REPORT OF THE THIRD WHOPES WORKING GROUP MEETING

WHO/HQ, GENEVA
23-24 SEPTEMBER 1999

REVIEW OF:
DELTAMETHRIN 1% SC AND 25% WT
ETOGENPROX 10% EC AND 10% EW

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1. Introduction

Dr Lorenzo Savioli, Co-ordinator of Strategy Development and Monitoring for Parasitic Diseases and Vector Control (PVC), Communicable Diseases Control, Prevention and Eradication (CPE) opened the meeting. He presented the new organizational chart of the Communicable Diseases and explained how different vector-borne disease control programmes, especially Roll Back Malaria, interact within the Communicable Diseases Cluster (CDS). He also informed participants of the specific role and function of Vector Control Group, within CDS.

Dr Morteza Zaim, Scientist in charge of the WHO Pesticide Evaluation Scheme (WHOPES) recalled that the first and second 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, were held in 1997 and 1998\(^1\). He informed that the present meeting was convened to review the reports of the testing/evaluation of deltamethrin 10% suspension concentrate (SC) and 25% water dispersible tablet (WT) (AgrEvo, Germany), as well as etofenprox 10% emulsifiable concentrate (EC) and 10% emulsion, oil in water (EW) (Mitsui Chemicals, Japan), for impregnation of bednets 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.

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The collection of data includes the information, which is already available in the literature, reports provided to WHOPES by Member Countries, 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\(^3\). The specifications are part of the International Code of Conduct on the Distribution and Use of Pesticides and are used in international trade for quality control.

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 population. Therefore, safety, determination of the application dose, residual activity, 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 noted that diagnostic concentration has been established for deltamethrin and etofenprox, for adult malaria vectors, as 0.05 and 0.5%, respectively, using WHO standard test tubes and one hour exposure.

The meeting was attended by 7 scientists (see list of participants, Annex 2). Mrs R. Njau was appointed as Chairperson and Dr J. Lines as Rapporteur. The meeting was convened in plenary sessions at WHO/HQ in Geneva, 23-24 September 1999, and the reports of the WHOPES supervised trials, relevant published literature, as well as the reports submitted by the national disease and vector control programmes (see bibliography, Annex 1) were fully

\(^3\) WHO specifications for public health pesticides are available on WHO homepage on Internet (www.who.ch/ctd).
discussed. Recommendations on the use of the above-mentioned products were made.

2. Review of Deltamethrin SC and WT

Deltamethrin was the first of the single-isomer alpha-cyano pyrethroids to be used widely: it was made in 1974 and first marketed in 1977. Suspension concentrate (SC) formulations of deltamethrin have been available for several years; the water disperseable tablet (WT) formulation (which is a freeze-dried SC) was developed more recently, specifically for treatment of mosquito nets.

The International Programme on Chemical safety (IPCS) (reference) has reviewed the human and environmental safety of deltamethrin (IPCS, 1990). The IPCS concludes that under recommended conditions of use, deltamethrin is not likely to present a hazard to the general population or to those who are occupationally exposed, and that it is not likely to attain levels of adverse environmental significance. Nevertheless, like all pyrethroids, deltamethrin is highly toxic to fish and aquatic invertebrates.

The following are the extracts of the IPCS Environmental Health Criteria on deltamethrin and the observations of the Group:

- deltamethrin is readily absorbed by the oral route, but less so dermally; the rate of absorption is strongly dependent on the carrier or solvent. Absorbed deltamethrin is readily metabolised and excreted.
- Deltamethrin is relatively immobile in the environment, as it is adsorbed strongly onto particles in soil and water. Degradation to less toxic products is rapid.

- The vapour pressure of deltamethrin is $2.0 \times 10^{-6}$ Pa at 25 °C and it is practically non-volatile.

- Deltamethrin is not a skin sensitiser in the guinea pig. Absorbed deltamethrin is rapidly metabolised and excreted; it does not accumulate. Rats and mice showed no systemic toxicity or raised tumour incidence after two years of feeding on 50 - 100 mg/kg. However, rats given 10 mg/kg per day showed hyperirritability. In a 2 year study on dogs, the no-observed-effect-level (NOEL) was 1 mg/kg per day (the equivalent for a 10 kg child would be 10 mg, or about one fortieth of the amount on a net, per day).

- Deltamethrin can induce skin sensations in exposed workers. Several non-fatal cases of poisoning have been reported, involving symptoms of numbness, itching, tingling, etc. [Such symptoms of paraesthesia are well-known to those professionally involved in dipping nets.] In all the reported cases, these symptoms were invariably transient, even in production workers who claimed to be regularly exposed.

- It appears to be quite difficult to kill oneself with deltamethrin. For example, a young man and a teenage girl swallowed 70 and 200 ml, respectively, of a 2.5% EC formulation. Although she lost consciousness and needed a stomach pump, he suffered no signs of neurotoxicity, and both survived. Several hundred cases of occupational
and accidental poisoning have been reported in China. Two of these were fatal.

