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**REPORT OF THE SECOND WHOPES WORKING
GROUP MEETING**

**WHO/HQ, GENEVA
22-23 JUNE 1998**

REVIEW OF:

**ALPHACYPERMETHRIN 10% SC and 5% WP
CYFLUTHRIN 5% EW and 10% WP**

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1. Introduction

The meeting was opened on behalf of the Director of the Division of Control of Tropical Diseases (CTD) of WHO by Dr M. Zaim, Scientist in charge of the WHO Pesticide Evaluation Scheme (WHOPES). He recalled that the first meeting of the WHOPES Working Group, the scientific committee to assist WHOPES in the review of the reports of testing/evaluation of pesticides in the Scheme, was held in June 1997¹ and the present meeting was convened to review the reports of the testing/evaluation of alphacypermethrin (OMS 3004) 10% SC and 5% WP (American Cyanamid, USA), and cyfluthrin (OMS 2012) 5% EW and 10% WP (Bayer AG, Germany), for indoor residual spraying and/or impregnation of bednets and fabrics, for malaria vector control.

Dr Zaim emphasized that one of the mandates of WHOPES is to collect, consolidate and disseminate information on the use of pesticides for public health use. The collection of data includes the information which is already available in the literature, or through the studies directly supervised by WHOPES.

Once a product is found to meet the requirements of the Scheme, specifications are prepared and published. The specifications include a description of the pesticide concerned and the formulations suitable for use in public health, together with sections concerning their physical and chemical characteristics. If necessary, the maximum contents of impurities are also included in the specifications. Methods for measuring the characteristics of the products are also described. The specifications are part of the International Code of Conduct on the Distribution and Use of Pesticides and are used in international trade and for quality control.

¹ Report of the first WHOPES Working Group Meeting, WHO/HQ, Geneva, 26-27 June 1997 (CTD/WHOPES/97.5)

Dr Zaim also emphasized that the main objective of the WHOPES testing/evaluation of insecticides is to study the properties of the products and their impact on the vector and/or pest population. Therefore, safety, determination of the application dose, residual activity on different surfaces, efficacy in different ecological settings, ease of application, acceptability, resistance assessment and cost-effectiveness are the main objectives of the programme. Epidemiological studies are only carried out where appropriate.

Dr Zaim informed the Group that the two compounds under the review by the Scheme have been reviewed for safety by the WHO/ILO/UNEP Joint Meeting on Pesticide Residues (JMPR)². The International Programme for Chemical Safety (IPCS) has classified, by hazard, the technical products of the two compounds in Class II “moderately hazardous”, with acute oral LD₅₀ (mg/kg of body weight) of 250 and 79 for cyfluthrin and alphacypermethrin, respectively³. It should however be noted that the final classification of any product is based on the formulation and thus the above-mentioned formulations of the two compounds are classified as “products unlikely to present acute hazard in normal use”.

Dr Zaim mentioned that based on the WHOPES laboratory studies, cyfluthrin and alphacypermethrin (=alphamethrin) have been found to be among the most potent pyrethroids, when tested against the susceptible laboratory strains of *Anopheles stephensi*, *Culex quinquefasciatus* and *Aedes aegypti* (Table 1).

² Inventory of IPCS and other WHO pesticide evaluations and summary of toxicological evaluations performed by the Joint Meeting on Pesticide Residues (JMPR), WHO/PCS/98.1

³ The WHO recommended classification of pesticides by hazard and guidelines to classification 1996-1997, WHO/PCS/96.3

Dr Zaim informed the Group that the tentative diagnostic concentration has been established by WHOPES for cyfluthrin and alphacypermethrin as 0.15 and 0.05%, respectively, using WHO standard test tubes and one hour exposure. More detailed studies, however, are needed to determine the diagnostic concentration for wider range of mosquito vector/pest species, to establish an accurate discriminative concentration.

Table 1. Activity of pyrethroids against the reference susceptible mosquito strains (LC₅₀ in tarsal contact tests, using technical products)

Compound	<i>An. stephensi</i> (Beech strain)		<i>Cx. quinquefasciatus</i> (PEL SS strain)		<i>Ae. aegypti</i> (Sri Lanka strain)	
	LC ₅₀	x per ¹	LC ₅₀	x per ¹	LC ₅₀	x per ¹
Permethrin	0.049	1	0.029	1	0.019	1
Alpha-cypermethrin	0.002	24.5	0.003	9.7	0.001	19
Cyfluthrin	0.0013	37.7	0.0024	12.1	0.002	9.5
Deltamethrin	0.005	9.8	0.008	3.6	0.007	2.7
Etofenprox	0.0029	16.9	0.0038	7.6	0.008	2.4
Lambda-cyhalothrin	0.004	12.2	0.004	7.2	0.006	3.2

¹ Permethrin as reference

Dr Zaim emphasized that pyrethroid resistance has already been reported in several major mosquito vectors and pests of public health importance (e.g., *An. albimanus*, *An. gambiae*, *An. sacharovi*, *An. stephensi* and *Cx. quinquefasciatus*) in which insensitive sodium channels (kdr) and monooxygenases have been the resistance mechanisms involved and which confer cross resistance to a wide range of pyrethroids, including cyfluthrin and alphacypermethrin. Hence, careful monitoring of pyrethroid resistance and their judicious use should be promoted.

The Meeting was attended by 8 scientists (see List of participants, Annex 2). Professor H. Townson was appointed as Chairman and Dr C. Lengeler as Rapporteur. The meeting was convened in plenary sessions at WHO/HQ in Geneva 22-23 June 1998, and the reports of the WHOPES supervised trials, published literature on the two compounds, as well as the reports submitted by the national disease and vector control programmes (see bibliography, Annex 1) were fully discussed and recommendations on the use of the above-mentioned products were made.

