field after 12 months (Pigeon, 2013a). At 36 months, chemical analysis was carried out on 50 ICON MAXX-treated nets (Pigeon, 2014c).

Nets were followed at six-month intervals for user acceptability, attrition and random sampling for biological assays. Thirty nets were removed at each time point for bioassays, except at the 36-month follow-up when 80 nets were removed. The CTNs were followed only until the 12-month time point. At the time of removal, owners were interviewed to assess the frequency of use and washing as these factors are likely to be related to the loss of insecticide and insecticidal activity over time.

WHO cone bioassays were initially conducted using wild-caught *An. fluviatilis,* which were demonstrated to be susceptible to lambda-cyhalothrin in standard WHO susceptibility tests. Twenty-five mosquitoes were exposed to the five netting pieces for a total of 25 mosquitoes exposed per net. However, inadequate numbers were obtained due to low mosquito densities and, beginning at 24 months, a susceptible colony of *An. stephensi* was used for the bioassays. At the 36-month follow-up, mosquitoes were exposed only to net pieces from positions 2 to 5, according to the recommended WHOPES sampling scheme.

Attrition and physical integrity of the ICON MAXX-treated nets were monitored, as recommended in WHOPES guidelines for the evaluation of factory-treated LNs. However, these data are not

presented as ICON MAXX may be used for a range of net types and, therefore, attrition and physical integrity are not relevant to the product claim.

Net use was high throughout the study, with more than 65% of respondents reporting using the nets year-round and every night. Those who did not use their nets year-round every night used their nets either occasionally or seasonally. Less than 10% of respondents reported not using their nets. Net owners were asked about the number of washes since the previous visit and responses were used to estimate an annual frequency of washing. The estimated rate of washing gradually increased over the course of the study from 0.9 at the six-month follow-up to 8.3 washes per year at the 36-month follow-up.

The bio-efficacy of the ICON MAXX-treated nets was high through 30 months. All nets tested through 24 months passed by the cone test alone, while 24 of 30 (80.0%) passed by the cone test alone at 30 months. At 36 months, bio-efficacy of the nets dropped, and 35 of 80 nets (56.3%) failed according to the cone test. Of the 35 nets that failed the cone test, two passed the tunnel test for an overall pass rate of 37 out of 80 (58.8%) (Table 3.1).

Baseline chemical analysis indicated that the mean lambda-cyhalothrin content of the ICON MAXX-treated nets was 62.0 mg AI/m^2, which is right at the target dose for ICON MAXX. The between-net variation of the AI content, as expressed RSD, was 12.0%. After 36 months of use, the mean lambda-cyhalothrin content of the ICON MAXX-treated nets was 34.5 mg AI/m^2 (n = 50, RSD = 59.2%), showing a loss of 44.4% of the original dose (Table 3.2, Figure 3.1). At baseline, the lambda-cyhalothrin content of the CTNs was 20.6 mg AI/m^2 against a target dose of 15 mg AI/m^2.

Muheza, United Republic of Tanzania. A Phase III field trial of ICON MAXX was conducted in two villages in Muheza District in Tanzania (Tungu et al., 2014). Most inhabitants were subsistence farmers growing maize, cassava and rice, with some sisal plantations, small-scale orange plantations and animal husbandry. Malaria transmission in the district is classified as holoendemic although some areas have a long history of use of insecticide-treated nets (ITNs). Villages and hamlets were enumerated at baseline. A census of the target villages recorded the geographical position of each household, and the number of people and number of sleeping spaces

per house. The name, age and gender of each resident of the household were recorded at baseline.

Before distribution, 2500 polyester nets in three sizes (180 x 180 x 150 cm, 150 x 180 x 150 cm, 120 x 180 x 150 cm) were conventionally treated with ICON MAXX according to the manufacturer's instructions, using 7.3 ml of lambda-cyhalothrin 10% CS and 7.7 ml of binding agent mixed in an appropriate amount of water for each net size. The target dose of these nets was 62 mg AI/m^2. A further 1250 polyester nets were conventionally treated with lambda-cyhalothrin 10% CS (ICONET) to a target dose of 15 mg AI/m^2. Treatment of the nets was carried out by a team of trained field-workers. Nets were treated individually in basins and then dried horizontally in the shade. While drying, nets were flipped periodically until there was no further dripping and then they were hung on a rope. Of the 2500 ICON MAXX nets, half were distributed at the beginning of the trial while the remaining nets were held back as replacement nets. All 1250 CTNs were distributed through house-to-house visits. Each net was given a unique code number that was written on the net with a permanent marker. The nets were randomly allocated to households and stratified by village so that each village received ICON MAXX nets and CTNs in a 1:1 ratio.

Thirty nets each of both treatment arms were randomly sampled at baseline and at six and 12 months after distribution. Thereafter, only ICON MAXX nets were sampled (30 nets each were sampled at 18, 24 and 30 months after distribution, while 50 nets were sampled at 36 months after distribution). At the time of sampling, net owners were interviewed to estimate the frequency of use and washing of the nets.

Cone bioassays were conducted using 2–5-day-old unfed female *An. gambiae* s.s. Kisumu strain. At baseline, five net pieces were removed from each net, in accordance with WHOPES guidelines, and 20 mosquitoes were exposed to each piece in plastic cones for three minutes. At all other time points, the piece at the bottom of the net (position 1) was excluded from bioefficacy testing. Knockdown was recorded after 60 minutes and mortality at 24 hours after exposure. For those nets in which average knockdown was <95% and average mortality was <80%, the tunnel test was performed on the sample closest to the average mortality for all four pieces.

At baseline and 12 months after distribution, a separate set of five pieces was cut from each of the 30 sampled ICON MAXX nets and CTNs for chemical analysis by GC-FID (Pigeon, 2013b). At 36

months after distribution, five pieces of 25 x 25 cm were cut from each of 50 ICON MAXX nets for chemical analysis using the CIPAC method 463/LN/M/3 (Pigeon, 2014d). As with the bioassays, the piece cut from the lowest point on the net (position 1) was not included.

Attrition and physical integrity of the ICON MAXX-treated nets were monitored, as recommended in WHOPES guidelines. However, these data are not presented as the ICON MAXX may be used to treat a variety of net types and, therefore, the attrition and physical durability of polyester nets distributed in this study were not considered relevant to the product claim.

Both the ICON MAXX nets and CTNs were well accepted by the communities. Reported net use was 100% at each time point. The frequency of net washing was converted to an estimated number of washes over a 12-month period. The mean frequency of washing was estimated at 1–6 times per year. Washing frequency was highest during the 18-month follow-up at 6 times per year. Estimated washing frequency was 4 times per year at all subsequent follow-ups.