The following are extracts from the Material Safety Data Sheet (MSDS) for the two deltamethrin formulations and the observations/comments of the Group:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Formulation of deltamethrin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SC</td>
</tr>
<tr>
<td>Trade name</td>
<td>K-Othrin 1% SC</td>
</tr>
<tr>
<td>Flash point</td>
<td>&gt; 100 °C</td>
</tr>
<tr>
<td>Hazards identification</td>
<td>EC: Not classified</td>
</tr>
<tr>
<td>Specific risks*</td>
<td>Dangerous to aquatic organisms</td>
</tr>
<tr>
<td>Protection in use</td>
<td>Absorbent mask, gloves, goggles, protective clothes and ventilation</td>
</tr>
<tr>
<td>Acute toxicity:</td>
<td></td>
</tr>
<tr>
<td>Oral LD₅₀ rat:</td>
<td>&gt;10,000 mg/kg</td>
</tr>
<tr>
<td>Dermal LD₅₀ rat:</td>
<td>&gt;10,000 mg/kg</td>
</tr>
<tr>
<td>Chronic toxicity</td>
<td>Not mutagenic, teratogenic or carcinogenic; NOEL = 1 mg/kg/day of active ingredient</td>
</tr>
<tr>
<td>Symptoms*</td>
<td>Transient cutaneous sensations, e.g. burning, stinging</td>
</tr>
<tr>
<td>Half-life in soil*</td>
<td>4-9 days</td>
</tr>
<tr>
<td>Ecotoxicity:</td>
<td></td>
</tr>
<tr>
<td>LC₅₀ fish:</td>
<td>10 µg/l</td>
</tr>
<tr>
<td>EC₅₀ Daphnia:</td>
<td>3.5 µg/l</td>
</tr>
</tbody>
</table>

* = General characteristics of deltamethrin technical rather than specific characteristics of the formulation.
- Absence of fire hazard makes shipment easier and cheaper compared to EC, a solvent-based formulation.

- Exposure to solvents is low with SC, absent with tablets, in contrast to EC.

- Acute toxicity: In order to appreciate these figures, it is helpful to consider how many single-net treatments a 1-year old 10 kg child would have to lick or swallow in order to consume the equivalent of a rat oral LD50. Although rodent toxicity is sometimes an unreliable guide to human toxicity, such calculations do give a useful point of reference for non-toxicologists.

- With a target dosage of 25 mg/m², and a 16m² net, some 0.4g of active ingredient are needed for an individual net treatment. This is one tablet (total weight 1.6g) or 40 ml of the SC. These amounts can be compared with the rodent LD50s quoted in the MSDS.

- In the case of the tablets, they imply that a 10kg child would have to swallow about 20g, or about 12 tablets, in order to consume the equivalent of a rat oral LD50. Few families are likely to store enough insecticide for 12 net treatments at home, and very few 10kg children would be able to swallow 12 tablets.

- To do the same with the SC, the child would have to swallow "more than" 100ml of the SC formulation. It is not clear how much more, as the quoted LD50 is a minimum estimate. But 100 ml is enough to treat only two or three nets, and it is much more likely that families will store
this amount at home. 100 ml could also be swallowed easily by a 10 kg child.

2.1 Laboratory studies:

In a conventional bioassay study, cotton, nylon or polyester mosquito nets treated with deltamethrin SC and WP or lambda-cyhalothrin EC, were compared (Jana-Kara et al., 1994). A factorial design was used to compare various formulations on different fabrics, over a range of concentrations (5 to 25 mg/m²), and a range of exposure times (0.5 to 3 minutes for An. stephensi and 0.5 to 10 minutes for Cx. quinquefasciatus).

All the main effects were significant. Time of exposure had a relatively slight but significant effect on mortality. There was a clear and significant interaction between fabric and insecticide. For example, with Anopheles, the mortality caused by deltamethrin SC was twice that caused by the WP on nylon and polyester, but slightly lower than the mortality caused by WP on cotton netting. These differences were not, however, consistent between the two species of mosquito. The effects of dosage were slightly more apparent with Culex than Anopheles. Washing reduced the insecticidal activity of all netting-formulation combinations.

Elissa and Curtis (1995) also studied efficacy and persistence of various formulations of deltamethrin and one of permethrin, for treatment of mosquito nets. Hungry An. gambiae females were introduced to one end of a long netting tunnel, at the other end of which was a guinea pig separated by a barrier of netting with five small holes. This method was intended as a slightly more realistic method of testing insecticidal activity than conventional
bioassays, in which the mosquitoes are forced into contact with the netting.

The netting was treated with 200 mg/m² of permethrin EC or with 25 mg/m² of various formulations of deltamethrin, i.e., wettable powder (WP), SC, and two different ECs, with and without aromatic solvents. These were tested on cotton and on nylon nets. Residual insecticidal activity was measured over 6 months.