2. Review of alphacypermethrin SC and WP

2.1 Background/supportive documents

India - Alphacypermethrin WP, sprayed in huts in two villages of Pondicherry, India, at the dosage of 100 mg/m², significantly reduced the density of *Cx. quinquefasciatus* and *An. subpictus* for 18-27 weeks (Amalraj *et al.*, 1987). Alphacypermethrin was found to be more potent as compared to other pyrethroids, i.e. fenfluthrin, permethrin and cyfluthrin, but less potent in comparison to decamethrin (deltamethrin). The bioassays conducted on mud, cement and thatched surfaces showed that the efficacy of the compound lasted for 20 weeks against *Cx. quinquefasciatus* and *An. stephensi*. No appreciable vapour borne toxicity was reported.

Taiwan - Lien *et al.* (1993) reported effective use of alphacypermethrin (SC) as indoor residual spray, at the target dosage of 20 mg a.i./m², to control an outbreak of *Aedes aegypti*, the vector of dengue in southern Taiwan. The study reported significant decrease in the density of larvae and the percentage of the villages with Breteau Index above 35.

Gambia - Acceptability and efficacy of bednets impregnated with alphacypermethrin SC at the target dosage of 40 mg/m² was compared to that of permethrin EC (500 mg/m²) and lambdacyhalothrin EC (10 mg/m²), in the malarious village of Saruja, Gambia, where mosquitoes of the *An. gambiae* complex are the vectors (Jawara *et al.*, 1998). Significantly fewer mosquitoes were found alive under treated nets as compared to the untreated nets. Also, significantly more dead mosquitoes were found under alphacypermethrin-treated nets than under nets impregnated with the other two insecticide products. This might have resulted from either, or both, the increased killing activity or decreased repellency, allowing greater contact of the mosquitoes with the treated nets. No severe side-effect was reported by the users of treated nets in this study. Unwashed nets impregnated with alphacypermethrin were significantly more effective at killing anopheline mosquitoes in bioassays than nets impregnated with permethrin or lambdacyhalothrin. Irrespective of the insecticide used, killing was reduced when nets were washed.

China - In a community-based intervention, Dapeng *et al.* (1994), evaluated the effectiveness of alphacypermethrin WP-impregnated bednets, at the target dosage of 20 mg/m², for control of *Plasmodium vivax* malaria and its vector, in an area of moderate endemicity in central China. Alphacypermethrin impregnated nets showed a good mass killing effect on the vector population. The outdoor man-biting density of *An. anthropophagus* and *An. sinensis* decreased by 70 and 29%, respectively. The former species is an endophilic, anthropophilic mosquito, whereas the latter is mainly an exophilic and zoophilic species. The resting density of these two species inside the treated nets were reported close to zero and no side effect was found among the users of the treated nets. The study showed that impregnation with alphacypermethrin was more effective on polyester than on cotton netting and the residual effects lasted for at least one year. Dapeng *et al.* (1994) have reported that

alphacypermethrin WP at the target dosage of 20 mg/m² to be more cost effective, compared to permethrin (500 mg/m²) and deltamethrin (15 mg/m²).

2.2 WHOPEs supervised trials

Burkina Faso - In the WHOPEs phase II study carried out in the Soumouso Experimental Station, Burkina Faso, in 1985, eight "Bobo" and "Mossi" huts were sprayed inside with 0.1 g/m² alphacypermethrin WP (Darriet *et al.* 1985). The impact of the spraying was evaluated through daily captures in trap huts and assessing the impact on the density of the mosquitoes, gorging rate and general mortality. Residual effect of the insecticide was evaluated by bioassay test, exposing laboratory reared *Aedes aegypti*, for one hour, to treated surfaces. No intoxication symptoms were noted either during the preparation of the mixtures, during spraying or in the weeks following treatment.

In comparison with the control huts, treatment with alphacypermethrin at the target dose of 0.1 g/m² reduced the number of *An. gambiae* females caught inside dwellings by 75%, in Bobo huts, and by 56% in the Mossi huts. The drop in the numbers of *An. funestus* was 86 and 66% in the Bobo and Mossi huts, respectively.

The repellent effect of alphacypermethrin was greater on *An. funestus* than on *An. gambiae* with an average reduction of 73% in the number of females entering the huts.

The average percentage of mosquitoes found in the trap verandas of the treated dwellings was 80% for *An. gambiae* and 82% for *An. funestus*, i.e., more than double (2.5) the exophilia recorded in the control huts.

The gorging rate for *An. gambiae* and *An. funestus* in treated huts, on average, dropped 10 to 15% in Bobo and Mossi huts, as compared to the control, with a very clear reduction of gorging rate (32%) for *An. gambiae* in Mossi huts.

The pattern of mortality caused by alphacypermethrin were divided into immediate (76%) and deferred (after 24 hours of holding) mortality (24%). The product had a particularly marked knock down effect.

Philippines - In a village scale trial carried out in Cagayan Province, 500 km north of Manila, in 1996 (Sadang *et al.*, unpublished report), alphacypermethrin WP was evaluated for indoor residual spraying against malaria vectors (mainly *An. flavirostris*).

One village, with a population of 2535 was sprayed with alphacypermethrin and another village of 2137 was assigned as control. The two villages were 8 kilometers apart. The houses were made of either wood, bamboo or cement.

The pre-intervention study began in October 1996 when mosquito collection and mass blood surveys were carried out. In November 1996, alphacypermethrin WP was sprayed indoors, at the target dosage of 30 mg/m², with 98% coverage.

The monthly contact bioassays, using WHO standard cones and wild caught *An. flavirostris* blood fed females (30 minutes exposure and 24 hour holding) gave 100% mortality up to 7 months, on all treated surfaces, except cement (90%).