The bioefficacy of ICON MAXX-treated nets remained high throughout the study period. The ICON MAXX-treated nets met the WHOPES efficacy criteria by the cone test alone through 12 months. Thereafter, less than 80% of nets met the WHOPES efficacy criteria for the cone test. However, when the tunnel test was included, more than 90% of ICON MAXX-treated nets met the efficacy criteria for the combined cone test and tunnel test at each time point, except at the 30-month follow-up when 86.7% of nets met the WHOPES efficacy criteria (Table 3.1).

At baseline, the lambda-cyhalothrin content of the ICON MAXX-treated nets was 60.1 mg AI/m^2, which was very close to the target dose of 62 mg AI/m^2. The between-net variation of the AI content, as expressed as RSD, was 17.1%. After 36 months, the lambda-cyhalothrin content of the ICON MAXX-treated nets was 15.8 mg AI/m^2 (n = 50, RSD = 93.4%), showing a loss of 73.7% of the original dose (Table 3.2, Figure 3.2). At baseline, the lambda-cyhalothrin content of the CTNs was 12.7 mg AI/m^2 against a target dose of 15 mg/m^2.

3.2 Conclusions and recommendations

The ICON MAXX is a "dip-it-yourself" kit manufactured by Syngenta, Switzerland, for long-lasting treatment of polyester nets and is designed to withstand multiple washes. The kit includes lambda-cyhalothrin 10% CS and a binder which, when used according to the manufacturer's instructions, should achieve a target dose of 62 mg AI/m^2 for a family-size net (130 x 180 x 150 cm). A safety assessment and review of the efficacy of ICON MAXX in Phase I and Phase II studies were published previously in the report of the 11th meeting of the WHOPES Working Group. On the basis of its performance in laboratory and experimental hut studies, ICON MAXX was given an interim recommendation as a long-lasting treatment for polyester nets. In this current review, data from two Phase III field studies were considered as a requirement for a full recommendation.

The two WHOPES-supervised studies were conducted according to the WHO guidelines for Phase III evaluation of LNs. In India, bioassays were conducted with wild-caught susceptible *An. fluviatilis* during the first two years, while a susceptible colony of *An. stephensi* was used for the 30-month and 36-month follow-ups. At 30 months, 80% of ICON MAXX-treated nets met the efficacy criteria for an LN on the basis of the cone test alone. At 36 months, 56.3% met the efficacy criteria for the cone test alone, while 58.8% met the efficacy criteria for either the cone test or the tunnel test. At baseline, the mean lambda-cyhalothrin content on the ICON MAXX nets was 62.0 mg/m^2. After 36 months of use, 44.4% of the initial dose had been lost.

In Tanzania, the performance of ICON MAXX in WHO cone bioassays using a susceptible colony of *An. gambiae* declined over time, with 100% meeting the efficacy criteria for the cone test at baseline but only 26% meeting the efficacy criteria for the cone test after three years. However, ICON MAXX performed well in the tunnel test and more than 80% of the ICON MAXX-treated nets met the efficacy criteria for either the cone test or the tunnel test at each time point through 36 months. Chemical analysis indicated that the lambda-cyhalothrin content of the ICON MAXX nets at baseline was 60.1 mg AI/m^2. After three years of routine use, 73.7% of the initial dose had been lost.

Noting the above, the meeting recommended:

- that on the basis of the WHOPES guidelines for the evaluation of LNs, which are largely based on efficacy criteria, and noting the

overall bio-efficacy of the ICON MAXX long-lasting treatment for polyester nets, full recommendation be granted with an estimated duration of insecticidal efficacy of 30–36 months depending on the local settings.

The meeting also recommended:

- that national programmes should monitor and evaluate the performance of the ICON MAXX long-lasting treatment applied to polyester nets under local conditions in accordance with procedures recommended in the WHO guidelines.[1]

Note: WHO recommendations on the use of pesticides in public health are valid ONLY if linked to WHO specifications for their quality control.

[1] Instructions for treatment and use of insecticide-treated mosquito nets. Geneva: World Health Organization; 2002 (http://whqlibdoc.who.int/hq/2002/WHO_CDS_RBM_2002.41.pdf?ua=1, accessed 29 October 2014).

Table 3.1 Results for cone bioassays of ICON MAXX-treated nets

Survey (month)	WHO cone tests				Tunnel tests				Number passing cone or tunnel	Overall pass rate (%)
	Number of nets	Mean % knock-down	Mean % mortality	Number meeting WHO criteria for cone test	Number of nets	Mean % mortality	% blood-feeding inhibition	Number meeting WHO criteria for tunnel test		
India										
6	30	100	100	30	---	---	---	---	30	100
12	30	100	100	30	---	---	---	---	30	100
18	30	100	100	30	---	---	---	---	30	100
24	30	100	88.3	30	---	---	---	---	30	100
30	30	97.1	67.5	24	6	34.5	30.7	0	24	80
36	80	90.1	76.2	45	35	41.5	29.0	2	47	58.8
United Republic of Tanzania										
6	30	97.7	87.2	29	1	98.0	91.0	1	30	100
12	30	96.7	91.1	28	2	81.3	62.2	1	29	96.7
18	30	80.9	83.0	21	9	NA	NA	8	29	96.7
24	30	85.1	75.2	21	9	81.6	60.2	6	27	90
30	30	78.0	61.6	10	20	81.3	61.8	16	26	86.7
36	50	71.8	49.2	13	37	81.5	54.7	32	45	90

NA: Data not available at the time of the report.

Table 3.2 Lambda-cyhalothrin content in treated nets*

Survey (month)	ICON MAXX-treated nets**			CTNs**		
	N	Mean g AI/kg	Mean mg AI/m^2	N	Mean g AI/kg	Mean mg AI/m^2
India						
0	30	1.45 (1.39–1.51)	62.0 (59.2–64.8)	30	0.50 (0.48–0.52)	20.6 (19.6–21.6)
12	30	1.03 (0.90–1.16)	45.2 (39.3–51.1)	30	0.32 (0.22–0.42)	13.7 (9.3–18.1)
36	50	0.76 (0.63–0.89)	34.5 (28.7–40.3)			
United Republic of Tanzania						
0	30	1.44 (1.35–1.53)	60.1 (56.3–63.9)	30	0.30 (0.27–0.33)	12.7 (11.5–13.9)
12	30	0.68 (0.56–0.80)	28.9 (23.9–33.9)	30	0.09 (0.02–0.16)	4.0 (0.9–7.1)
36	50	0.37 (0.27–0.47)	15.8 (11.5–20.1)			

*The target dose at baseline is 62 mg AI/m^2 for ICON MAXX on a family-size (130 x 180 x 150 cm) polyester net (corresponding to 1.55 g AI/kg for a 100-denier fabric) and 15 mg AI//m^2 for CTNs.

