

# Pyrethroids in Bed Nets: deltamethrin, etofenprox, lambda-cyhalothrin permethrin, piperonyl butoxide

Small-meshed bed nets have been used for many years to prevent mosquitoes and other insects biting people when they sleep. However, more recently, synthetic pyrethroid insecticides have been applied to some types of bed net to repel or kill the insect, and these nets are known as 'Insecticide-treated Bed Nets' (ITNs). They have become particularly prevalent in malaria-prone countries, and are regarded as an important tool in the 'Roll Back Malaria' Campaign. Insecticides recommended by the World Health Organization (WHO) for these nets are *alpha-cypermethrin*, *cyfluthrin*, *deltamethrin*, *etofenprox*, *lambda-cyhalothrin* and *permethrin*.

The nets are theoretically retreated every 6-12 months, or more frequently if washed, by dipping in a mixture of water and insecticide and leaving to dry in a shady place. However because of the cost of retreatment and problems with efficacy, several companies have developed 'Long-lasting Insecticide-treated Nets' (LLINs) which are claimed to be effective for 3 years. The WHO Global Malaria Programme recommends that only LLINs should be used and that they be distributed to all people in areas of malaria.

WHO has given interim or full approval to 12 of these LLINs in the prevention of malaria. The insecticide is incorporated within or bound around the fibres of the net, and in theory kills all mosquitoes that come in contact with it. Production is now massive, and occurs in a number of countries including China, Vietnam, and Tanzania.

For example in 2009 Tanzania alone was producing 29 million Olyset nets with the assistance of the Japanese Government and UNICEF 145 million ITNs were delivered in 2010 in sub-Saharan Africa with a further 74 million from Jan to Nov 2011.

The active ingredients included in the LLINs are *alpha-cypermethrin*, *deltamethrin*, and *permethrin*, and the synergist *piperonyl butoxide*. In addition *lambda-cyhalothrin* is regarded as a long-lasting re-treatment. Other chemicals are also added including 'stabilizers, plasticizers and other formulants'.

This factsheet reviews the adverse effects of the pyrethroids recommended by WHO for treated bed nets, that are regarded as HHPs for human health reasons – namely *deltamethrin*, *etofenprox*, *lambda-cyhalothrin*, and *permethrin*. It also includes *piperonyl butoxide*, which is not a pyrethroid but a synergist used to enhance the toxicity of pyrethroids by protecting them from metabolic breakdown.

## Classifications and risk statements

*WHO*: Class II, moderately hazardous – *deltamethrin*, *lambda-cyhalothrin*, *permethrin*.

Table 5, unlikely to present acute hazard in normal use – *etofenprox*, *piperonyl butoxide*.

*US EPA*:

- *lambda-cyhalothrin*: risk concerns for aquatic organisms.
- *permethrin*: likely to be carcinogenic to humans.
- *piperonyl butoxide*: Class C possible



### Pesticide Action Network Asia and the Pacific

P.O. Box 1170  
10850 Penang, Malaysia  
Tel: (604) 657 0271 / 656 0381  
Fax: (604) 658 3960  
Email: panap@panap.net  
Homepage: www.panap.net

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Meriel Watts, PhD  
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## Trade names and manufacturers

Active ingredient	Trade Name	Manufacturer
alpha-cypermethrin <sup>1</sup>	Duranet	Clarke Mosquito Control, USA
alpha-cypermethrin <sup>2</sup>	Interceptor	BASF, Germany
alpha-cypermethrin <sup>1</sup>	MAGNet	VKA Polymers, India
alpha-cypermethrin <sup>1</sup>	Royal Sentry	Disease Control Technologies, USA
deltamethrin <sup>2</sup>	DawaPlus 2.0	Tana Netting, Thailand
deltamethrin <sup>2</sup>	LifeNet	Bayer CropScience, France
deltamethrin <sup>1</sup>	Netprotect	Intelligent Insect Control, France
deltamethrin <sup>2</sup>	PermaNet 2.0, 2.5	Vestergaard-Frandsen, Switzerland
deltamethrin + piperonyl butoxide <sup>1</sup>	PermaNet 3.0	Vestergaard-Frandsen, Switzerland
deltamethrin <sup>2</sup>	Yorkool LN	Tianjin, China
permethrin <sup>3</sup>	Olyset	Sumitomo, Japan

- 1 incorporated into polyethylene fibres at rates between 1.8 and 5.8 gm/kg for the pyrethroid and 25gm/kg for *piperonyl butoxide*
- 2 bound onto polyester fibre at rates between 2 and 8.5 gm/kg
- 3 incorporated into polyethylene fibres at a rate of 20 gm/kg, with wide mesh of 4mm x 4mm

The above nets have all received interim or full recommendation from WHO, but the following net did not meet its specifications:

*deltamethrin* Yahe Fujian Yamei Industry, China

The following retreatment chemical has WHO interim recommendation:

*lambda-cyhalothrin* ICON MAXX Syngenta, Switzerland

Although *etofenprox* does not appear on the above list of WHO-approved bed nets it is used on ITNs.

human carcinogen; acute and chronic risk to amphibians, estuarine/marine and freshwater invertebrates, freshwater fish.

