WHITE PAPER – MGK

FIGHTING MOSQUITO RESISTANCE:

What every control professional should know

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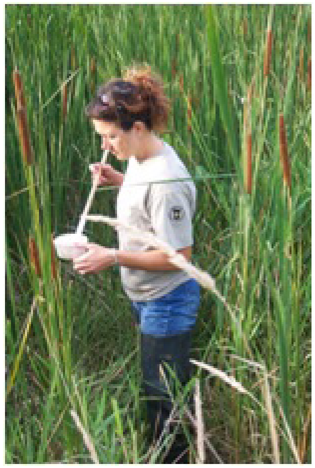
MGK® Insect Control Solutions



Focus on mosquito control is intensifying from many angles as mosquito-borne diseases make headlines on a daily basis. Increased public awareness of the mosquito as a vector, combined with real, and often emotion-laden, public concern over pesticide use are shining a light on mosquito control efforts like never before. What was once considered a nuisance pest, can now present as a grave public health concern. Mosquito control professionals are truly the front line in this fight. Mosquito resistance to control is often suspected but much less often verified. Now is the time to take mosquito resistance to control seriously. Now is the time to build a better understanding of the resistance issues we are facing and to use any and all tools at our disposal in the most efficient manner.

In the continental U.S., there have been 216 cases of locally acquired mosquito-borne cases of Zika reported and an additional 4,618 travel-associated cases reported.

CDC - January 4, 2017
https://www.cdc.gov/zika/geo/united-states.html

In this paper, we aspire to arm our partners in mosquito control efforts with information and resources to assist in the fight against mosquito resistance.

STEPS TO IDENTIFY AND FIGHT MOSQUITO RESISTANCE

- Surveillance
- Define the resistance situation locally
- Determine the activity period for treatment
- Scrutinize the application and its dose
- Repeat

Surveillance

Before beginning surveillance, devise a plan that will encompass treatment for resistance if detected. First and foremost, all resistance management solutions must be based on data. If tests indicate a site is positive for resistance, then understanding how to change insecticide usage to counter resistance is required. The type of resistance detected should inform resultant product changes. The susceptibility status of a target mosquito population must be tested. Establish a surveillance protocol and continually monitor the sensitivity to the appropriate dose of a given product.

Define the resistance situation locally

Identify all species from the site in question. Keep in mind that a single mosquito species can show different levels of resistance city or county-wide. Based on resistance testing data from locally-sourced mosquito species, first, determine if resistance is present and second, what type or types of resistance. Reach out to resistant management scientists for guidance.

Determine the activity period for treatment

Use mosquito traps to determine which species is the most prominent and at what time of day. Many species of mosquito are active during dusk. Others, such as those in the genus *Aedes*, can have peak activity times during daylight hours.

Scrutinize

Ensure that all application equipment is appropriately calibrated and that droplet size is optimized for the particular product to be used. Confirm that the dose is adequate and compliant with the product label. Incorrect droplet size (i.e. too large) can waste resources and expose the mosquito to less than a lethal dose.

Repeat

Continue periodic surveillance for resistance at least once a season.

For help finding the right vector control solution to address your specific needs or find your local representative, go to MGK.com for details.

Additional resources:

MGK entomologist Dr. Jennifer Williams – jennifer.williams@mgk.com

CDC information on bottle testing for resistance monitoring
https://www.cdc.gov/parasites/education_training/lab/bottlebioassay.html

The International Resistance Action Committee (IRAC) – www.irac-online.org

Since 1999, nearly 44,000 cases of West Nile Virus infection have been reported in the US.
Of those, over 20,000 were neuro-invasive cases and more than 1,900 have died.

cdc.gov/features/westnilevirus

THE SCIENCE BEHIND THE INSECTICIDES (*continued*)

Organophosphates

Organophosphates exert their toxicity by inhibiting the activities of acetylcholinesterase, resulting in accumulation of acetylcholine, over-exciting and exhausting the mosquito nervous system. Because organophosphates bind to a different binding site than pyrethroids, they are considered to be a separate insecticide class. The organophosphates malathion and naled are commonly used as adulticides. This class of insecticide is most commonly used for aerial applications in vector control due to their hazardous classification and corrosive properties.

PBO - a Synergist

Synergists are not insecticides. Synergists, such as PBO, make a pesticide more potent. PBO blocks detoxification enzymes within mosquitoes. As such, PBO is a useful tool when fighting metabolic resistance. When a mosquito population has evolved a level of metabolic resistance that renders synthetic pyrethroids less effective, the addition of PBO to the pyrethroid spray application effectively bolsters its activity by preventing, or reducing, the capacity for pyrethroid detoxification by mosquitoes.