**Figures in brackets represent 95% confidence limits.

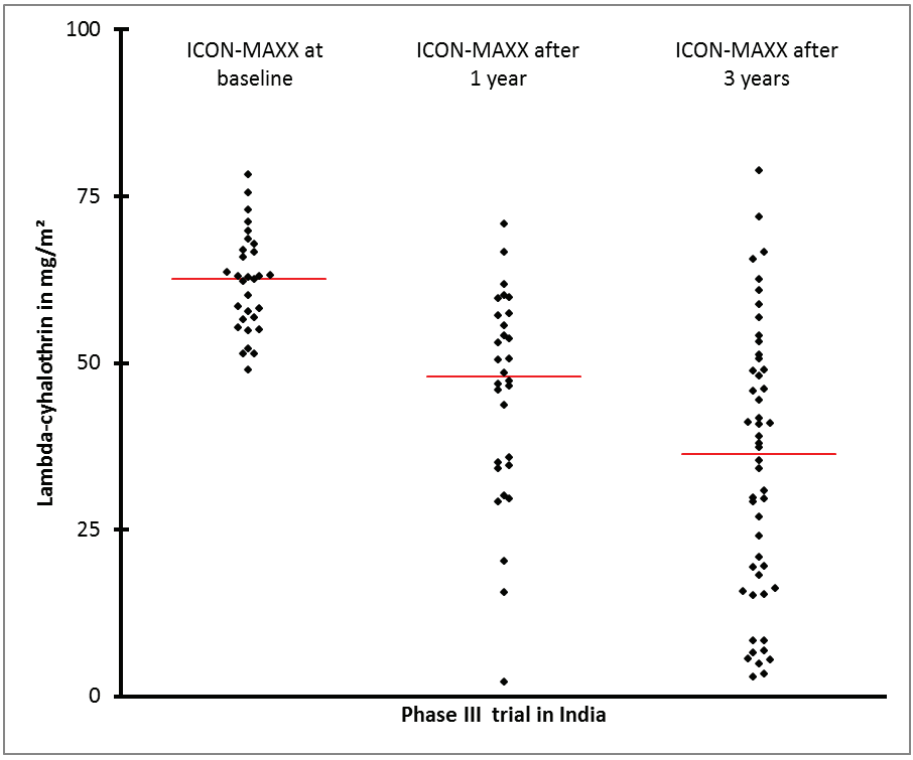

Figure 3.1 Lambda-cyhalothrin content (in mg AI/m^2) on individual ICON MAXX netting samples at baseline and after 1 and 3 years of household use in India (mean doses are shown as short red lines)

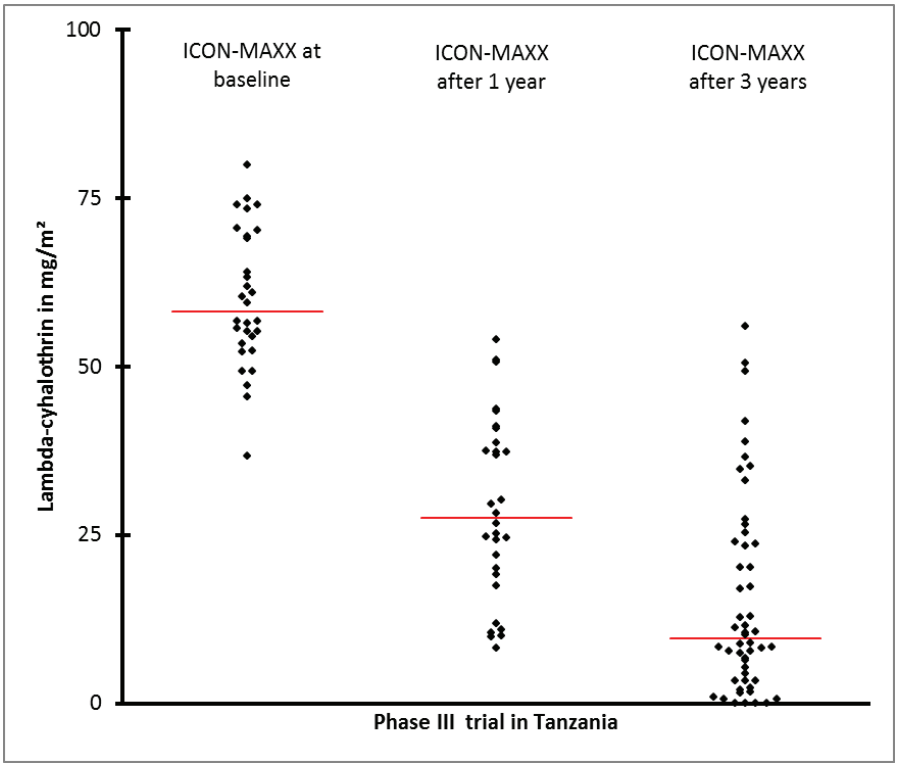

Figure 3.2 Lambda-cyhalothrin content (in mg AI/m^2) on individual ICON MAXX netting samples at baseline and after 1 and 3 years of household use in Tanzania (mean doses are shown as short red lines)

4. RE-EVALUATION OF NETPROTECT LN

Netprotect is a deltamethrin long-lasting (incorporated into polyethylene) insecticidal net (LN). Deltamethrin is incorporated into 118-denier, monofilament polyethylene fibres of different densities, with the target dose of 1.8 g AI/kg, corresponding to 68.4 mg of deltamethrin per square metre of fabric (weight 38 g/m^2). Netprotect is manufactured by Bestnet A/S, Denmark.

WHO has been advised that, as from 21 October 2005, the owner of Netprotect, Intelligent Insect Control, licensed the manufacture and commercialization of Netprotect to Bestnet Europe Ltd. and subsequently to Bestnet A/S.

A safety assessment of Netprotect LN and WHO's interim recommendations for the use of the product in the prevention and control of malaria were published in the report of the 11th meeting of the WHOPES Working Group.[1] In 2013, the 16th meeting of the WHOPES Working Group assessed reports of the Phase III studies of Netprotect. Taking into account all the available information, the 16th meeting concluded:

- "that sufficient evidence is not available to grant full recommendation to Netprotect. The meeting recommended that until more evidence on performance of the product is available from large-scale studies, the WHO interim recommendation on the use of the product be withdrawn; and

- that national programmes currently using Netprotect for malaria prevention and control be urged to monitor efficacy and performance of Netprotect under local conditions, using WHO guidelines[2] and provide any feedback to the WHOPES secretariat."