As expected, permethrin was less persistent on cotton than on nylon. With deltamethrin, by contrast, there was little or no sign of lower insecticidal activity on cotton.

In terms of mosquito mortality, all the deltamethrin formulations performed better than the permethrin. There was no significant difference between the two EC formulations of deltamethrin, and the persistence of these was marginally better than that of the WP formulation. The aqueous SC formulation gave intermediate results.

Washing reduced the insecticidal activity of deltamethrin and after 4 months and 3 washes in detergent and cold water, bioassay mortality rates were approximately 60%.

Even without washing, there was a surprising loss of insecticidal activity of nets that had been stored unused at 4 °C for 6 months.

2.2 Field studies

Tanzania — Verandah trap huts in a Tanzanian village were used to assess the effectiveness of nylon treated mosquito nets against An. gambiae s.l. and An. funestus (Curtis et al., 1990). Permethrin EC (200 mg/m²), deltamethrin SC (15 mg/m²), lambda-cyhalothrin EC (15
mg/m²), were compared, treating damaged and undamaged mosquito nets. Each treatment was tried on a total of 12 nights.

Such trials are able to differentiate three ways in which treated nets can protect against mosquitoes: deterreny (fewer mosquitoes enter the room), feeding inhibition (those that do enter have a lower probability of feeding), and killing (a fraction of blood-seeking females are killed, before or after they have succeeded in feeding. The first two of these give personal protection, and benefit individual users. The fact that some blood seeking females are killed is primarily important because community-wide use of treated nets can, in some circumstances, produce a "mass effect", i.e. a reduction in the density of infective mosquitoes in the area.

There was no statistical difference in performance of the three synthetic pyrethroid insecticides, except that permethrin was better at preventing feeding. All three treatments caused significantly increased mortality (70% to 90%) compared to the untreated nets.

Ivory Coast – In a comparative study in experimental huts, the efficacy of deltamethrin 1% SC and 25% WT treated mosquito nets were studied (Darriet et al. 1998). There were two series of comparisons carried out in parallel over six months in five huts. In one series of comparisons, intact nets were tested with high (25 mg/m²) or low (15 mg/m²) doses of either the WT or the SC formulations. The other series tested the effect of a single wash (with soap and cold water) on intact nets treated with 25 mg/m² of the two formulations. Each treatment was tried out twice a week.
The concentration actually on the net was measured using gas chromatography (GC) carried out by two laboratories: the WHO Collaborating Centre and the manufacturer. The results from the two laboratories were similar and were found to be close to, or a little below, the target concentration. Washing reduced the concentration on the net by approximately half.

Over the study period, a total of about 1000 mosquitoes entered the huts with the untreated nets. Both formulations at both high and low dosages greatly reduced the number entering (by 60-80%). The proportion exiting from the hut into the verandah trap was also increased, and there was indication that this “induced exophily” was stronger at higher dosages.

Of the mosquitoes which entered, a remarkably small proportion succeeded in feeding, even in the presence of the control (untreated) intact net. There was some evidence that treatment further reduced the proportion feeding, but this was not consistent.

Mortality rates were 40% to 70% with the treated nets, but less than 10% with the untreated net. There was some evidence that mortality rates were higher with the WT than the SC, but no statistical analysis was performed. There was no consistent evidence that mortality was higher with the increased doses, or that it was lower after washing.

Of the female mosquitoes that entered the huts, very few (7% - 20%) succeeded in feeding in the presence of the treated nets. However, the proportion feeding was also very low (14%) with the intact untreated net. In all these outcomes, nets treated with WT formulation appeared to be slightly more effective than the SC-treated nets. There was some evidence that high dosage nets might be a little more effective than low dosage nets. Washing in the
laboratory had little impact on the performance of the nets in the huts, although GC analysis showed that the insecticide concentration was approximately halved.

Bioassays involving 3 minute exposure to treated netting were also performed with nets of various materials (cotton, nylon and polyester), using the same two formulations at the same two doses. Twenty-four hour mortality rates remained at > 80% throughout 6 months in all cases. Knockdown within the 3-minute exposure period was consistently greater at higher doses.

*Gambia* – In a field trial in the village of Saruja (Pinder *et al.*, 1999), 255 nets were randomly divided into 3 groups. One group was treated with permethrin 10% EC (target dosage 500 mg/m²), the second group with 1% SC deltamethrin (25mg/m²), and the third group of nets was treated with deltamethrin WT (25 mg/m²).

The nets comprised a wide variety of materials, and were treated individually by a field-worker. The volumes of water used to dilute the insecticide were estimated for each net by the field workers, and ranged from 0.5 litres to 3.6 litres with a median of 0.9 litres. The amounts of insecticide on the nets (14 nets for each treatment) were measured using gas chromatography on samples taken a few days after dipping and at intervals thereafter.

