Insecticide Mode of Action Classification: A Key to Effective Insecticide Resistance Management in Mosquitoes

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Introduction and background
Mosquitoes are vectors of many of the world's key human diseases, including malaria. The emergence of species resistant to insecticides widely used in vector control has the potential to impact severely on the control of these disease vectors. This may have a dramatic effect in Africa, as few affordable alternative insecticides are available for vector control. The lack of suitable alternative insecticides for vector control has also been an issue, for example only pyrethroids are currently recommended by WHO for use on long lasting insecticide treated mosquito nets. Industry is now working in collaboration with the Innovative Vector Control Consortium (IVCC) to find new classes of insecticides with novel modes of action for use in public health. However the identification and approval process of a new active can take up to 10 years and ~$200 million. It is therefore vital that effective insecticide resistance management (IRM) strategies are implemented to ensure that the efficacy of existing controls can be maintained for as long as possible.

In order to help prevent or delay the incidence of resistance, IRAC promotes the use of a Mode of Action (MoA) classification of insecticides in effective and sustainable IRM strategies. Available insecticides are allocated to specific groups based on their target site as described below. By using sequences or alternations of insecticides from different MoA classes, resistance is less likely to occur. Available at the IRAC website www.irac-online.org. This IRAC MoA classification list along with the IRAC Vector Manual provides NGOs, ministers, advisors, extension staff, consultants and public health professionals with a guide to the selection of insecticides and planning of IRM programs.

Nerve and Muscle Targets
Most current insecticides act on nerve and muscle targets. Insecticides that act on these targets are generally fast acting

- **Group 1 Acetylcholinesterase (AChE) inhibitors (Adults or Larvae)** Inhibit AChE, causing hyperexcitation. AChE is the enzyme that terminates the action of the excitatory neurotransmitter acetylcholine at nerve synapses.
  - 1A Carbamates (e.g. propoxur & bendiocarb),
  - 1B Organophosphates (e.g. temephos, malathion, fenitrothion, pirimiphos-methyl)
- **Group 2 Sodium channel modulators (Adults only)** Keep sodium channels open, causing hyperexcitation and, in some cases, nerve block. Sodium channels are involved in the propagation of action potentials along nerve axons.
  - 2A Pyrethroids, Pyrethrins (e.g. deltamethrin, permethrin, cypermethrin, alphacypermethrin, lambda-cyhalothrin, bifenthrin, etofenprox)
  - 2B DDT
- **Group 3 Nicotinic acetylcholine receptor (nAChR) allosteric modifiers (Larvae only)** Allosterically activate nAChRs, causing hyperexcitation of the nervous system. Acetylcholine is the main excitatory neurotransmitter in the insect central nervous system.
  - 3A Spinosad
  - 3B Spinosyns (e.g. spinoasoid).

Growth and Development Targets
Insect development is controlled by the balance of two principal hormones: juvenile hormone and ecdysone. Insect growth regulators act by mimicking one of these hormones or directly perturbing cuticle formation/deposition or lipid biosynthesis. Insecticides that act on individual targets in this system are generally slow to moderately slow acting.

- **Group 7 Juvenile hormone mimics**
  - 7A Juvenile hormone mimics (e.g. methoprene, hydroprene)
  - 7C Pyriproxifen
- **Group 15 Inhibitors of chitin biosynthesis Type 0**
  - 15 Antimicrobials blocking the action of N-acetylglucosaminyl transferase

Midgut
Derived from bacteria, these toxins need to be ingested and disrupt the insect midgut membranes

- **Group 11 Microbial disruptors of insect midgut membranes**
  - 11A Bacterium thuringiensis
  - 11B Bacillus thuringiensis var. israelensis and Bacillus sphaericus

Effective IRM strategies
Sequences or alternations of MoA
All effective insecticide resistance management (IRM) strategies seek to minimise the selection of resistance to any one type of insecticide. It is recommended that alternations, mosaics or rotations of compounds from different MoA groups can provide sustainable and effective IRM for mosquitoes. This ensures that selection by compounds in the same MoA group is minimised, and resistance less likely to evolve. The practice of using an insecticide until resistance occurs becomes a limiting factor in public health and is rapidly eroding the number of suitable insecticides for vector control. The limitations of current public health interventions such as IRS and LNs mean that in many cases the mosquitoes are exposed to compounds from the same MoA group. This makes IRM in public health more challenging than in agriculture. Therefore insecticide resistance monitoring is of vital importance, this can be done using bioassays (WHO) and/or CDC standard test kits and procedures and also biochemical/ molecular methods. This testing should ideally be conducted annually to monitor any changes in susceptibility that may occur and thus allow timely intervention of alternative vector control methods.

Further reading:
Prevention and management of insecticide resistance in vectors and pests of public health importance
WHO (2006); Pesticides and their application
WHO/CHD05/WHOPES/GCDPP/6th edition, 114 pp
www.who.int/whopes/en/