Twelve hour mosquito, indoor and outdoor landing catches, performed 3 times per month, did not yield any mosquitoes indoors, for 8 months after the intervention, while in the control area, bites/man/night varied from 0 to 0.66. Outdoors, the bites/man/night ranged from 0 to 2 in the treated vs. 0.33 to 1.33

in the control area. Also, more mosquitoes were collected in animal bait collections (carried out once a month) in the control as compared to the treated village.

The parous rate of mosquitoes collected in the treated village ranged from 0 to 60%, while in the control village the parous rate varied between 60 to 100%. Due to the very low number of mosquitoes caught in the trial, however, no clear impact of the spraying on the vector population could be shown.

Mass blood surveys, carried out in the treated and control villages, before and twice after spraying, showed a clear reduction in the slide positivity rate in the sprayed village, as compared to the control. In the treated village, parasite rate was reduced from 1.7%, before spraying, to 0.67% and 0.36% at 3 and 6 months after spraying, respectively. Whereas in the control area, the parasite rate remained at 0.28% for 3 months and then increased to 0.33% after 6 months.

Except for some spraymen who developed transitory skin irritation on the face no adverse side effects were reported by the spraymen or the local residents.

Pakistan - In a comparative WHOPES Phase III trial, alphacypermethrin WP and SC were sprayed indoors at the target dosage of 25 mg a.i./m², in the Sheikhpur District, Punjab Province in 1997 (Mehmood *et al.*, unpublished report). The study area comprised of 3 union councils, with a total population of about 18000, covering an area of 175 km². Each of the study area was randomly assigned to either alphacypermethrin WP, SC or control.

The comparative efficacy of alphacypermethrin WP and SC was evaluated by space spray catches in 6 rooms (2 sleeping rooms, 2 store rooms, 2 animal rooms), carried out early in the morning, at 15 day intervals. The monitoring rooms were deliberately left

unsprayed and used throughout the study. Collected anophelines were classified according to blood meal digestion. Mosquito dissections were done for parity status. One night of buffalo bait collection was carried out from dusk to dawn inside and outside of an animal shelter in each sub area each month. The residual effect of WP and SC was tested on various surfaces at 15 day intervals using standard WHO cones with exposure for 30 min. Active case detection (ACD) was carried out by visiting 400 houses in each sub-area every fortnight. Blood smear was taken from any member of household reporting fever during the previous 3 days. Cross sectional parasite prevalence surveys were carried out in all sub areas in April and May (one month before spraying) and again in September. A record of any complaint of health effects of alphacypermethrin by the spraymen and villagers was maintained.

In the sprayed villages densities of all anophelines except *An. hyrcanus* were significantly less. *Anopheles stephensi* was the most dominant vector species and in the control area its parous rate increased from 62% in May-June to 80% in July-November, whereas in the sprayed areas, parity rates decreased from 81% to 24% (WP) and from 91% to 26% (SC). *Anopheles culicifacies* showed similar trends.

The proportion of 4 gonotrophic stages were similar in sprayed and control sub-areas as the collection rooms were left unsprayed. More mosquitoes were collected from control than sprayed areas, from the buffalo bait. All surfaces treated with 25 mg/m² alphacypermethrin - mud, cement, wood and thatch gave 100% mortality of *An. culicifacies* and *An. stephensi* for at least 112 days after spraying, and even after 184 days (when testing was stopped) all types of surface were still giving at least 50% mortality.

Spraying produced dramatic effect on transmission. Between July and January the mean incidence of *Pl. falciparum* was 15 per

thousand in the control, but only 1.6 and 0.8 per thousand in the SC and WP sprayed groups. Mean incidence of *Pl. vivax* was 10 per thousand in the control and 2.2 - 2.5 per thousand in the SC and WP groups. The relative risk of falciparum malaria was 0.09% in the SC and 0.05% in the WP, compared to the control, whereas, the relative risk of vivax malaria was 0.23% in the SC and 0.20% in the WP groups.

The odds ratio suggested that spray interventions had controlled falciparum and vivax malaria by 100% and 77% in the SC area, respectively. These figures were 86 and 63%, respectively, for WP area. WP and SC formulations of alphacypermethrin performed equally well and results were statistically insignificant.

Indoor residual spraying of alphacypermethrin produced transitory skin irritation primarily in the spraymen but also in some householders shortly after spraying. No persistent odour or residue was present afterwards. Spraying was highly appreciated by the villagers as mosquitoes and malaria was controlled.

Tanzania - In a WHOPES phase II and III evaluation of alphacypermethrin SC for impregnation of bednets (polyester, polyfilament, 100 denier) in the high perennial transmission area of Tanzania, the dosage, efficacy, persistence and wash resistance of alphacypermethrin SC was compared to lambdacyhalothrin CS, in 4 villages divided into a number of discrete collection of houses or hamlets, covering a population of about 6000, including 1000 children under the age of 6 years (Curtis *et al.*, unpublished report).

The comparison included:

1. Bioassays on unwashed and washed nets in domestic use at monthly intervals, after treatment with the two products (alphacypermethrin SC 20 mg/m² and lambdacyhalothrin CS 10 mg/m²);

2. Experimental hut trials before and after repeated washing to compare the protection from biting (in simulated damaged nets) and the entomological impact of the two products (alphacypermethrin SC 20 and 40 mg/m² and lambdacyhalothrin CS 10 and 20 mg/m²);
3. Assessment of the mosquito mass killing through human landing catches, light trapping and sporozoite rates;
4. Pyrethrum space spray catches and window trap collections in/on rooms with treated nets vs. those with untreated nets; and
5. Assessment of the rate of incidence of re-infection with the malaria parasite of children living in the hamlets with each type of treated net, after treatment with chlorproguanil-daspose.

Major reduction in the amount of blood feeding by anophelines (*An. gambiae* and *An. funestus*) and *Cx. quinquefasciatus* were observed on the sleepers in all the treated nets compared with the untreated nets. Also, all treated nets caused considerable mortality in anopheline mosquitoes, but with no appreciable impact on the density of *Cx. quinquefasciatus*.