MGK entomologist, Jennifer Williams Ph.D., examines mosquitoes collected from the Minneapolis area.

OUTSMARTING A KILLER THROUGH INTEGRATED VECTOR MANAGEMENT

The importance of rotating classes of insecticides

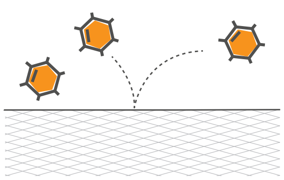
Integrated Vector Management (IVM) is a decision-making process that optimizes the use of resources for vector control by recommending a rotation or mixture of insecticides to hinder mosquito resistance development and to fight any existing resistance. By instituting IVM, we leverage locally-based surveillance to more precisely target the species of concern with the most useful tool. By making connections through collaboration with industry and other institutions to aid in monitoring methods, mosquito control professionals can make control decisions resulting in higher efficacy and decreased cost. Surveillance aids in the customization of mosquito control efforts on the local level because the location-specific understanding of resistance can be gained and mitigated. In short, by implementing IVM, we achieve better control by making decisions based on the evidence from the very mosquitoes we are targeting. And the good news is if mosquito resistance is detected, it doesn't mean it will exist permanently. By removing the pesticide for a sufficient time, resistance usually decreases. Use of IVM helps mosquito control efforts become more efficient, cost-effective, ecologically sound and sustainable.

> "Blindly rotating isn't an effective strategy for fighting resistance. Understanding the resistance situation on the ground and choosing the appropriate tool based on evidence is necessary."
>
> **Janet McAllister, Ph.D**
> *Entomologist*
> *Center for Disease Control*

WHAT IS RESISTANCE?

Resistance is the result of gradual, genetic changes in the mosquito population over generations that lead to pesticide tolerance. Resistance development in mosquito populations is practically inevitable if control methods remain unchanged over time. The reason for this is that mosquitoes evolve rapidly. We know that all populations of living organisms change over the course of many generations. Some organisms, like plants, may take one year to produce their next generation as seeds. People may take between 20, or even 30, years to yield the next generation. Mosquitoes can produce their next generation in just two to three weeks. Rapid reproduction of thousands of mosquito offspring in a matter of weeks results in swarms that can evolve around our control efforts. Research has shown that resistance to pesticides can happen in more than one way. Understanding whether any resistance is present and the type or types of resistance present on the ground, is paramount. As Janet McAllister, Ph.D., entomologist, of the Center for Disease Control shared recently, "Blindly rotating isn't an effective strategy for fighting resistance. Understanding the resistance situation on the ground and choosing the appropriate tool based on evidence is necessary."

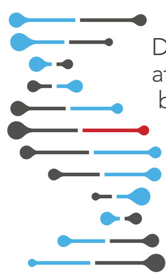
TYPES OF RESISTANCE



Reduced penetration of mosquito cuticle by insecticide

CUTICULAR:

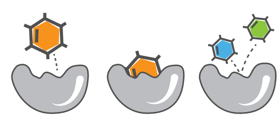
The mosquito cuticle can become less penetrable by one or more insecticides, which can slow absorption of the chemicals into their bodies.



DNA change at insecticide binding site

TARGET SITE:

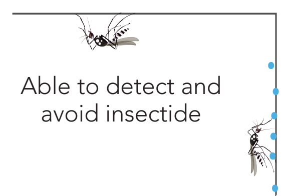
Target site resistance occurs when the pesticide binding site changes such that the pesticide can no longer bind properly inside a mosquito. Without proper binding at the target site an insecticide may lose some or all of its effectiveness.



Enzymes inside the mosquito break down the insecticide

METABOLIC:

Metabolic resistance is the result of increased detoxification of one or more insecticides by enzymes produced within the mosquito. New research suggests the possibility that this type of resistance may, at times, occur inside the insect cuticle – the first point of contact between a mosquito and an insecticide. Many times, metabolic resistance to one class of insecticide will cause increased susceptibility to another class. Other times, metabolic resistance will decrease susceptibility to another class of insecticide. This is known as cross-resistance.



BEHAVIORAL:

Behavioral resistance can occur through a change in the activity, or behavior, of a mosquito population in response to a prolonged and consistent use of a control measure. Behavioral avoidance of insecticide-treated bed nets by mosquitoes is an example in which behavioral resistance has resulted in the decreased effectiveness of a control measure.