Accepting these recommendations, WHO withdrew the interim recommendation on the use of Netprotect in October 2013. The

[1] Report of the Eleventh WHOPES Working Group meeting, 10–13 December 2007. Geneva: World Health Organization; 2008 (http://who.int/whopes/recommendations/wgm/en/, accessed 22 October 2014).
[2] Guidelines for monitoring the durability of long-lasting insecticidal mosquito nets under operational conditions. Geneva: World Health Organization; 2011 (http://whqlibdoc.who.int/publications/2011/9789241501705_eng.pdf, accessed 22 October 2014).

manufacturer subsequently informed WHO of two ongoing Phase III studies being conducted by the United States Centers for Disease Prevention and Control (CDC) in Kenya and Malawi and requested WHO to re-evaluate Netprotect on the basis of the findings of these two additional trials. The present re-assessment therefore includes a review of these two additional field studies as potential new evidence for further consideration of Netprotect.

4.1 Efficacy – Phase III (large-scale) field trial reports submitted by the manufacturer

Kisumu, Kenya

A field study of Netprotect LN was conducted in western Kenya in an area known locally as Gem, within Siaya County (Ombok et al., 2014). In December 2009, a total of 663 Netprotect nets were distributed to cover all sleeping spaces in 367 compounds in two selected villages. A master list was generated with the code of each net, the name of the owner and the compound identification code to facilitate follow-up. On average, 1.8 coded nets were distributed to each compound. No positive control arm was mentioned in the report. Surveys took place approximately 8, 14, 20, 26, 32 and 36 months after distribution of the nets. Randomization of nets did not take into account the cluster effect of the households. Nets removed from the households for destructive sampling (around 30 per survey and 50 for the last survey) were replaced with new LNs and removed from the master list.

Eight months after distribution, 10% of nets had been lost, with 29% lost after 36 months (Table 4.1). Most loss of nets was due to factors other than damage or degradation (e.g. nets were stolen, given away or used elsewhere). Of the nets that were lost after 36 months, only 4.3% were lost due to physical damage, fire or perceived loss of insecticidal activity.

Testing of the physical integrity of sampled nets was performed in the laboratory by draping nets over a frame to count the holes and measure their size. The proportion of nets with any hole increased from 17% after 8 months to 74% after 36 months (Table 4.2). The median number of holes was relatively low (≤ 4) up to 32 months post-distribution and increased to 8.5 after 36 months of use. The median hole area increased substantially after 32 months. The hole index per net was not reported.

Bioassay data were available only for the last survey (at approximately 37 months). On the basis of the WHOPES efficacy criteria for Phase III trials (thresholds of 80% mortality or 95% knockdown), 30 of the 50 tested nets (60%) passed the cone test. The remaining 20 nets were subjected to tunnel tests, of which 11 passed, thus providing a combined pass rate of 41 out of 50 (82%). However, for nine nets tested by cone assay, mortality in the control was above the acceptable threshold of 10%. Moreover, after adjusting for mortality in the control, one net failed the tunnel test. Such discrepancies may have affected the outcome and interpretation of the results.

The insecticide content was measured at CDC in Atlanta (GA), USA. For each net analysed, five pieces of netting measuring 10 x 10 cm were cut from each side and the top of the net and were pooled before determination of deltamethrin content using a method based on the CIPAC method 333/LN/(M2)/3. Deltamethrin was extracted by heating to boiling under reflux for 30 minutes in xylene with an internal standard; the xylene extract was evaporated to dryness and dissolved in the HPLC mobile phase. Initially dibutyl phthalate was used as the internal standard, as recommended in the CIPAC method. However, an unexpected compound in the Netprotect nets interfered with the internal standard and therefore dipropyl phthalate was substituted as the internal standard. The final extract was then injected into high-performance liquid chromatography with UV detection (HPLC-UV) for determination of deltamethrin. As part of the internal standard was lost during evaporation, the calculations were finally performed using calibration of the external standard. The content of both the biological active S-stereoisomer (deltamethrin) and the inactive R-alpha stereoisomer was measured on all samples.

Only eight nets were analysed for baseline insecticide determination. The mean deltamethrin content of these nets was 1.31 g/kg. Five of the eight nets had deltamethrin content below the lower tolerance limit of the target dose of 1.8 g/kg (range of tolerance limit: 1.35–2.25 g/kg). Mean deltamethrin content of 0.86 g/kg was recorded for 10 nets after 14 months and 12 nets after 26 months. The ratio of R-isomer to deltamethrin (S-isomer) increased from 0.22:1 at the baseline to 0.40:1 and 0.36:1 after 14 and 26 months, respectively (Table 4.3). Samples from five nets (5 pieces per net) were submitted to the WHO Collaborating Centre for Quality Control of Pesticides at the Walloon Agricultural Research Centre, Gembloux, Belgium, for AI content testing. The mean deltamethrin content was 1.50 g/kg and all nets complied with the target dose of 1.8 g/kg (tolerance limit: 1.35–

2.25 g/kg). The ratio of R-isomer to deltamethrin (S-isomer) was 0.20:1.

Chikhwawa, Malawi. The field study villages were located in Chikhwawa District, approximately 40 km south of the city of Blantyre in southern Malawi (Mzilahowa et al., 2014). In September 2009, a total of 670 Netprotect nets, labelled with a unique identifier, were distributed to cover all sleeping spaces in 379 households in four selected villages. Randomization of nets did not take into account the cluster effect of households. On average, 1.8 nets were distributed to each household. No positive control arm was mentioned in the report. Surveys took place approximately 4, 11, 16, 24, 30 and 37 months after distribution of the nets. Nets removed from the households for destructive sampling (around 30 per survey) were replaced with new LNs and were removed from the master list.

Four months after distribution, 27% of nets had been lost and net attrition increased to 56% after 37 months (Table 4.1). A large number of the nets that were lost had belonged to study participants who temporarily moved out of the study area. Significant loss of nets due to damage (9%) began only after two years and reached 20% at 37 months. The physical integrity of sampled nets was assessed in the laboratory by draping nets over a frame to count the holes and measure their size. The proportion of nets with any hole increased from 28% after 4 months to 97% after 37 months (Table 4.2). After approximately 1 year of use, the median number of holes was 8 and the median hole area was 9.8 cm^2. Damage gradually increased over the next two years, reaching a median of 26 holes at the 37-month follow-up.

Bioassay data were available for only 26 nets in the last survey (approximately 39 months after net distribution). On the basis of the WHOPES efficacy criteria for Phase III trials (thresholds of 80% mortality and/or 95% knockdown), 21 of the 26 tested nets (80.8%) passed the cone test. The remaining 5 nets were subjected to tunnel tests in the Centre Suisse de Recherche Scientifique, Abidjan, Cote d'Ivoire, and all passed the tunnel test criteria. Taking into account both cone and tunnel assays, the pass rate was 26 out of 26 (100%).