### Regulatory status

#### International

No international regulatory action.

#### National

*Permethrin*: banned in EU countries.

### International standards

On PAN International's list of Highly Hazardous Pesticides (2010) for global phase-out for human health reasons:

- *deltamethrin*: endocrine disruptor
- *etofenprox*: carcinogenicity
- *lambda-cyhalothrin*: R26 (very

toxic by inhalation), endocrine disruptor

- *permethrin*: carcinogenicity, endocrine disruption
- *piperonyl butoxide*: carcinogenicity, endocrine disruption.

On PAN International's list for bee toxicity: *alpha-cypermethrin*.

Not on PAN International's list: *cyfluthrin*.

Because this factsheet is on use of HHPs in insecticide-treated bed nets, *alpha-cypermethrin* and *cyfluthrin* are not further discussed.

### Residues in humans

*Deltamethrin*, *lambda-cyhalothrin* and *permethrin* found in breast milk.

Pyrethroid metabolites found in urine of children and adults.

### Health effects

#### Mechanism of toxicity

Neurotoxic, interfere with the way nerves and brain function. They act on axons in the peripheral and central nervous systems by interacting with sodium channels in mammals and insects. Inhibit GABA receptors. Some (including *deltamethrin* and *lambda cyhalothrin*) can inhibit acetylcholinesterase.

*Piperonyl butoxide*: inhibits an enzyme system involved in catalysing oxidative processes.

#### Poisonings

USA: a large number of incidents involving *lambda-cyhalothrin* with dermal, neurological, gastrointestinal and respiratory symptoms of 'low to moderate severity', and 2 deaths; a

'moderately large number' involving *piperonyl butoxide* in combination with another active ingredient.

China: 27% of cotton workers who sprayed 'pure' pyrethroids had poisoning symptoms; in another case, cotton workers reported symptoms after spraying *deltamethrin* for 3 days; 2 deaths from occupational exposure to pyrethroids; other deaths resulted from accidental and intentional ingestion.

Bed nets treated with *permethrin* or *deltamethrin* are reported to have caused rash, runny nose, sneezing, and cough in about 11% of households studied.

### Acute toxicity

High acute oral toxicity: *deltamethrin*, *lambda-cyhalothrin*.

Moderate acute oral toxicity: *etofenprox*, *permethrin*.

Low acute oral toxicity: *piperonyl butoxide*.

Signs and symptoms include dizziness, headache, nausea, anorexia, reduced energy, fatigue, listlessness, altered awareness, involuntary movements, twitching, tremors, convulsions, pulmonary oedema, loss of consciousness, hyperexcitability, and paralysis. In addition:

- *deltamethrin*: numbness, itching, tingling, burning of skin, blotchy erythema; vertigo; salivation, choreoathetosis ('sinuous writhing'); high acute oral toxicity.
- *lambda-cyhalothrin*: itching, redness, swelling, tingling and burning sensation of skin; prickling feeling around the face; eye irritant including tearing and blurred vision; irritation of throat and nose; lack of appetite; fatigue; ataxia, unsteady gait, and hyperexcitability; salivation, choreoathetosis.
- *Permethrin*: incoordination, hyperactivity, prostration, dizziness, twitching, paralysis; respiratory irritation; core temperature markedly increased; mild skin and eye irritation.

### Chronic toxicity – pyrethroids in general

*General*: oxidative stress; alter blood parameters.

*Neurotoxicity*: "Evidence is accumulating that pyrethroid

exposure may also be neurotoxic during development" (US EPA); exposure of rat foetuses to pyrethroids via their mothers resulted in persistent alterations in brain neurotransmitter numbers; developmental exposures caused oxidative stress, decreased antioxidant levels, cholinergic dysfunction leading to learning and memory deficits.

*Endocrine disruption*: blood levels of pyrethroid metabolites associated with decreased levels of testosterone and free androgens in men.

*Reproductive and developmental toxicity*: reduced sperm concentration in humans; early developmental exposure impairs testicular development.