There was no significant difference in the performance of the two pyrethroid compounds or for a reduction in effectiveness due to 5 times washing. There has been a tendency for better reduction in feeding at the higher of the doses of each of the insecticide products.

There was no appreciable difference in the speed of knockdown (KT₅₀) in the nets treated with alphacypermethrin SC 20 mg/m² and lambdacyhalothrin CS 10 mg/m². Nor there has been any significant reduction in the KT₅₀, due to washing.

There has been a significant reduction in the entomological inoculation rate (95%) for the population protected by the treated nets as compared to the control group. Results have been similar for alphacypermethrin 20 mg/m² and lambdacyhalothrin 10 mg/m².

Pyrethrum space spray catches and window trap collections also confirmed the good impact of the intervention on anopheline mosquito densities (95-96%) and the feeding rate (95-97%).

Re-infection rates in the two cohorts of children after radical treatment with chlorproguanil-dapsone were similar with both alphacypermethrin 20 mg/m² and lambdacyhalothrin 10 mg/m².

Questionnaires about side effects perceived by the net users showed that significantly more users noticed cold-like symptoms (nasal irritation) with lambdacyhalothrin (19/105) than with alphacypermethrin (3/117). With each insecticide very high rates were noted of elimination of nuisance from bedbugs and headlice.

3. Review of cyfluthrin EW and WP

3.1 Background/supportive documents

India - Cyfluthrin WP was evaluated for its efficacy, acceptance by the community and effect on human health and non-target organisms in the two malarious states of Maharashtra and Gujarat, India, from 1988 to 1990 (Yadava *et al.*1996). Two dosage schedules were used: in Maharashtra State, cyfluthrin was sprayed indoors at the target dosage of 25 mg/m², for two rounds per year, and in the comparison areas of the same state, malathion was sprayed at 2 g/m², 3 rounds/year; in the Gujarat State, cyfluthrin was sprayed indoors at the target dosage of 15 mg/m², 3 rounds/year, and in the comparison areas of the same state, DDT was sprayed at the target dosage of 1 g/m², 2 rounds/year. In both areas, the principal malaria vector, *Anopheles culicifacies* is resistant to DDT, dieldrin and malathion, but susceptible to cyfluthrin.

Contact bioassays showed, cyfluthrin bioefficacy to be high, on all types of wall surfaces (mud, wood and cement/brick) for more than 12 weeks with the 15 mg/m², and more than 15 weeks with 25 mg/m². DDT in the comparison area produced 0-10% mortality after 2 days, and 7-12% after 6 days of spraying. Aerial bioassays on caged mosquitoes showed no air-borne effect of cyfluthrin.

There were no signs of toxicity with both dosages of cyfluthrin, nor any abnormalities in ECG, SGOT, SGPT, serum alkaline phosphate, etc., on spray personnel or the inhabitants of the sprayed area. Enzymatic activity was normal. Few complaints of transitory skin burning, and lacrimation. No toxic effects on domestic animals.

In cyfluthrin 25 mg/m² sprayed areas of Maharashtra State, indoor resting vector density reduced from 3.00 to 0.05 per man/hour, with 83.3, 90 and 93.3% reductions over 3 years of the study. With malathion, some reductions occurred initially, not later.

Cyfluthrin 15 mg/m² spraying in Gujarat State changed indoor resting vector density from 37.3 (pre-spraying), to 6.9 and 4.3 after spraying; percent reductions in the 3 years were 81.5, 88 and 92%, respectively.

The cyfluthrin spraying gave a good impact on malaria transmission in both trial areas, but the effect was not so pronounced in recorded malaria cases as it was in the case of vector mosquito density, possibly because of the influence of migrant mosquitoes from neighbouring areas and the movement of human population.

Philippines - In a two round comparative study of cyfluthrin WP (target dosage of 15 mg/m²) and DDT WP (1.5 g/m²) on reducing malaria prevalence in Philippines, Asinas *et al.* (1991) reported

93% mortality of *An. flavirostris*, 197 days after spraying. Comparable reductions were reported in vector density, human biting and parous rates with both insecticides. Community surveys showed that cyfluthrin was accepted by the people as residual spray and that refusal to spraying was minimal. There was no adverse reaction with the use of cyfluthrin and there was no toxicity reported in chicken, pets and animals.

India - Efficacy of cyfluthrin EW-impregnated mosquito nets, target dosage of 50 mg/m², was investigated for malaria vector control, in the mining settlements in Orissa (Sharma and Yadav, unpublished report). Three settlements received bednets (nylon), whereas three comparable settlements were used as comparison (no mosquito nets). All age groups were covered. Fortnightly active malaria surveillance was established to monitor parasitological indices.

Indoor resting vector density declined sharply and remained at about zero level (0-0.25 indoor man hour density) for the 2 year study period. Whereas in the control area the mosquito density, for the same period were 0.8-19.9 and 0-6.5.

Vector biting density also declined sharply after the introduction of the impregnated nets. While in the control area, the biting density varied between 0.75 to 19 bites/man/night, this was almost zero in the treated area.

Malaria incidence and hospital bed occupancy were also reported to be significantly affected by this intervention.

The average usage of the impregnated nets was reported to be more than 74% and was highly appreciated by the mining population as it was effective not only against malaria, but also nuisance insects and headlice.

Tanzania - In comparative hut trial studies, Curtis *et al.* (1996) investigated the efficacy of different insecticides for impregnation of different kind of fabrics in Muheza, where wild, free-flying *Anopheles gambiae*, *An. funestus* and *Cx. quinquefasciatus* entered the huts. No significant difference was reported in the % fed and % mortality of anophelines and *Cx. quinquefasciatus*, when Cyfluthrin EW, at the 2 target dosages of 30 and 50 mg/m², were used on polyester nets. Curtis *et al.* (1996) reported that holed nets treated with cyfluthrin EW at the target dosage of 50 mg/m² performed well even after 15 months of domestic use.