The insecticide content was measured at CDC, Atlanta (GA), USA. For each net analysed, five pieces of netting measuring 10 x 10 cm were cut from each side and top of the net and were pooled before determination of deltamethrin content using a method based on the CIPAC method 333/LN/(M2)/3. Deltamethrin was extracted by heating to boiling under reflux for 30 minutes in xylene with dibutyl phthalate

as internal standard; the xylene extract was evaporated to dryness and dissolved in the HPLC mobile phase. The final extract was then injected into HPLC-UV for determination of deltamethrin using the internal standard calibration.

Only one net was available for baseline insecticide determination. The deltamethrin content of this net was 1.29 g/kg, which is below the target dose of 1.8 g/kg (tolerance limit: 1.35–2.25 g/kg) (Table 4.3). After 1 and 2 years, the nets had a mean deltamethrin content of 1.08 g/kg (n = 10 nets) and 0.64 g/kg (n = 21 nets). The ratio of R-isomer to deltamethrin (S-isomer) increased from an initial value of 0.31:1 to 0.36:1 and 0.56:1 after years 1 and 2, respectively.

4.2 Conclusions and recommendations

Two study reports were provided to the WHOPES Working Group for re-assessment of the efficacy and durability of Netprotect LN under field conditions. Neither of the studies, however, fully complied with the WHO requirement for testing and evaluation of LN in Phase III trials. The sample size used for the determination of the deltamethrin content in nets at the baseline survey was inadequate – i.e. 8 nets in Kenya and 1 net in Malawi instead of 30 nets for each site as specified in the WHO guidelines. The one net tested in Malawi was below the lower tolerance limit of the target dose of 1.8 g AI/kg ($\pm$25%) deltamethrin. The nets tested in Kenya could not be analysed for deltamethrin content according to the CIPAC method because of an unexpected peak in the HPLC chromatogram that obscured the internal standard. Tests at the CDC, USA, using an external standard showed that five of eight nets tested were below the specifications, while tests of these five nets by the WHO Collaborating Centre for Quality Control of Pesticides at the Walloon Agricultural Research Centre, Gembloux, Belgium, using an alternative internal standard to the one recommended by CIPAC found that all nets were within the specifications. No data on deltamethrin content were available for nets collected after 3 years. The ratio of R-isomer to deltamethrin (S-isomer) content increased over time in both studies, as previously reported in the report of the 16th WHOPES Working Group meeting.

The control mortality in bioassays was adjusted using Abbott's formula when mortality was between 5% and 20%, although WHOPES guidelines recommend repeating bioassays when control mortality is above 10%. Control mortality for 9 nets was above this threshold and this may have affected the results.

Noting the above, the meeting recommended:

- that sufficient evidence using Phase III criteria on the efficacy of Netprotect LN should be provided for reconsideration; and

- that the evidence should be generated in compliance with WHO requirements for testing and evaluation of LNs. The WHO guidelines specify that Phase III trials should be conducted at a minimum of three study sites.

Table 4.1 Attrition of Netprotect by survey, in field trials in Kenya and Malawi

Months after distribution	Nets surveyed	Nets lost	% nets lost	Number of nets lost due to damage[a]	% nets lost due to damage
Western Kenya					
8	663	66	10.0	0	0.0
14	634	78	12.3	0	0.0
20	604	65	10.8	1	0.2
26	575	87	15.1	8	1.4
32	544	150	27.6	6	1.1
36	514	151	29.4	22	4.3
Malawi					
4	670	184	27.5	4	0.6
11	641	209	32.6	6	0.9
16	617	312	50.6	8	1.3
24	593	201	33.9	56	9.4
30	565	163	28.9	66	11.7
37	536	299	55.8	107	20.0

[a] Includes nets lost due to fire, discarded because they were too torn or perceived to be ineffective against mosquitoes.

Table 4.2 Physical integrity of Netprotect by survey round

Surveys (months)	Number of nets	% nets with any hole	Mean number of holes	Median number of holes	Mean hole area (cm^2)	Median hole area (cm^2)
Kenya						
8	29	17.2	0.8 (0–1.6)	0 (0–0)	174 (0–447)	0 (0–0)
14	30	26.7	1.8 (0.5–3.2)	0 (0–3)	308 (0–700)	0 (0–4.7)
20	30	53.3	3.8 (1.9–5.7)	1.5 (0–7)	536 (0–1114)	3.5 (0–215)
26	30	80.0	5.3 (3.7–7.0)	4 (2–8)	64 (18–109)	8.6 (3.1–65.2)
32	30	73.3	6.6 (3.7–9.4)	3.5 (0–11)	1895 (239–3550)	59 (0–360)
36	50	74.0	10.2 (6.8–13.6)	8.5 (0–14)	2911 (1398–4423)	278 (0–4223)
Malawi						
4	28	28.6	1.4 (0.2–2.5)	0 (0–1)	19.8 (0–46.3)	0 (0–1.2)
11	24	58.3	9.6 (3.6–15.6)	8 (0–10)	25.2 (3.1–47.3)	9.8 (0–31.4)
16	25	92.0	39.4 (11.2–67.6)	17 (4–37)	198 (56.6–339)	35.7 (4.9–286)
24	30	93.3	34.2 (20.1–48.3)	21.5 (3–64)	325 (11.0–639)	46.1 (8.6–263)
30	29	93.1	26.7 (16.6–36.8)	16 (8–35)	287 (110–464)	55.4 (13.5–295)
37	30	96.7	29.0 (20.9–37.1)	26 (14–38)	441 (240–641)	188 (30.8–792)

Figures in parentheses are 95% CI for mean, or Interquartile for medians.

Table 4.3 Mean deltamethrin content in g AI/kg in Netprotect, relative standard deviation of the content between nets and percentage of AI lost over time in the two study sites (the *R*-alpha isomer content [g AI/kg] and the ratio of R-isomer to deltamethrin [S-isomer] content are also presented)

Site	Test parameters	Months after net distribution		
		0	14	26
Kenya	N	8[a]	10	12
	Mean	1.31 g/kg	0.86 g/kg	0.86 g/kg
	RSD	6.6%	29.8%	19.6%
	% lost	–	34%	34%
	R-alpha	0.29 g/kg	0.35 g/kg	0.31 g/kg
	Ratio	0.22:1	0.40:1	0.36:1
Malawi	N	1	10	21
	Mean	1.29 g/kg	1.07 g/kg	0.62 g/kg
	RSD	–	11.4%	34.4%
	% lost	–	16%	51%
	R-alpha	0.40 g/kg	0.41 g/kg	0.35 g/kg
	Ratio	0.31:1	0.38:1	0.56:1

According to the WHO specification, the target dose of deltamethrin in Netprotect at baseline is 1.8 (tolerance limit: 1.35–2.25) g/kg.

[a]5 of 8 nets are below the lower tolerance limit of deltamethrin target dose.