*Immunotoxicity*: "Recent studies of children reported immunotoxic effects following exposure to pyrethroids, with increased incidence of anti-nuclear antibodies associated with autoimmune disease" (US EPA).

*Metabolic effects*: abnormal glucose regulation; alter liver enzyme activity.

### Deltamethrin

*General*: oxidative stress in fish.

*Neurotoxicity*: chronic human exposure may cause disruption of autonomic nervous system, including unsteadiness, body tremors, abnormal head movements, vomiting and liquid faeces, reduced food consumption and body weight gain, skin lesions; in lab animals neurobehavioural effects include altered locomotory behaviour.

*Genotoxicity*: genotoxic in fish, plants, mice; mutagenic in human and rodent cells.

*Cancer*: increased mammary tumours in rats; inhibits 'gap junction intercellular communication' (GJIC), which increases risk of tumour growth.

*Endocrine disruption*: decreases growth hormone and growth factors which may affect growth, reproduction and development; decreases testosterone levels; anti-androgenic; oestrogenic, increasing growth of breast cancer cells.

*Reproductive and developmental toxicity*: birth defects (craniofacial) in fish; reduced male fertility in rats.

*Immunotoxicity*: suppresses humoral immune responses; caused significant decrease in enzyme activity in lymphocytes, decreased numbers of splenic plaque-forming cells, decreased percentages of rosette-forming lymphocytes in lymph nodes and spleen, depressed cell-mediated immune response.

*Metabolic effects*: exposure of pregnant rats increased activity of cytochrome P450 dependent enzymes in brain and liver of offspring; modified activities of several xenobiotic-metabolizing enzymes in liver of rats.

### Etofenprox

*General*: target organs are thyroid, liver, kidney; accumulates in fat, tissues and organs with high fat content, and breast milk; alters blood parameters; increases kidney and liver weight.

*Neurotoxicity*: decrease in spontaneous motor activity, increase in induced sleeping time and changes in EEG of frontal lobe in rats.

*Genotoxicity*: DNA damage in sperm.

*Cancer*: thyroid follicular tumours in rats.

*Endocrine disruption*: anti-oestrogenic; thyroid hormone receptor antagonist; has endocrine disrupting potential because of disruption of Aryl hydrocarbon receptor, hence implicated in birth defects, immunotoxicity, neurotoxicity, lethality, tumour promotion, and enzyme induction.

*Reproductive and developmental toxicity*: reduced sperm concentrations in humans; early embryonic mortality and late abortions in rabbits.

*Immunotoxicity*: adverse effects on immune system through endocrine disruption.

*Metabolic effects*: in lab animals, increased glucose, cholesterol, and liver enzymes; induces hepatic microsomal enzyme system, CYP1A.

### Lambda-cyhalothrin

*General*: oxidative stress; alters blood parameters; damages liver, kidney, lungs, heart.

*Neurotoxicity*: decreases binding of muscarinic-cholinergic receptors in brain consequently impairing learning activity; alters brain

dopaminergic and serotonergic systems and decreases motor activity in developing rats.

*Genotoxicity*: damages DNA.

*Cancer*: promotes MCF-7 human breast cancer cell proliferation.

Endocrine disruption: represses mRNA and protein expression levels of oestrogen receptors; anti-androgenic; decreases testosterone levels; decreases serum thyroid hormone T3/T4 ratio; increased serum thyroid stimulating hormone levels.

*Reproductive and developmental toxicity*: decreases semen quality, relative weight of testes and epididymis; blocks spermatogenesis; damages seminiferous tubules; delayed descent of testes into scrotum.

*Immunotoxicity*: suppresses immune system, damages macrophages.

*Metabolic effects*: alters activity of various enzymes.

### **Permethrin**

*General*: adverse effects on adrenal glands (dogs), liver (rats); oxidative stress; damages red blood cells; alters enzyme activity.

*Neurotoxicity*: neurobehavioural effects in lab animals include aggression and abnormal movement; can produce Parkinson's disease-associated changes in the dopaminergic nigrostriatal pathway; significant decreases in expression of genes important for neurological development.

*Genotoxicity*: mutagenic in hamster and fruit fly; genotoxic in rat and human cells.

*Cancer*: lung and liver tumours (rodents); epidemiological link with multiple myeloma, leukaemia, lymphatic cancers; increases growth of breast cancer cells; affects development of mammary gland to increase susceptibility to breast cancer (increases proto-oncogene); inhibits GJIC, which increases risk of tumour growth.

Endocrine disruption: disrupts testosterone production; anti-progestagenic; oestrogenic causing growth of human breast cancer cells.