3.2 WHOPEs supervised trials

India - In a WHOPEs phase II study, cyfluthrin was evaluated for adulticidal efficacy in a hut-scale trial in two localities in Pondicherry, at the application rates of 20 and 50 mg/m², against the urban filariasis vector *Cx. quinquefasciatus* (Rajavel *et al.* 1986). The indoor resting density in the treated huts remained low in comparison to untreated huts for fourteen weeks at 20 mg/m² and eighteen weeks at the rate of 50 mg/m². No appreciable vapour toxicity was shown in this study.

In contact bioassays, using test kits improvised locally, at 20 mg/m², the bio-efficacy of the product lasted for 6 weeks against *Cx. quinquefasciatus*, *Ae. aegypti* and *An. stephensi* on thatch surfaces. At 50 mg/m², the bio-efficacy lasted for 12 weeks against *Cx. quinquefasciatus* and *Ae. aegypti*, and only 4 weeks against *An. stephensi*. On cement and mud surfaces, the efficacy was negligible against all species.

Iran - Cyfluthrin WP was evaluated at a target dosage of 50 mg/m², for indoor residual spraying against malaria vectors in Bandar Abbas, Southern Iran (Motabar *et al.*, unpublished report). Vivax malaria is predominant and the main vector is

An. stephensi followed by *An. dthali*, *An. fluviatilis* and *An. culicifacies*. *Anopheles stephensi* is mainly endophilic, whereas other species are considered exophilic and exophagic. The former species is resistant to DDT, dieldrin and malathion.

A population of 41,616 living in several villages was sprayed to monitor the impact on vectors and malaria. Three villages with a population 579 were selected as control villages (without any anti-vector interventions). One village each of the sprayed (population 440) and untreated (population 267) group was selected for reference purpose. Although malaria incidence was not homogenous but malaria trends were comparable for API, SPR and for *Pl. falciparum* and *Pl. vivax* distribution. Spray coverage was 82.4% in human dwellings and 94% in animal shelters.

The efficacy of cyfluthrin was studied weekly by indoor mosquito collections in 8 fixed shelters (4 animal and 4 human in each village), using pyrethrum space spray catches, twice a month in the morning. Mosquitoes were classified according to the blood digestion stages and dissected for parity. Indoor resting densities and outdoor adult collections were made from 4 places at 15 day intervals. Exit window trap collections were made by means of 4 traps installed in each village and mortality checked after 24 hrs. Entry window trap collections were made in months when people slept outdoors. Men and animal biting collections were made on 4 men and 2 cows from 6 pm till midnight, at fortnightly intervals. Blood slides were collected at the beginning, middle and at the end of transmission season. Annual blood examination rate (ABER), slide positive rate (SPR) and annual parasite incidence (API) were calculated to reveal the epidemiological impact of spraying. Bioassay tests were carried out on wood, thatch, lime wash cement and mud plasters, with *An. stephensi*. The vapour effect of cyfluthrin in treated rooms was assessed in cylinder cages on laboratory bred *An. stephensi*, with 60 min exposure in sprayed rooms. Safety of cyfluthrin to

spraymen and people living in sprayed villages was monitored by recording complaints of possible adverse health effects.

In the sprayed villages, there was 70-80% reduction in adult *An. stephensi* densities after 162 days. Parous rate was reduced by 75% and stayed at that level. Fifty percent reduction was recorded in the day time resting population of mosquitoes in outdoor pit shelters, as well as a sharp decrease in larval density of *An. stephensi*. Autumn peak of *An. stephensi* was missing, due to the intervention. *Anopheles stephensi* densities did not return to normal level even after 174 days post-spraying.

A 10-fold reduction in night biting collections of *An. stephensi* was recorded. Mortality in the exit window trap collections was 100% for over 5 months. No mortality was observed in the entry window traps. Air borne effect of cyfluthrin was negligible.

Residual efficacy of cyfluthrin on the non-absorbent surfaces was 100% and on the absorbent surfaces 80-90% for 4 to 5 months with a slow declining trend afterwards. There were no *Pl. falciparum* cases. The incidence of *Pl. vivax* was reduced by 50%. API dropped from 51.1 to 20.4 and SPR from 0.7 to 0.4.

Product safety and acceptance was high. Some people complained of upper respiratory tract sensation and burning sensation on the contaminated skin. These symptoms were transitory and reversible. Spraying had broad spectrum activity on the other domestic arthropod pests and there was no negative effect on pets and livestock.

Sri Lanka - In a comparative study, the efficacy of cyfluthrin WP, at the target dosage of 30 mg/m², sprayed at 6-monthly (two rounds) was compared to malathion (3-monthly, 4 rounds, 2 g/m²) for indoor residual spraying against malaria vectors in Ratnapura District, located in the “intermediate malaria zone”,

with unstable malaria (Wickramasinghe *et al.*, unpublished report).

Both areas had mixed type of houses (mud walls/cadjan roofs, brick walls/tile roofs, and lime plastered walls/tile roofs). The two areas were comparable in physical features, vegetation, rainfall, temperature and relative humidity, were 3 km apart, and separated by a range of hillocks.

In the year before the trial (May 1994 to April 1995), treatment area was reported with a total of 897 malaria cases (440 *Pl. falciparum* and 457 *Pl. vivax*) and the comparison area with a total of 289 malaria cases of which 104 were *Pl. falciparum* and 185 *Pl. vivax*.

Anopheles culicifacies, the main vector of malaria, and *An. subpictus*, are endophilic species, resistant to DDT and malathion.