There was considerable variation between and within the treated nets, as determined by chemical residue analysis. The mean concentrations observed were 446 mg/m² (s.d. 109 mg/m²) for permethrin EC, 23 mg/m² (s.d. = 15 mg/m²) for deltamethrin SC, and 15 mg/m² (s.d. = 3.8 mg/m²) with deltamethrin WT.
After 4 weeks, 17% of nets had been washed. After 5 months, 40% had been washed once and 18% had been washed at least twice. Without washing, the concentrations of all three insecticide formulations on the nets had declined to about half the target dosage after three months. There was some evidence that the tablet formulation persisted better on unwashed nets after 5 months (despite the relatively low initial values). A single wash decreased the concentration of all three treatments about equally (by 50% to 60%). After 5 months, further GC analysis indicated an even greater degree of variation between nets (partly reflecting variation in washing history), with an overall reduction of 60% to 80% in the mean deposit densities.

Insecticidal activity was assessed by collecting mosquitoes under nets, and in bioassays. All the treatments were highly effective at excluding mosquitoes from nets: more than 90% of nets contained no mosquitoes at all. With all three treatments, about half the mosquitoes found under nets were dead. Bioassay mortalities with 3 minutes exposure to deltamethrin SC remained high (>90%) throughout the 5 month period. With permethrin they began slightly lower (72%), then increased in months 3 and 4 (perhaps because the lower repellent action of the deposit allowed more contact with the mosquitoes), and then declined again to 75% in month 5. With the tablet, they remained high for the first 4 months, but declined to 65% in month 5. Looking at the detailed data, it is clear that these reductions in mean bioassay mortality towards the end of the study were attributable to a few nets which had especially low insecticidal activity and which had been washed several times. Nevertheless, even including these nets, overall average bioassay mortalities at the 5-month time point remained satisfactory.
A variety of side effects and symptoms were investigated, including several that have been reported with alpha-cyano pyrethroids in other studies. In this study, such effects were apparently uncommon, and there were no striking differences between the treatments. Reports of a smell in a freshly treated net were most common with permethrin (58 / 83) and least common with the tablet (35 / 84). Most people said that the smell was “not too pleasant”.

There were no clear differences in the perceived effectiveness of different treatments. More than 90% of people in all three groups approved of the treatment on their net, even after 3 and 5 months.

Syria – Deltamethrin 1% SC (25 mg/m²) treated mosquito nets were used for the control of cutaneous leishmaniasis in villages near Aleppo (Tayeh et al. 1997). The trial involved 4,500 people in four villages. Deltamethrin treated nets were given to all the inhabitants of two villages; the other two villages were given untreated nets.

Sandfly densities were measured indoors and outdoors, using sticky traps. There was no consistent difference in observed densities between treated and untreated villages.

Annual prevalence of leishmaniasis was estimated in the four villages during the baseline year (year 0, June 1993 – June 1994). Annual incidence was estimated in the three subsequent years.

In the pre-intervention baseline year, prevalence in the first of the two intervention villages was estimated as 4.9%. Over the next three years, estimated incidence in
this village declined consistently: it was 2.5% the year after intervention and 1.8% and 1.3% in the two following years. The pattern in the second intervention village was very similar. Prevalence was 5.1% in the baseline year, 2.4% in the year after intervention and 1.2% in both the last two years of the trial. In one of the two villages which remained untreated, prevalence was 3.8% in the baseline year, but rose to an incidence of 6.3% in the second year, declining again to 3.7 % and 1.7% in the two subsequent years. The second control village began with a lower level of prevalence (1.7%) in the baseline year, but showed wide fluctuations in incidence over the following three years: 3.8% in year 2, 1.7% in year 3, and 8.0% in year 4.

Although these data points are based on adequately large denominators (600 – 1500 person-years), there was considerable variation in incidence between years and between villages within treatment groups. The number of replicate villages was too small to allow statistical analysis with each village as a separate sampling unit. It is therefore not possible to be completely confident that the reduction in leishmaniasis rates observed in the treated villages was due to the introduction of the nets. Nevertheless, this reduction apparently coincided with intervention, and was sustained over three years. The tentative conclusion is that treated nets did not completely interrupt transmission of cutaneous leishmaniasis, but did produce a considerable reduction in incidence.

_Tanzania_ – A study was conducted with a sample net-owning residents of a suburb of Dar es Salaam (Jones and Miller, 1997). 120 participants were divided into 2 groups, and were initially asked to wash their nets. Group A was then given “dip-it-yourself” kits containing a sachet of lambda-cyhalothrin, while group B was given kits containing a K-O Tab (deltamethrin 25% WT). The target
dosage for the tablet was 25 mg/m², as determined by the manufacturer. The sachets of lambda-cyhalothrin (2.5% CS) contained 6 ml of the formulation, i.e. the target dosage was 10 mg/m². Thus this trial was not intended primarily as a comparison of actual or perceived efficacy of the two preparations; rather the main aim was to compare convenience and acceptability.