5. RE-EVALUATION OF CHLORFENAPYR 240 SC

Chlorfenapyr 240 SC is a suspension concentrate formulation containing 240 g of active ingredient per litre. The product is manufactured by BASF Germany for IRS against malaria vectors.

The safety assessment for the use of chlorfenapyr 240 SC for use in the prevention and control of malaria was published as part of the report of the 16th meeting of the WHOPES Working Group in 2013.[1] Considering the information available, the 16th Working Group meeting recommended:

- that multi-centre studies on different well-characterized strains of different mosquito species, with priority on major malaria vectors, be carried out to establish the diagnostic concentration(s) for chlorfenapyr;

- that further evidence be gathered to assess the impact of indoor residual application of chlorfenapyr on malaria vector populations. The current estimate of the duration of effective action of chlorfenapyr on different surfaces at 250 mg AI/m^2 is 0–9 weeks; and

- that manufacturers develop novel formulations or methods of application of chlorfenapyr for vector control, noting the potential of the compound in addressing insecticide resistance in malaria vectors.

Consequent to the recommendation that further evidence be gathered, BASF submitted results from some additional studies and requested WHO to re-evaluate the product on the basis of these results. The present assessment is therefore based on the additional data provided to WHO by the manufacturer in 2014.

[1] Report of the Sixteenth WHOPES Working Group meeting, Geneva 22–30 July 2013. Geneva: World Health Organization; 2013 (http://www.who.int/iris/bitstream/10665/90976/1/9789241506304_eng.pdf?ua=1, accessed 29 October 2014).

5.1 Efficacy – dataset submitted by the manufacturer

BASF provided to WHOPES a consolidated dataset supporting the use of chlorfenapyr for IRS (Austin et al., 2014). The report included one Phase II trial against pyrethroid-resistant *Anopheles gambiae* carried out in Burkina Faso and additional laboratory studies on various mosquito species (i.e. *Anopheles* spp., *Culex quinquefasciatus*, *Aedes aegypti*).

The background information from the manufacturer provided information relevant to a better understanding of the mode of action of chlorfenapyr against mosquitoes. Unlike all other insecticides recommended for adult anopheline control, the mode of action of chlorfenapyr is not on the nervous system but through disruption of respiratory pathways (oxidative phosphorylation) in the mitochondria of cells. The state of the metabolism of the mosquitoes is an important factor that influences the insecticidal activity of chlorfenapyr. Performance of chlofenapyr against mosquitoes can be influenced by extrinsic factors such as time of exposure, temperature during exposure and holding period, and time of the day or night when the test is conducted. It was noted that the increase of holding period to 72 hours did not systematically cause an impact on mortality rates according to the studies provided by the manufacturer. Consequently, some of the experiments and assays did not comply with WHO standard guidelines for testing and evaluation of insecticides. Phase I studies provided useful information for understanding the mode of action of chlorfenapyr. A new Phase I assay system for chlorfenapyr as IRS has so far not been developed.

BASF provided results of a new Phase II study to WHOPES in support of the request to reconsider the recommendation on the use of chlorfenapyr 240 SC for IRS. The efficacy and residual activity of chlorfenapyr SC 240 formulation for IRS was tested in Phase II experimental huts in Burkina Faso. The efficacy was compared to formulations of bendiocarb and alphacypermethrin alone and to a mixture of chlorfenapyr and alphacypermethrin. A total of 7 arms were tested as follows:

- chlorfenapyr SC 240 g/L, 150 mg/m²
- chlorfenapyr SC 240 g/L, 250 mg/m²
- alphacypermethrin, 30 mg/m²
- mixture of chlorfenapyr 150 mg/m² and alphacypermethrin 30 mg/m²

- mixture of chlorfenapyr 250 mg/m² and alphacypermethrin 30 mg/m²
- bendiocarb, 200 mg/m²
- untreated control.

WHO cone tests were performed to evaluate the residual efficacy using susceptible laboratory *An. gambiae* Kisumu strain and wild females of *An. gambiae* collected at larval stages in the field. The wild population was resistant to alphacypermethrin and susceptible to bendiocarb, as determined by CDC bottle bioassays. The exposure time of mosquitoes on the wall was two hours and observation time was 24, 48 and 72 hours after exposure.

The in situ cone bioassays showed that one day after treatment the cut-off point of 80% mortality was achieved for all treatments on the Kisumu strain. The mortality with alphacypermethrin was below 80% for the pyrethroid-resistant population. For all treatments, mortality dropped below 80% after 1 month, except for the treatment containing alphacypermethrin and tested with a susceptible strain. However, mortality rates of all treatments were below 30% at 1 month after treatment of the resistant population.

The trial in huts was conducted for 15 weeks (between 3 August and 3 December 2013). Overall 20 000 *An. gambiae* specimens were collected during the four months of evaluation in the 7 huts. The pooled data (Table 5.1) showed a higher mortality of free-flying mosquitoes for both treatments with chlorfenapyr (32–38%) than for the treatments with alphacypermethrin (5%) and bendiocarb (11%). As for the cone bioassays, the mortality rates did not increase with increase of observation time from 24 to 72 hours. Blood-feeding inhibition was low and ranged from 0% to 15% regardless of the treatment.

To assess the quality of the spray application, a total of 35 filter-papers (5 control, 30 treated) were wrapped in aluminium foil and sent to the WHO Collaborating Centre for Quality Control of Pesticides at the Walloon Agricultural Research Centre, Gembloux, Belgium. The chemical analysis of filter-papers sprayed with chlorfenapyr and/or alphacypermethrin was performed using an analytical method based on the CIPAC method for alphacypermethrin coated onto filaments LNs. Chlorfenapyr and alphacypermethrin were extracted by refluxing for 5 minutes with tetrahydrofuran with dioctyl phthalate as internal standard. The chlorfenapyr and alphacypermethrin content were measured by gas chromatography

with flame ionization detection (GC-FID) using internal standard calibration. The chemical analysis of filter-papers sprayed with bendiocarb was performed using an analytical method based on the CIPAC method for bendiocarb in technical and formulated products. Bendiocarb was extracted in acetonitrile by ultra-sonication for 20 minutes with propiophenone as internal standard. The bendiocarb content was measured by ultra-high-performance liquid chromatography with UV diode array detection (UHPLC-DAD) using internal standard calibration.

Chlorfenapyr, alphacypermethrin and bendiocarb were not detected in all the control filter-papers. For the treatment with chlorfenapyr at 150 and 250 mg/m², the average ratio of applied dose to the target dose was much higher than expectation (2.25–2.36). This was also the case for treatment with alphacypermethrin alone for which the applied to target dose ratio was 2.73. The treatment with bendiocarb was at less than half the expected target dose (applied to target dose ratio of 0.42). The AI content variation between filter-papers, expressed as RSD, ranged from 10.8% to 46.3% (Table 5.1) (Pigeon, 2014e).