Cyfluthrin persistence was assessed by analysis of scrapings from sprayed surfaces (mud, lime plaster, brick), taken 4, 8, 12, 16, 20 and 24 weeks after spraying and contact bioassays on different surfaces, at different intervals after spraying, for bioefficacy. Few aerial bioassays were also carried out in the first week after spraying, to assess the vapour effect.

The other entomological evaluation criteria included, indoor resting mosquito collections by pyrethrum space spray catch, mosquito collection in bovid-baited net traps and bovid-baited huts, and human-bait night collections indoors and outdoors, in the test and comparison areas.

Safety and toxicological effects were assessed on selected spraymen, before, 2 weeks after, and at the end of spraying, with clinical examinations and pre- and post-spray analysis of blood

and urine samples (full count, liver profile, kidney function, levels of cyfluthrin and its metabolites).

Microscopic examination of blood films taken from fever cases presenting at the medical institution, serving the population in the 2 areas, and that taken from 150-200 school children under 10 years, and 3-monthly fever surveys on those with fever or with history of fever in the preceding month, were the criteria used to assess the impact of spraying on the diseases.

Amounts of cyfluthrin deposits on the sprayed surfaces, based on the results of the chemical analysis, fluctuated over time, with more, after second application; this was attributed to cumulative effects, uneven applications, or physical and chemical factors of the treated surfaces. Persistence was less on lime plaster and brick surfaces, than on mud.

Contact bioassays carried out up to 14 weeks after spraying caused greater mortality on wood and thatch surfaces (90-100%), compared to mud (67%).

The number of indoor resting *Anopheles culicifacies* mosquitos collected in both areas were very low. Slightly higher number of *An. subpictus* (mostly gravid stage) were collected indoors in comparison area, which may have been due to its resistance to malathion in the area.

Spraymen reported burning and irritant effects on skin and mucous membrane. *Cis* and *trans* DCCA and FPBA were detected in the urine samples of 5 spraymen, with one having relatively high levels (32.2) of *trans* DCCA. Absorption into body was negligible.

Compared to the same period in the previous year, there was a reduction in malaria cases in both areas. In the cyfluthrin area,

the reduction was more pronounced (74% in *Pl. vivax*, 86.4% in *Pl. falciparum*, and 80% overall).

Philippines - In a randomized trial, the effectiveness of cyfluthrin treated mosquito nets was compared to untreated nets, for malaria control, in the northern part of the country, 500 km away from Manila (Quilala *et al.*, unpublished report).

The nets were impregnated with cyfluthrin EW at the target dosage of 50 mg/m². The nets were reimpregnated at 6 months.

Mass blood surveys were carried out before the distribution of the nets (6 months and just before) and quarterly thereafter, in at least %29 and %38 of the population in the treatment and comparison villages, respectively. Indoor man-landing densities were assessed. KAP and acceptability survey was also conducted, in both areas.

Chemical residue analysis of bednet samples 1,2,3 and 4 months after impregnation showed that the average dose was in accordance with target dose of 50 mg/m² and maintained unchanged during 4 months. However, huge variability in dosages was observed.

Contact bioassays, using WHO standard cones and wild caught *An. flavirostris* females (3 minute exposure), gave 100% mortality up to 174 days after treatment.

The density and biting rate of *An. flavirostris* in the treated area was reduced from 0.43, during the baseline, to 0.03 bites/man/night until the third month after impregnation. In contrast, the number of *An. flavirostris* in the control area showed no significant change from 0.2 to 0.13 after the first month but increased during the 2nd and 3rd month.

There was also a significant decrease in the indoor man-landing captures of *Culex* mosquitoes, after the introduction of the treated nets, however, gradually the population began to increase after two months.

There were no major complaints of negative effects related to the use of cyfluthrin impregnated nets from the inhabitants, except for the bad odour which lasted for one week and an occasional headache which lasted for a day.

All throughout the study, after the introduction of the cyfluthrin treated mosquito nets, the overall parasite rate and the *Pl. falciparum* rate were constantly significantly lower than in the untreated mosquito net area.

Iran - In a randomized controlled trial in Baluchistan, the entomological and morbidity impact of cyfluthrin EW-treated nets (target dose of 40 mg/m²) were compared to that of untreated nets (Zaim *et al.*, unpublished report). The main vector is *An. culicifacies* (mainly zoophilic, endophilic and endo/exophagic) and the annual parasite index is 30-50 per 1000. There is a marked traditional use of untreated nets (mainly cotton).

The following methods were used for evaluation:

1. Monthly chemical residue analysis and bioassays (laboratory reared *An. stephensi*, 3 minute exposure) of randomly sampled nettings;
2. Monthly indoor pyrethrum space spray catches in the treatment (13 villages) and control villages (3) and the determination of the parous and sporozoite rates and human blood index; and
3. Parasitological surveillance, mainly passive and active case detection (every 10 days)

Analysis of insecticide residues on the netting showed surprisingly low results, especially with nylon nets (12 instead of 40 mg/m²). A rapid decrease in the concentration on the netting after 3 months was also observed for all types of nets (nylon, light-, medium- and heavy-cotton). Bioassays were within the expected range just after treatment, with the exception of one measure (heavy cotton). However, killing rates decreased substantially after 3 months.

There was a clear impact on the overall mosquito density during the initial 4 months. However, no impact was measured on the parous rates, human blood index, or on the sporozoite infection rates of *An. culicifacies*. Month-to-month variability in all entomological parameters was important.

No impact could be found on the number of malaria cases between the intervention and the control area. However it should be noted that the area has had intensive indoor residual spraying for many years before the trial (which was stopped only 6 months before the treatment of the bednets), the mosquito fauna had seriously been affected by the previous control, and that over 50% of malaria cases were relapses and less than 20% of total cases were due to *Pl. falciparum*

Cameroon - The entomological impact of cyfluthrin EW impregnated bednets (target dosage of 50 mg/m²) were evaluated in the medium-sized town of Mbandjock, where malaria is typically stable (Bouchite *et al.*, unpublished report). The main vector is *Anopheles gambiae s.s.* (with *An. funestus* as an important secondary vector) and main transmission is during the dry season. Very important nuisance is induced by *Mansonia* during the rainy season. There is no pyrethroid resistance in this area (bioassay with 0.2 % impregnated filter paper and PCR for kdr).