*Reproductive and developmental toxicity*: decreases sperm numbers and motility; damages testes (mice);

birth defects (craniofacial) in fish; intrauterine growth retardation (rats); increased deaths of newborn (rats); epidemiological link with damaged sperm; alters vascular development, and neocortical and hippocampus thickness in the foetal brain in rats leading to decreased postnatal locomotor ability; exposure in 3rd trimester of pregnancy linked to delayed mental development in children at 3 years of age.

*Immunotoxicity*: suppresses immune system; inhibits T-lymphocytes and natural killer cells; elevated levels of permethrin in cord blood associated with reduced levels of anti-inflammatory cytokine, part of immune mechanism involved in asthma and allergy; reduced levels increase asthma and allergy; linked to presence of antinuclear antibodies in blood, a marker of autoimmune disease; children developed immune-mediated respiratory and dermal irritation.

*Metabolic effects*: affects human liver enzyme activity, in cats causes anaemia, hyponatraemia, hypochloreaemia, hypokalaemia, hyperkalaemia, hypoproteinaemia and hypoalbuminaemia.

*Other*: primary irritant contact dermatitis.

### **Piperonyl Butoxide**

*General*: major target organ is the liver; damages liver and kidneys; oxidative stress.

*Neurotoxicity*: exposure in 3rd trimester of pregnancy linked to delayed mental development in children; adverse effects on exploratory behaviour in mice.

*Genotoxicity*: has shown mutagenicity in human cells.

*Cancer*: liver carcinogen in rats and mice.

*Endocrine disruption*: listed as endocrine disruptor by EU.

*Reproductive and developmental toxicity*: in rodents reduced foetal weight and increased resorption; limb deformities; adverse effects on reproductive, developmental and behavioural parameters, increasing in subsequent generations.

*Immunotoxicity*: immunotoxic.

*Metabolic*: increased cholesterol in rats.

### **Sensitive populations**

The young are more sensitive to pyrethroids, especially *deltamethrin* and *permethrin* than adults, because of the lack of enzymes to metabolise them.

Males are more susceptible than females to etofenprox.

Those with impaired liver function, or susceptibility to asthma.

### **Exposure**

For nets in which the insecticide is incorporated into the fibre, the WHO stipulates that while the majority of the insecticide resides within the fibre as a reservoir, an "adequate amount" must be present on the surface to kill the mosquitoes. The reservoir is released with washing.

This means that anyone touching any of the treated mosquito nets is in contact with the insecticide. Children may be exposed by touching, or sucking on netting. Adults may be exposed by touching netting and when washing it. All may be exposed to low levels by inhalation as the pyrethroids evaporate slowly.

## **Environmental and agroecological effects**

### **Toxicity**

Aquatic toxicity is relevant because of the re-treatment and washing of bed nets, which is likely in some circumstances to result in discharge of contaminated water into water sources.

*Aquatic*: all the pyrethroids are highly to very highly toxic to fish and aquatic invertebrates. *Piperonyl butoxide* is moderately toxic to fish and freshwater invertebrates, highly toxic to estuarine invertebrates, and increases the toxicity of pyrethroids to aquatic species.

### **Resistance**

39 countries have reported mosquitoes resistant to pyrethroids, 27 in sub-Saharan Africa. Resistance has been found to *deltamethrin*, *etofenprox*, and *permethrin*, but *permethrin* is showing by far the most widespread resistance.

## Environmental fate and contamination

**Soil:** pyrethroids are strongly adsorbed to soil particles and are moderately persistent; half-lives are *permethrin* = 4–40 days; *deltamethrin* = 21–46 days; *etofenprox* = >30 days; *lambda-cyhalothrin* = 25–65 days;

**Aquatic:** half-life in water/sediment system: *lambda-cyhalothrin* = 12 days; *permethrin* = 40 days; *deltamethrin* = 65 days.

**Air:** evaporate slowly.

**Bioaccumulation:** pyrethroids can bioaccumulate in aquatic organisms, especially *lambda-cyhalothrin* which, in fish, has a bioconcentration factor (BCF) of 1950–4,600; *deltamethrin* BCF = 1,400; *permethrin* BCF = 300–600. Aquatic plants accumulate *deltamethrin* and *permethrin* from water. *Etofenprox* is also described as persistent.

## Alternatives

The traditional mosquito nets with small mesh and no insecticide treatment can be produced locally and sustainably at less cost, and if properly maintained (i.e. free of holes) are effective and present less risk to human and environmental health. *Permethrin*-treated nets present the worst risk in terms of the effects of the *permethrin* on people, and combination of a high level of resistance by mosquitoes and the larger hole size in these nets dramatically increases the risk of malaria.

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