The instructions given with the two preparations were essentially the same, except that one featured line drawings of a sachet while the other included similar drawings of a tablet. These instructions had been specifically developed for the Dar es Salaam context, and were different from those issued at the time by manufacturers of dip-it-yourself kits. Many of the devices and design features used in these instructions have since been incorporated into the manufacturers' instructions for kits intended for African markets.

A wide variety of shapes, sizes and materials of nets were encountered. Convenience in use was assessed by direct observation of the dipping process, and by subsequent focus group discussions.

Of the participants who were observed as they dipped their nets, most (42 out of 47) successfully identified the appropriate size category for their net using the instructions, and thus used approximately the right amount of water. 18 out of 26 participants were seen to have some difficulty opening the packet with the tablet, compared with 9 out of 21 with the sachet. Although in a few cases the tablet was broken before the packet was opened, none of the tablet was lost, and the entire contents could be added to the water. This contrasts with the sachets, which some participants found to be difficult to empty completely. The tablet dissolved completely within 1 minute in all cases.
In the focus groups, users expressed the usual positive impressions of sleeping under a treated net, noting effects on mosquito noise as well as biting, and effects on other pests such as bedbugs. They said that the instructions were easy to follow. Only a few participants expressed concerns or fears about toxicity. It appeared that the word "poison" (sumu) on the packet had the desired effect of ensuring that users followed the instructions for use and disposal carefully, without deterring them from using the kit at all.

A second round of treatment and focus groups was held after 3 months. This time, group A was given tablets and group B sachets. In the focus groups, women who had not washed their nets at all in the previous three months noted that the visible signs of the effectiveness of the treatment were just beginning to wear off, i.e. mosquitoes were returning to the room. By contrast, those who had washed their nets twice said that after the second wash, the effect of the treatment had completely disappeared.

When asked to compare ease of use, the participants' comments reflected the results of the direct observation: some found the sachet easier to open than the tablet, while others found it harder. Several participants commented that the tablet dissolved more easily, and that some liquid had been left in the sachet.

Opinions were also mixed on the degree to which the tablet and sachet represented a hazard for children. For example some women pointed out that the tablet looked like medicine or a cough sweet, while others said that it was too big to be medicine and too big to swallow. Some thought that the liquid insecticide looked like ice-cream, while others said that the sachet looked more strange and more like a poison. Two advantages of the tablet and its
packaging over the sachet were that it would not leak if broken, and that you could feel the condition of tablet inside.

In a questionnaire, about three quarters of respondents expressed a preference for the tablet over the sachet, and cited as reasons for this choice that the tablet packaging was easier to use and safer.

In GC analyses, samples from the sides of 6 nets treated with the KO tab gave a mean deposit concentration of 14.7 mg/m² (range 6.9 – 31.0), while samples from the roofs of these nets had much higher concentrations, with a mean of 53.6 mg/m² (range 28.6 - 85.3). Noting the fact that the deltamethrin tablets are being sold in Dar es Salaam as part of a social marketing project, the monitoring of the residue of the insecticides on nets that have been routinely washed and retreated (or not treated) by their owners, were recommended by the authors.

3. Review of Etofenprox EC and EW

Etofenprox is a non-ester pyrethroid insecticide with comparable insect toxicity and a similar mode of action to other pyrethroids. The toxicology and safety of the technical product has been reviewed by the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (1993). The following are the extracts from the report of the above-mentioned meeting:

- Etofenprox has a very low acute toxicity in mice, rats and dogs. WHO has classified etofenprox as unlikely to present acute hazard in normal use. In rats, the oral LD₅₀ has been >42.88 g/kg body weight.
Based on the results of the available \textit{in vitro} and \textit{in vivo} genotoxicity data there was no evidence that etofenprox is genotoxic.

Based on the results of the available special study on sensitisation, skin and eye irritation there was no evidence that etofenprox produce sensitisation, skin and eye irritation. In rats, the dermal LD\textsubscript{50} was >2.14 g/kg body weight.

In an acute inhalation toxicity study in rats, LC\textsubscript{50}s were >5.9 g/m\textsuperscript{3}.

In long-term toxicity studies, there has been no teratogenic, carcinogenic or mutagenic effect in experimental animals.

Health assessments were carried out once or twice each year on a group of 21 operators engaged in the production of technical etofenprox for periods ranging from 1.5 to 5.5 years. No compound-related effects were observed.

Based on the No Observed Effect Level (NOEL) of 3.1 mg/kg bw/day in the long term study in mice and a safety factor of 100, an Acceptable Daily Intake (ADI) of 0.03 mg/kg bw has been established.