Polyester multifilament nets (75 denier, 156 Mesh, 2 sizes, family and X-family with a polyester sheeting border) were impregnated in bulk of insecticide solution. Reimpregnation was carried out after 6 months.

The evaluation criteria were:

1. Chemical residue analysis of bednet samples.
2. Residual efficacy by bioassays, using WHO standard cones (3 minute exposure, KD after 20 and 60 minutes, and mortality at 24 hours) and irritability test based on time for first take-off. Both biological tests were carried out in the laboratory with a reference susceptible strain of *An. gambiae s.s.*
3. Entomological evaluation, monthly indoor and outdoor landing catches and pyrethrum space spray catches, parity and sporozoite infection rates.

Chemical residue analysis revealed that the average concentration on the nets after the first impregnation round was 35.5 mg/m² (17 to 56.8) on the wall and 61.5 (35.8 to 113.4) on the sheeting border of the treated nets.

Although high KD rates were observed (over 90% during 4 months, then drop to 60%), mortality rates in contact bioassays varied with 46% after impregnation, an increase up to 60 % after 4 months and a drop to 30-40 % after 5 and 6 months.

Except just after impregnation, mortality and KD rates were decreasing from the upper part to the lower part (sheeting border) of the nets. Irritability varied greatly over time and was much reduced by dirtiness of the nets.

Mosquito biting rates and transmission were dramatically reduced after distribution of the nets. However, an increase was observed including in protected houses with significant biting rates and some transmission 5 and 6 months after distribution of

the nets. Parous rates were lowered from an average of 70% to 20-40%, after the introduction of impregnated nets.

Cyfluthrin is non repellent and mosquito landing densities observed in houses and rooms fitted with one or several impregnated bednets were not much different. Nuisance induced by *Mansonia* and *Culex* was not successfully controlled by the treatment, either indoor or outdoor.

Uganda - To assess the effectiveness of insecticide treated curtains to reduce malaria transmission and the number of malaria episodes experienced by children in a holoendemic area in Uganda, in a randomized controlled trial with 4:4 villages in two blocks, existing as well as new curtains supplied by the trial team were treated with cyfluthrin EW at the target dose of 50 mg/m² (Killian *et al.*, unpublished report). The main vectors are *An. gambiae s.l.* and *An. funestus*, which are still fully susceptible to pyrethroids.

The following criteria were used for the evaluation:

1. Chemical residue analysis and bioassays on fabric samples;
2. Pyrethrum space spray catches, human landing catches;
3. Weekly active surveillance as well as passive case detection in children aged 0-9 years over a period of one year (initially, all children were treated with a single dose of sulphadoxine-pyrimethamine); and
4. Regular cross-sectional surveys at 3, 6, 9, 26 and 52 weeks to follow re-infection with *Pl. falciparum* as well as to assess anaemia status.

Chemical residue analysis showed that concentrations of cyfluthrin were close to the target dose for both synthetic and cotton curtain fabrics used in this study. Bioassay mortality rates were moderate for synthetic materials (64%) but remained at a

constant level for 6 months, while for cotton they were higher initially (79%) but declined more rapidly.

A clear impact was noted on mosquito densities with pyrethrum catches, but only for the first 10 weeks with human landing catches.

While at base line pyrethrum space spray catches showed higher vector density in the treatment site, compared to comparison, there was a significant overall reduction of vector density of 80% at the treated villages between 3 and 6 months after impregnation. The magnitude of reduction was the same whether all vectors or only freshly fed vectors were considered.

The picture for human landing catches, however, were to some extent different from pyrethrum space spray collections. No difference was found in vector density at base line, between the treatment and comparison villages. However, the reduction of vector density was quite high at 5 and 10 weeks after impregnation, but reduced to 22% and 24% at 16 and 25 weeks at the peak of the transmission season. The overall cumulative vector density between 5 and 25 weeks after impregnation was 23.8 vectors/person/night (95% CL 21.5-26.4) at comparison and 16.4 (14.5-18.5) at villages using treated curtains, a significant reduction of 31%.

4. Conclusions and recommendations

1. On the basis of the trials reviewed it is concluded that **alphacypermethrin 10% SC** is a highly effective and safe insecticide for the impregnation of bednets, when used at dosages of 20-40 mg/m². The chosen dosage will depend on the epidemiological situation, netting fabric, expected frequency of net washing and cost considerations. Based on bioassays and entomological impact, the nets remain effective for 6-9 months or more.

2. The impregnation of cotton bednets with alphacypermethrin WP at 25-30 mg/m² has been found highly effective in studies in China. Since there may be cost advantages in the use of a WP formulation, it is recommended that further studies be conducted to determine the efficacy and persistence of alphacypermethrin WP for impregnation of cotton bednets, under differing epidemiological conditions, with its acceptability and safety.
3. The accumulated experience and trials reviewed confirmed that **alphacypermethrin 5% WP and 10% SC** are safe and effective insecticide products for indoor residual spraying for malaria vector control at the target dosage of 25-30 mg/m², with expected residual activity of 4-6 months.
4. On the basis of the trials reviewed it was found that **cyfluthrin 10% WP** is a safe and effective insecticide for indoor residual spraying against malaria vectors at target dosages of 15-50 mg/m², depending on the nature of the wall surfaces. The lower dosage is only suitable for non-absorbent surfaces, such as wood or bamboo. At the higher dosage of 50 mg/m², cyfluthrin WP persisted for 18-23 weeks, although on cement surfaces this time was reduced.
5. On the basis of the trials reviewed it is concluded that **cyfluthrin 5% EW** is an effective and safe insecticide for the impregnation of bednets and curtains when used at the dose of 50 mg/m². Based on bioassays and entomological impact it remains effective at this concentration for 3-6 months. In some trials, the concentration achieved on the netting was very variable and, hence, further studies of the source of this variability would be helpful.