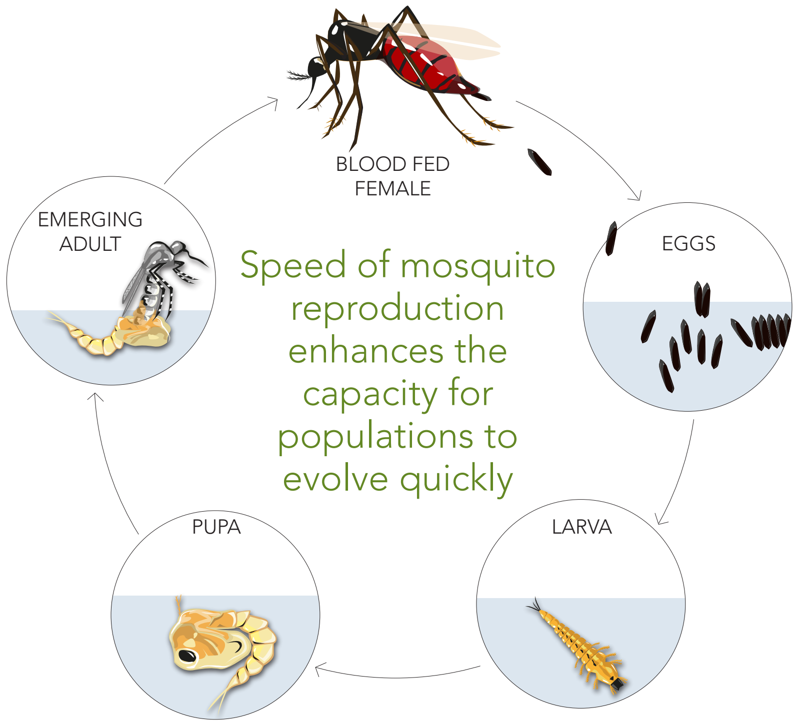
In the United States, approximately 80-100 La Crosse encephalitis virus (LACV) neuroinvasive disease cases are reported each year.

www.cdc.gov/lac/tech/epi.html

CASE STUDY:
RICE WATER WEEVIL

The rice water weevil is a major pest in the U.S. rice crop. Synthetic pyrethroids used in rice agriculture to control rice water weevil encounter mosquito populations which live and breed in rice lands. Some rice growers tank mix a pyrethroid with a pre-flood herbicide to control the rice water weevil.

http://www.ricefarming.com/departments/specialists-speaking/specialist-speaking/



RECIPE FOR RESISTANCE

Insects in general, and mosquitoes in particular, evolve quickly to changes in their environment, such as the presence of insecticides, since they are capable of producing many generations in a short time. One female mosquito may produce between one thousand and three thousand eggs in her lifetime. In two, maybe three weeks, thousands of eggs will have become adult females laying eggs. The high numbers of individual mosquitoes in field populations combined with rapid reproduction results in their ability to evade control at an alarming rate.

Prolonged and consistent use of a single control measure is conducive to resistance evolution. This dynamic is greatly exacerbated and complicated by forces other than mosquito control efforts: 1) by far, most insecticides present in the environment come from agriculture, 2) many of the insecticides used in agriculture and for mosquito control are of the same class, pyrethroids and 3) there are few alternative control measures for adulticide use.

Synthetic pyrethroids are ubiquitous in many insect control scenarios. This is for a good reason: synthetic pyrethroids are very effective insecticides and, due to their low mammalian toxicity, are relatively safe to use. Paradoxically, the relative safety and high efficacy of synthetic pyrethroids in insect control have resulted in their prolonged and consistent use thereby favoring resistance evolution by targeted pests.

THE SCIENCE BEHIND THE INSECTICIDES

The use of adulticides is common when there is a dense population of nuisance mosquitoes or if there is a need to combat an outbreak of mosquito-borne disease because they work instantaneously. At present, there are few adulticide options available to mosquito control professionals. Therefore, understanding if resistance to an insecticide exists in the target mosquito population and identifying the resistance type are necessary to choose the appropriate control option at any given time and to make resistance evolution less likely. This level of understanding on a local basis is critical for the success of a mosquito abatement plan. The importance of achieving effective control is heightened immensely in situations involving an outbreak of mosquito-borne disease. Below, the modes of action of these pesticide classes, pyrethroids, and organophosphates, are described. Also, the synergist piperonyl butoxide (PBO), which is not an insecticide, is explained.