The following are the extracts from the MSDS for the etofenprox 10% EC and 10% EW and the observations/comments of the Group:
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EW</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Vectron 10% EW</td>
<td>Vectron 10%EC</td>
</tr>
<tr>
<td>Flash point</td>
<td>Nonflammable</td>
<td>29 °C</td>
</tr>
<tr>
<td>Protection in use</td>
<td>Mask, rubber gloves, goggles, ventilation</td>
<td>Mask, rubber gloves, goggles, ventilation</td>
</tr>
<tr>
<td>Acute toxicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral LD₅₀ rat:</td>
<td>&gt;5,000 mg/kg</td>
<td>&gt;5,000 mg/kg</td>
</tr>
<tr>
<td>Dermal LD₅₀ rats:</td>
<td>&gt;5,000 mg/kg</td>
<td>&gt;2,000 mg/kg</td>
</tr>
<tr>
<td>In case of accidental ingestion</td>
<td>Drink a glass of water and induce vomiting (not in unconscious person). See a physician</td>
<td>Do not induce vomiting because of the possible pulmonary damage via aspiration of the solvent. Drink one or two glasses of water. See a physician</td>
</tr>
</tbody>
</table>

- Exact figures for the acute oral LD₅₀ of etofenprox EW and EC are not available. However, it is expected to be much higher than the 5,000 mg/kg reported in the MSDS, based on the acute oral toxicity known for the active ingredient.

- The EW formulation of etofenprox is more suitable for the treatment of mosquito nets, since there is no hazard related to the solvent used in the EC formulation as well as its nonflammability.

- The safety factor of etofenprox EW, especially for supply "over the counter" for treatment of mosquito nets is higher than the other common insecticides
available, on the market, for impregnation of bednets.

3.1 Laboratory studies

As mentioned above, etofenprox is an insecticide with an action similar to the pyrethroids. In cross resistance studies (Hemingway, 1995) on standard susceptible and resistant laboratory strains of *An. gambiae*, *An. albimanus*, *An. stephensi* and *Culex quinquefasciatus*, showed no effect of carboxylesterase, elevated esterase, altered acetylcholinesterase or glutathione S-transferase-based resistance mechanisms, while cross resistance to etofenprox occurred in a pyrethroid-resistant strain of *Cx. quinquefasciatus* with both oxidase and *kdr*-like resistance mechanisms. The author’s results are similar to those of Curtis (1993) which reports etofenprox cross resistance in a pyrethroid resistant strain of *An. stephensi* from Dubai.

Chandre *et al.* (1999) also showed cross resistance to all pyrethroids, including etofenprox, induced by the *kdr* mutation in *An. gambiae s.s.* from West Africa.

Todd *et al.* (1996) conducted tests by chemical assay and bioassay, of the persistence of permethrin, deltamethrin and etofenprox in relation to storage in light or darkness and washing in a standardised laboratory way in SDS solution on a shaker. Chemical assay of persistence after washing of permethrin deposits showed that this was much dependent on duration of washing and concentration of SDS. This suggests that people who feel the need to wash their impregnated nets should be encouraged to wash them gently in water or with minimal amounts of soap.

Chemical assays showed loss of all three insecticides as a result of months of storage in the light, but little loss in the
dark. Three washes, each for 5 minutes, in 2% SDS reduced deposits of deltamethrin to 50-75% of the initial level, and those of etofenprox deposits to 35-45% of their initial levels. A single wash reduced a permethrin deposit to 42% of the initial level.

Bioassays with An. gambiae and 3 minutes exposure gave much greater apparent losses of insecticidal activity due to storage and washing than those reported by other workers. The activity of deltamethrin persisted better than that of etofenprox, which persisted better than that of permethrin.

### 3.2 Field studies

**Thailand** – In an experimental hut study (Prasittisuk et al., 1995), the residual life of three dosages of etofenprox EC (100, 200 and 400 mg/m²) were studies on cotton and nylon mosquito nets. Three minutes exposure bioassays showed dose dependent persistence of insecticidal effect. Mortality on treated mosquito nets at the target dosages of 200 mg/m² remained close to 100% for 6 months, but declined thereafter. No significant difference was reported on the residual life of the product on nylon and cotton nets.

**Tanzania** – Curtis et al. (1996 and 1998) have reported results of bioassays of etofenprox treated nets, with or without washing. They have concluded that a net treated with 200 mg/m² and in domestic use for a year continued to give about 60% kill in bioassays. Only after 15 months and washing did the insecticidal power drop to a low level. A net treated with 25 mg/m² deltamethrin retained its insecticidal power better than the etofenprox net - 90% kill at 15 months after one wash.
Curtis et al. (1998) have also reported that observations of time for knockdown seems to provide a more sensitive method of bioassay for highly active pyrethroids, which tend to give close to 100% kill with a 3 minute exposure. Tests with etofenprox at target dosages of 100, 200 and 400 mg/m², using either the EC or EW formulations, showed slightly, but significantly, quicker knock down activity of EW over the EC formulation, but no clear relationship to the dose used. Gentle hand washing in cold water with a little detergent gave a slight, but significant, reduction in knockdown activity with both formulations.