5.2 Conclusions and recommendations

Considering the information available, the Working Group noted:

- that chemical analysis of filter-papers from the Phase II study revealed that the average of the applied to target dose ratio was 2.25–2.36 for chlorfenapyr and 2.73 for alpha-cypermethrin. For bendiocarb, the applied to target dose ratio was 0.42. Consequently, the efficacy of chlorfenapyr and bendiocarb cannot be compared;

- that chlorfenapyr provided higher mortality than alphacypermethrin in experimental huts against pyrethroid-resistant population of *Anopheles gambiae* in Burkina Faso; and

- that the exposure time (2 hours instead of 30 minutes) for in situ cone bioassays in the Phase II study was modified from WHO guidelines for testing and evaluation of adulticides for IRS.

Noting the above, the Working Group recommended:

- that, considering the potential efficacy of chlorfenapyr to kill pyrethroid-resistant *Anopheles*, further evidence be gathered in Phase II to assess the efficacy of indoor residual application of chlorfenapyr 240 SC against malaria vectors, following the WHO guidelines for IRS. It is recommended that the trials should be conducted at a minimum of three study sites, the applied doses should comply with target doses, the vectors are susceptible to chlorfenapyr, and use should be made of appropriate positive controls (i.e. WHO-recommended insecticides for IRS[1]) to which local vectors are susceptible (control 1) and resistant (control 2). If, in a specific situation, local vectors are not susceptible to the positive controls, in at least the two other study sites the local vectors should be susceptible to the positive controls.

[1] See: http://who.int/whopes/en/ (accessed 1 November 2014).

Table 5.1 Chemical analysis of filter-papers collected from IRS Phase II study with chlorfenapyr 240 SC and duration of residual activity and overall % mortality of free-flying *Anopheles* gambiae mosquitoes in Burkina Faso over a period of 3 months

Study arm (doses of AI/m^2)	Number of papers analysed	AI content (mg/m^2)	Applied/ target dose ratio	RSD[a]	Residual activity (months)	Mortality (24 hours)
Chlorfenapyr 240 SC 150 mg	5	354.7	2.36	23.8%	< 1	32%
Chlorfenapyr 240 SC 250 mg	5	562.7	2.25	10.8%	< 1	38%
Alphacypermethrin 30 mg	5	82.0	2.73	13.7%	1	5%
Chlorfenapyr 240 SC 150 mg	5	237.0	1.58	46.0%	1	29%
+ alphacypermethrin 30 mg	5	44.7	1.49	46.3%		
Chlorfenapyr 240 SC 250 mg	5	368.4	1.47	42.6%	1	28%
+ alphacypermethrin 30 mg	5	43.6	1.45	44.4%		
Bendiocarb 200 mg	5	83.3	0.42	40.1%	< 1	11%

[a] RSD = Relative standard deviation of the AI content between filter-papers.

6. GENERAL DISCUSSION

6.1 Improving data quality through standard operating procedures and GEP/GLP criteria

WHOPES testing of vector control products is currently undertaken by the Organization's collaborating centres/institutes and their trial sites. With a changing vector control environment, WHOPES and its partners have recognized the need to increase the institutional and technical capacity of these institutions and to create a testing environment with transparent standards and criteria to ensure high data quality. To this end, WHOPES and CropLife International have convened a task force to identify gaps in data quality and to begin developing standardized frameworks for testing public health pesticides that meet the standards of Good Experimental Practices (GEP) and/or Good Laboratory Practices (GLP). The scope of this task force is broad but it will initially focus on trials of IRS products intended for submission to WHOPES. This focus on IRS has been initiated through initial meetings with potential stakeholders (IVCC, WHOPES, CropLife, Swiss TPH, IHI and others) to discuss the burden of effort required to move from IRS guidelines to standard operating procedures (SOPs) within a GEP/GLP framework. Key areas of activity for the task force include collating information on available SOPs[1] for IRS product-testing, developing and validating the SOPs, and building institutional capacity to move towards a GEP/GLP accreditation system.

Participants in the session discussed the relative advantages and disadvantages of GEP and GLP standards for product-testing and the cost–benefit ratio in developing these levels of quality criteria for data-generation. In particular, internal and external quality control systems need to be developed for individual trial centres – a process that will take time and significant cost. Additionally, there is a need for evidence that the use of new SOPs will serve better than current practices and can generate better data and more transparency. The role of WHOPES in a system involving an independent network of GEP/GLP laboratories was also discussed.

The Working Group drew attention to the need to improve the capacity of testing institutions and, in the long term, to develop a global network of laboratories/institutions accredited for the testing of

[1] For example, some relevant SOPs developed by Avecnet are available at: http://avecnet.eu/downloads/documents/ (accessed 29 October 2014).

vector control products. While this would take time and require funding, it is essential to generate high-quality data in testing of vector control products. It is an ethical imperative to ensure that products go to market based on high-quality data from the outset.

6.2 WHOPES procedures

The need for clear and more transparent procedures for the evaluation of products was discussed. This would build trust with industry and accelerate the evaluation and approval process without jeopardizing quality. It was reported that the issue is already under discussion in WHO with a view to introducing formal procedures. A document outlining proposals will be shared with the Working Group for review and advice as soon as possible and the WHOPES procedures will be made available on the WHOPES website.

6.3 Standard databases

WHOPES makes use of a global network of collaborating trial centres and institutes which conduct independent testing and evaluation of pesticides for vector control. Although testing guidelines and oversight from the WHOPES secretariat aim to harmonize experimental protocols across this network, there is a great deal of variation in formats for data entry and database generation across trial sites. The creation of standard databases for the entry of WHOPES trial data would greatly simplify the analysis of efficacy trial data by allowing data from divergent sites within a WHOPES trial to be directly comparable. Raw data entered into such databases could be used to generate summary statistics and figures in a harmonized manner, thus facilitating access to the raw data as well as summary data provided to the Working Group. This would improve the detection of any deviations from trial protocols and would enable recommendations to be better tailored to the datasets available. The standardization of data entry formats may also allow for future use of datasets for internal comparative, statistical purposes. Additionally, presentation of data in a standard report framework that enables inclusion of text, tables and figures within WHOPES Working Group reports will facilitate easier understanding of the data generated in WHOPES trials. Members of the Working Group discussed the issue in depth. It was agreed that formats for data entry would be proposed and circulated for review and use.

6.4 Semi-field systems for Phase II evaluation of pesticide products

The meeting reviewed the potential of semi-field systems (SFS) for Phase II evaluation of pesticide products. SFS are defined as enclosed environments, ideally situated within the natural ecosystem of a target disease vector and exposed to ambient environmental conditions. SFS comprise a concrete base with a water channel (to reduce entry of insects such as ants that might scavenge mosquitoes), an impermeable roof (to allow work regardless of rain), with UV-resistant durable netting to retain mosquitoes while still allowing airflow so that the conditions (temperature, humidity, air movement) inside the SFS are similar to ambient conditions during the night. SFS are built with double-door entry systems to retain insects released inside (Figure 6.1).