General recommendations

1. Sampling methods for chemical residue analysis for insecticide sprayed on walls with hard surfaces are currently unsatisfactory and should be improved and standardized.
2. A number of reviewed trials presented sub-optimal design features which affected the value of the results that were presented. The main aspects that should be considered when designing trials to test the impact of a new insecticide are the following:
 - There should be more than one intervention and one control unit in the comparison. It is important to note that these units need to be truly independent and not lumped together as two "blocks" (for example as groups of villages). Based on basic epidemiological and statistical principles it is unlikely that less than five intervention "units" versus five control "units" will be appropriate.
 - All these units should be allocated randomly to either receive the new intervention or to act as control. This is very important in order to avoid investigator or community preferences affecting the validity of the results. The randomization process needs to be carefully explained to the communities beforehand and provided this is well done, public ballot were found to be acceptable in most trial settings.
 - A proper sample size calculation should always be performed before the start of the trial in order to ensure that the trial has enough power to detect the difference that is looked for.

- In order to facilitate trials with a larger number of units alternative and less demanding entomological sampling methods could be considered. As an example, CDC light traps could be used in conjunction with human landing catches to estimate mosquito densities, where appropriate.

- The reporting of trials should ensure that all relevant data are included in a concise form. Numerical values of measured variables should include estimates of their variance, preferably in the form of confidence intervals.

Annex I. Bibliography

1. Amalraj KD, *et al.* Evaluation of alphasmethrin, a synthetic pyrethroid for insecticidal activity against mosquitoes. *Indian Journal Medical Research*, 1987, 86:601-609.
2. Asinas CY, Santos MN, Puriran JA. Comparative study of solfac 10 WP (cyfluthrin) and DDT 75% WDP on reducing malaria prevalence in the Philippines. *Philippine Journal of Public Health*, 1991, Jan-Dec: 27-30.
3. Bouchite B, *et al.* Résultats préliminaires d'évaluation entomologique du Solfac EW50 (cyfluthrin, Bayer AG), 1998 (Unpublished report).
4. Curtis CF, Maxwell CA, Greenwood BM. A comparative trial of bednets impregnated with alphacypermethrin or lambdacyhalothrin near Muheza, Tanzania, 1998 (Unpublished report).
5. Curtis CF, Myamba J, Wilkes TJ. Comparison of different insecticides and fabrics for anti-mosquito bednets and curtains. *Medical and Veterinary Entomology*, 1996, 10:1-11.
6. Dapeng L, *et al.* Alphasmethrin-impregnated bed nets for malaria and mosquito control in China. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1994, 88: 625-628.
7. Darriet F, Carnevale P, Robert V. Phase II assessment at the Soumouso experimental station (Burkina Faso) of the effectiveness of 2 insecticides: WHO 3002 @ 1 g/m² & WHO 3004 @ 0.1 g/m² when sprayed inside huts of the Bobo and Mossi type on carriers of Malaria. Antenne ORSTOM at the Muraz Centre, Bobo-Dioulasso, Burkina Faso, 1985, Nb 8679/85-DOC Tech. OCCGE.

8. Jawara M, *et al.* Comparison of bednets treated with alphacypermethrin, permethrin or lambdacyhalothrin against *Anopheles gambiae* in the Gambia. *Medical and Veterinary Entomology*, 1998, 12:60-66.
9. Kilian AHD, *et al.* Comparison of the effectiveness of cyfluthrin impregnated curtains to reduce malaria morbidity in two areas with differing transmission intensity in Kabarole District, Uganda, 1998 (Unpublished report).
10. Lien JC, Lin TH, Huang HM. Dengue vector surveillance and control in Taiwan. *Trop. Med.*, 1993, 35 (4): 269-276.
11. Motabar M, Kazemi SH. Results on large area-scale trial of cyfluthrin (Solfac WP 10, OMS2012) as a residual spraying operation for control of malaria (vector and parasite) carried out in Bandar Abbas, Southern Iran (1995-1996), 1997 (Unpublished report).
12. Pervez-Mehmood M, *et al.* Field trial of alphacypermethrin in Punjab Province, Pakistan, as an indoor residual spray to control malaria, 1998 (Unpublished report).
13. Rajavel AR, *et al.* Evaluation of cyfluthrin (OMS-2012), a synthetic pyrethroid, for insecticidal activity against different mosquito species. WHO/VBC/86.935, 1986.
14. Sadang RA, *et al.* Evaluation of Fendona (alphacypermethrin) a synthetic pyrethroid for one-cycle spraying in the control of malaria in the Philippines, 1998 (Unpublished report).
15. Sharma VP, Yadav RS. Cyflutrin (Solfac EW 050) impregnated mosquito nets to control malaria in the mining settlements in Orissa, India, (Unpublished Report).

16. Wickramasinghe MB, *et al.* Evaluation of cyfluthrin 10% WDP (OMS 2012) for malaria control in Sri Lanka - Results of a WHOPES phase 3 field trial, 1997 (Unpublished report).
17. Yadava RL, Krishna C, Biswas H. Field trial of cyfluthrin as an effective and safe insecticide for control of malaria vectors in triple insecticide resistant areas. *J. Communicable Diseases*, 1996, 28 (4):287-298.
18. Zaim M, *et al.* Cyfluthrin (EW 50)-impregnated bednets in malaria control programme in Ghassreghand (Baluchistan, Iran), 1996 (Unpublished report).

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