Curtis et al. (1996, 1998) also reported the results of etofenprox treated nets in experimental huts in Tanzania which allow wild mosquitoes to enter, while occupied by sleepers. The huts were fitted with verandah traps to catch exiting mosquitoes and ant traps to attempt to exclude scavengers and hence to allow mosquitoes killed during the night to be found and counted in the morning. Thus, unlike the use of catches of biting mosquitoes on subjects outside nets or of mosquitoes landing on nets, one can hope to estimate the level of personal protection provided to a net user, as well as the contribution of a treated net to mass killing of the vector population in a community. Data were obtained with intact nets and with nets in which 6 holes 4x4 cm had been cut to simulate torn nets with which effective chemical treatment is particularly important. Each net was tested in rotation in each of the 2 huts for a total of a minimum of 12 nights. The data for each replicate night were tested by non-parametric Kruskal-Wallace tests for significance of differences between net treatments.

Intact nets provided good protection against biting, even when untreated, and caused deaths of some Anopheles by starvation. Only permethrin significantly improved protection from blood feeding by Anopheles, but only etofenprox significantly increased Anopheles mortality. Neither
insecticide significantly improved protection from *Culex* blood feeding. There was very little mortality of *Culex*, which is pyrethroid resistant in this area of Tanzania.

The insecticides made a major difference to rate of blood feeding and mortality when nets were holed. A domestically used etofenprox net performed as well as a permethrin treated net, except in respect of prevention of *Culex* feeding. Performance of EC and EW formulations did not differ significantly except in respect of *Anopheles* mortality for which EW was better. There was no consistent differences in performance associated with differences in dosage between 100 and 400 mg/m², nor between washed and unwashed nets.

**Cambodia** – A small scale field trial was carried out in Cambodia, where *An. minimus* (exophilic and zoophilic) and *An. maculatus* (endophilic and partly anthropophilic), are the main malaria vectors, and susceptible to etofenprox. The majority of malaria cases were due to *Plasmodium falciparum* (Lek and Yeang, 1992). Etofenprox EW treated mosquito nets (target dosage of 200 mg/m²) were used in one village, and another village was used as control. Etofenprox treated nets were introduced in June 1992 and assessed using year to year comparisons with the control area.

The study revealed that mosquito densities in the treated village were lower than in the previous year, and were also lower than in the comparison village in the same year. Slides from fever cases from the treatment area showed a marked decline in slide positivity rate between the pre-treatment year and immediately post-treatment.

**Southern Viet Nam** - A field trial was carried out to compare
village nets treated with etofenprox EW (200 mg/m²) (coverage of >97%) with untreated nets in a control village (Institute of Malariology, Parasitology and Entomology, 1993). Entomological studies on vector population densities included human landing catches, carried out indoors and outdoors in each area plus daytime indoor resting catches. The nets were re-treated after 6 months. Susceptibility test carried out with 0.2% etofenprox indicated the full susceptibility of the main malaria vector, An. sundaicus, to the compound.

The window trap catches showed the well known excito-repellency effect of treated nets in driving mosquitoes out of rooms. The outdoor landing catches from the first 6 months after treatment suggest a "mass effect" of the nets on the village mosquito populations. However, in the following 6 months, control and treated villages gave similar catches. There was an apparent difference in trend between the control and treated villages, interpretation is, however, uncertain because of the limited amount of baseline data and only two villages studied.

Active malaria surveillance was carried out by taking blood slides from: (a) children; (b) cases with fever and malaria-like symptoms; (c) patients with previous positive slides. From data on slides positive for Pl. falciparum and Pl. vivax there appears to be downward trend in the treated area, however, no statistical analysis is provided. Passive surveillance for malaria cases also suggested a favourable downward trend in the treated area.

Northern Viet Nam – In a village scale trial in North Viet Nam, where An. minimus, is the main malaria vector (susceptible to etofenprox), 4 hamlets were selected. One hamlet was designated for bednets treated with etofenprox EC (200 mg/m²), two hamlets for nets treated with
etofenprox EW (200 mg/m²), and one hamlet was the control (untreated nets) (Nguyen et al., 1993).

Indoor human landing catches were made 0.5 m from treated nets. None were caught after the first month post-treatment with either the EC or EW formulation, but a few continued to be caught for next 6 months in the control hamlet. Indoor resting data on An. minimus also indicated a slow disappearance of mosquitoes from the treated houses.

Bioassays with Aedes aegypti and local Anopheles species showed equal persistence of the insecticidal effect up to 6 months on cotton and nylon nets with the EC formulation, and better persistence on nylon than cotton with the EW formulation.