SFS may have a role to play in the evaluation of vector control tools.[1,2,3,4] Experimental huts can be built inside the SFS to allow the evaluation of IRS products and long-lasting insecticidal nets. Known numbers of laboratory-reared mosquitoes of desired species are released in the SFS and standard WHO measurements – including deterrence, blood-feeding success and mosquito mortality – can be measured. The advantage of the system is that evaluations are rapid and robust because sufficient numbers of mosquitoes can be released each night regardless of weather conditions, and sources of variation and bias are reduced in comparison to field evaluations. This increases power to accept or reject the null hypothesis correctly, with fewer replicates than are required in equivalence field studies.

As field populations of mosquitoes become smaller, and populations of susceptible mosquitoes become more difficult to find, SFS may

[1] Ferguson HM, Ng'habi KR, Walder T, Kadungula D, Moore SJ, Lyimo I et al. Establishment of a large semi-field system for experimental study of African malaria vector ecology and control in Tanzania. Malar J. 2008;7(1):158.
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[4] Sangoro O, Lweitojera D, Simfukwe E, Ngonyani H, Mbeyela E, Lugiko D et al. Use of a semi-field system to evaluate the efficacy of topical repellents under user conditions provides a disease exposure free technique comparable with field data. Malar J. 2014;13(1):159.

provide a useful means of conducting standardized evaluations of vector control tools. Furthermore, the mosquitoes released are pathogen-free so the work can be conducted without risk to participants, even in areas with transmission of endemic disease pathogens. To prevent accidental release of new mosquito species or strains into the local environment, it must be ensured that only local strains are used. Working Group participants agreed this is a promising way to conduct research on insecticides against mosquitoes, although evaluators must bear in mind that SFS do not use wild mosquitoes for testing and the mosquito behaviour in SFS will need to be compared to wild mosquito behaviour in each local setting.

Figure 6.1 Semi-field system for testing insecticides for vector control
Photo courtesy of Dr Sarah Moore, Ifakara Health Institute (IHI), United Republic of Tanzania.

6.5 New guidelines under development

Guidelines on testing and evaluation of molluscicides

WHOPES currently recommends a single molluscicide product for use in schistosomiasis control. Currently, however, guidelines do not exist for the testing and evaluation of molluscicide products. Development of mulluscicide products for schistosomiasis control is ongoing in China and has generated interest in a number of schistosomiasis-endemic countries in the African Region. Requests have been received for WHOPES evaluation of two new molluscicides, as a result of which WHO is developing guidelines for

efficacy testing of molluscicides. A draft document has been prepared and will soon be circulated for peer review by the members of the Working Group and other experts and stakeholders, including CropLife and AgroCare. It is proposed to finalize the guidelines through a WHO consultation in 2015.

Statistical guidelines

The *Guidelines for laboratory and field-testing of long-lasting insecticidal nets* were published by WHO in 2013. The Working Group discussed the need to develop statistical guidelines to accompany current LN testing guidelines in order to bring more statistical power to datasets and encourage consistent and reproducible data reporting. Dr Pie Müller presented a proposal on the objectives of, and annotated outlines for preparing, a draft for consideration by the Working Group.

6.6 Long-lasting insecticidal nets: testing and evaluation

Overcoming problems of net retention in WHOPES Phase III trials

WHOPES Phase III trials of LNs are required to test efficacy and measure net integrity and survivorship over the course of 36 months. WHOPES is especially interested in the question of attrition due to loss of net integrity (net deterioration and accumulation of holes). Nets are lost to follow-up for a variety of other reasons, which may include migration of trial families and giving away or misuse of nets. Attrition due to reasons other than loss of integrity is a drain on the trial in terms of time and resources and creates the risk of leaving the trial underpowered for measuring true attrition due to loss of integrity. In some cases, such losses may make up more than 50% of the nets distributed at the start of a trial. Consequently, it is desirable to devise new procedures to limit such losses to follow-up.

How can net retention be improved? Any form of coercion would be both unethical and impossible to enforce in practice. In current trial procedures, participating families are under no obligation to use or retain their nets. However, it might be possible to specify certain terms in the participant consent form that would help to improve net retention while not affecting participants' right to withdraw at any stage of the trial. The Working Group considered important modifications to the consent forms used in Phase III trials and suggested the following procedures:

a) Cohort surveys: Study participants/families enrolled into the cohort component of the trial would be requested to consent to the following:

- participants would not give away or sell the study nets;
- participants would retain the freedom to stop using the nets at any time but should let investigators know the reasons when asked during the follow-up survey;
- investigators would inform participants that the nets will be replaced after 3 years (at the end of the trial period and not before) regardless of net condition but only on production of the trial net; and
- if participants stop using the trial net for any reason, including accumulation of holes, they must store the net for replacement after 3 years, or give it to the investigators who will replace it after the 3-year trial period has elapsed.

Such consent by participants would fulfil the needs of the trial and may reduce non-attrition losses, but would not affect participants' right to stop using their nets at any time for whatever reason.

Other ways to improve net use and retention were discussed, such as providing payment to families to substitute trial nets for existing nets at the beginning of the trial, or deploying a social scientist to investigate the reasons for not using the nets.

b) Cross-sectional surveys: Other families who are eligible to be selected for cross-sectional surveys would have their nets replaced at the time of destructive sampling and would not be eligible for a second substitution at the end of the trial. Their consent form would be amended differently. They would be informed:

- that they should not give away or sell the study nets; and
- that they retain the freedom to stop using the nets at any time but are required to let investigators know the reasons when asked during the follow-up survey.

Quality control and durability parameters

WHO has long been concerned to ensure high quality and durability of LNs. Currently, WHO specifications of LNs include only bursting strength and denier as the fabric strength parameters that can be tested in a textile laboratory for quality control. WHO's Global Malaria Programme and the Department of Control of Neglected Tropical Diseases have conducted a joint study to assess the use of textile tests to determine their applicability to net specifications. In parallel, the Nonwovens Innovation and Research Institute, United Kingdom, has conducted a field study to assess how damage occurs in nets when used by communities. This study has identified the main forms of damage to nets in the field as snags, tears, abrasions, cuts, seam failure and rodent damage. Tests have been developed for each type of damage except for cuts and rodent damage. For the four types of damage tested, a resistance-to-damage score was developed and most tests met the minimum criteria. WHO was recommended to coordinate inter-laboratory validation of the textile tests, in collaboration with industry, to determine if the resistance-to-damage approach can be used and, if so, to update methods and scores regularly.

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