Pyrethroids

Pyrethroids (i.e. permethrin, deltamethrin, etc.) are synthetic mimics of pyrethrins. The relationship between pyrethrins/pyrethroids is very much analogous to nicotine/neonicotinoids. Synthetic versions of natural products allowed chemists to change the molecule in desirable ways, such as increasing the robustness of the molecule in the presence of UV light, thereby increasing the duration of the product outdoors, while maintaining the low mammalian toxicity. Unlike pyrethrum, synthetic pyrethroids contain fewer chemical variants (usually one to two versus six for pyrethrum). It is suspected that this may contribute to the lack of flushing or excitation behaviors induced by synthetic pyrethroids. Both pyrethrins and synthetic pyrethroids bind to proteins on the nerve cells which affect the function of these cells. Since pyrethroids and pyrethrins both exert their toxicity by the same route, they are considered to be part of the same insecticide class, generally, pyrethroids.

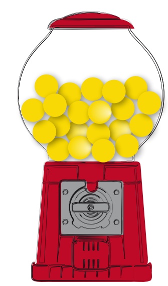
Natural Pyrethrum

Pyrethrum ("pie-wreath-rum") is a naturally occurring insecticide produced by certain species of chrysanthemum plants. The insecticidal capacity of pyrethrum depends on the concentration of pyrethrins it contains, which are found at highest concentration in the flowers of the plant. Pyrethrins, of which there are six, include type 1 and type 2 forms: pyrethrin I, cinerin I, jasmolin I, pyrethrin II, cinerin II and jasmolin II. Although highly toxic to insects, pyrethrum has very low mammalian toxicity. Like many naturally-occurring substances, pyrethrum is very susceptible to degradation by UV light resulting in low environmental persistence. As such, pyrethrum has a relatively lower impact on the environment due to its susceptibility to degradation. Pyrethrins are unique because they induce behavioral excitation that other natural and synthetic insecticides cannot. This excitation or 'flushing' behavior results in increased and erratic movement by the mosquito. This behavioral effect is highly relevant and desirable in the field of vector control since it often results in mosquitoes colliding with more droplets of the pyrethrum spray via this increase in movement. Due to this behavioral response, these mosquitoes will receive a higher dose of active ingredient as they fly erratically throughout the cloud of pyrethrum-laden droplets.

PYRETHRUM vs PYRETHROIDS

Natural pyrethrins are made up of six chemical variants

- Naturally occurring insecticide
- Very low mammalian toxicity
- Induces 'flushing' behavior
- Very susceptible to degradation by UV light resulting in relatively lower environmental persistence



Pyrethroids are synthetic mimics of pyrethrins and contain fewer chemical variants

- Synthetic mimics of pyrethrins
- Very low mammalian toxicity
- Does not induce 'flushing' behavior
- Less susceptible to degradation by UV light resulting in longer environmental persistence than natural pyrethrins

COLLABORATING TO CONQUER THE KILLER

Mosquito resistance is rampant; new diseases are emerging at an alarming rate and old diseases are here to stay. Never before has the role of mosquito control professionals been so important nor as challenging. It is also true that understanding of resistance and how to fight it is a major focus of academic research and the pest control industry. And the pressure is on. Headlines appear regularly about new diseases cropping up in more communities, raising the public's awareness of mosquito-borne disease and the mosquito control industry in general. If mosquito control professionals will take the necessary action to find answers relating to the resistance status of their local populations and make the necessary strategic changes to their control measures, then everyone wins.

MGK and Sumitomo Chemical Corporation, Ltd., are focusing intensive research efforts to deliver new adulticide and larvicide products which will incorporate alternatives to fight resistance in all its forms. By striving to provide more product options with alternative modes of action, we intend to increase the number of strategies available to vector control generally so that everyone will gain the upper hand in the resistance fight. Through our research and product development efforts, we aim to provide more product options allowing a more robust rotational strategy with immediate benefits to mosquito control. Resistance to a particular insecticide class is usually reversible when a mosquito population can develop for many generations in the absence of that insecticide class. Novel control tools will decrease overreliance on the few insecticide classes currently available, preserving and improving the efficacy of the safe options (i.e. pyrethroids) that already exist.

Together, by implementing surveillance, open communication and ongoing cooperation, we can help you keep the public safe from the constant and evolving threat of mosquito-borne disease.

In order to delay or prevent the development of insecticide resistance in vector populations, integrated vector management programs should include a resistance management component.

Ideally, this should include annual monitoring of the status of resistance in the target populations, or resistance assessments in local areas ahead of decisions for chemical applications.

https://www.cdc.gov/zika/public-health-partners/vector-control-us.html

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For more information or help getting started with resistance testing, contact:

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