In a larger scale field study in Northern Viet Nam, using 9 hamlets with etofenprox EW treated nets (target dose of 200 mg/m²) (4580 population) and 4 hamlets with untreated nets (1904 population), Nguyen et al. (1994) showed the positive impact of the treated nets by comparing the indoor resting and landing mosquito catches indoor and outdoor one month before, and each month for a year after treatment. Mass blood examinations, taken in the month before treatment and subsequent months, showed a decline associated with treatment, but numbers of positives were too few to allow any statistical analysis.

4. Conclusions and Recommendations

In most respects, the two deltamethrin products and the "non-ester pyrethroid" etofenprox are typical of pyrethroids formulated for use on nets.
4.1 Conclusions Concerning Deltamethrin SC and WT

1. Deltamethrin is highly biodegradable, is not mobile in the environment, and is broken down quickly without accumulating in the body. Deltamethrin has been in common use for longer than any other alpha-cyano pyrethroid, and has an excellent safety record.

2. The tablet and SC formulations performed well in both bioassays and experimental huts, in a variety of circumstances and studies. Their effectiveness was equal to or slightly better than that of permethrin EC. There is some evidence, from experimental hut and laboratory tests, that compared to permethrin they are more persistent, more wash-resistant, better at killing but worse at preventing feeding. Overall, there was little difference between the two formulations, either in terms of their insecticidal activity in bioassays or in their effects on vector behaviour in experimental huts.

3. The manufacturers' recommended target dosage 15 to 25 mg/m² appears to be appropriate. Nets treated at these dosages with either formulation remain effective for at least six months (and perhaps longer) without washing, with either cotton or synthetic netting, but a significant degree of activity is lost after two or more washes. Washing appears to remove 40% to 60% of the insecticide deposit.

4. The studies reviewed did not include any large scale field trials, but the SC was apparently effective in a trial of cutaneous leishmaniasis control in Syria.

5. In an acceptability study with home treatment kits, urban residents had no problems in handling the
tablets in an appropriate manner, and preferred the tablet to a sachet of liquid insecticide.

6. Both these formulations are suitable for use as a treatment on nets. The tablet formulation is especially suitable for use in home treatment kits.

4.2 Conclusions Concerning Etofenprox EC and EW

1. Etofenprox is considered to be of very low mammalian toxicity, and has the highest safety factor for supply "over the counter", for home treatment of mosquito nets, as compared to all other pyrethrroids.

2. Most of the studies reported for the Group used dosages in line with the manufacturer’s recommendation of 200 mg/m². Bioassays showed that this dose remained effective for 6 months or more. There are indications that etofenprox deposits are more wash resistant than permethrin and less resistant than deltamethrin. The EW formulation performed at least as well, and in some respect better, than the EC in experimental hut trials.

3. Pyrethroid resistant mosquito strains with the kdr resistance gene are cross resistant not only to all pyrethrroids tested (to variable degrees) but also to the non-ester pyrethroid, etofenprox.

4. While the safety record and the results of the filed trials presented to the Group warrants the recommendation of etofenprox EW for impregnation of bednets, well planned larger scale trials in different epidemiological settings are recommended.
4.3 Recommendations

1. On the basis of accumulated knowledge and trials reviewed it is concluded that deltamethrin SC & WT and etofenprox EW are safe and effective insecticides for treatment of mosquito nets, and are recommended for use at dosages of 15-25 and 200 mg/m², respectively. Use of etofenprox EC for such application is not recommended, due to its flammability and potential solvent-related hazards.

2. The Group considered the general practice of specifying a range for the recommended target dosage for insecticides for net treatment. Doses at the higher end of the recommended range are to be preferred if the transmission season and the interval between treatments are longer than 6 months, if nets tend to be washed frequently, or if Culex mosquitoes are perceived a biting nuisance. Similarly, given the large range of concentrations actually achieved in routine dipping operations, there is a case to be made for aiming for a higher dose in order to ensure a margin of safety in the doses actually achieved. On the other hand, using higher doses makes a significant difference to overall cost.

3. The Group noted that there appears to have been no investigation of the possible impact on freshwater fish when treated nets are washed in small streams colonised by fishes and invertebrates. Such an investigation would be desirable.

4. Neonatal administration of certain pyrethroids was recently reported to induce protracted changes in brain chemistry and behaviour in rodents. Guidance on the validity of these findings and on their significance as
predictors of adverse health effects should be sought from the IPCS.

5. In future, the use of home-treatment kits for net-impregnation is likely to spread. Although this is a new way of using insecticide, and involves introducing insecticide concentrates into the home, no authoritative and comprehensive risk assessment appears to have been carried out. At present, we know very little of how such kits will be used in practice. It is recommended that WHO should consider the need for periodic risk assessments of this kind, and should attempt to determine what data may be needed.

6. The Group recommended that unit doses should generally be used for home net treatment, and stressed the need for proper packaging (child-proof) with appropriate labelling and tested instruments for use. Education in the safe and proper use of such home treatment kits is recommended.

7. Quality control in design and manufacture is always of primary importance for any insecticide, but is especially critical for products to be used at home.
Annex 1  Bibliography


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