



PPDC May 2, 2018 Regulatory Updates
Novel Mosquito Products

Wolbachia and Oxitec GE Mosquito

Aedes albopictus (Asian tiger mosquito)

Asian tiger mosquito



Source: CDC

Estimated range in the U.S., 2016



- Prefer forested areas
- Active during the day
- Can carry Zika and other viruses of concern for human health
- Invasive to U.S.

Current methods for mosquito control

- Adulticides
 - Fogging
 - Spraying
- Larvicides
- IPM

Aedes aegypti (Yellow fever mosquito)

Yellow fever mosquito



Source: CDC

Estimated range in the U.S., 2016



- Anthropophilic
- Active during the night
- Major carrier of Zika. Also carries other viruses of concern for human health
- Invasive to U.S.

Wolbachia Mosquitoes – EPA Regulates the Wolbachia microbial pesticide.

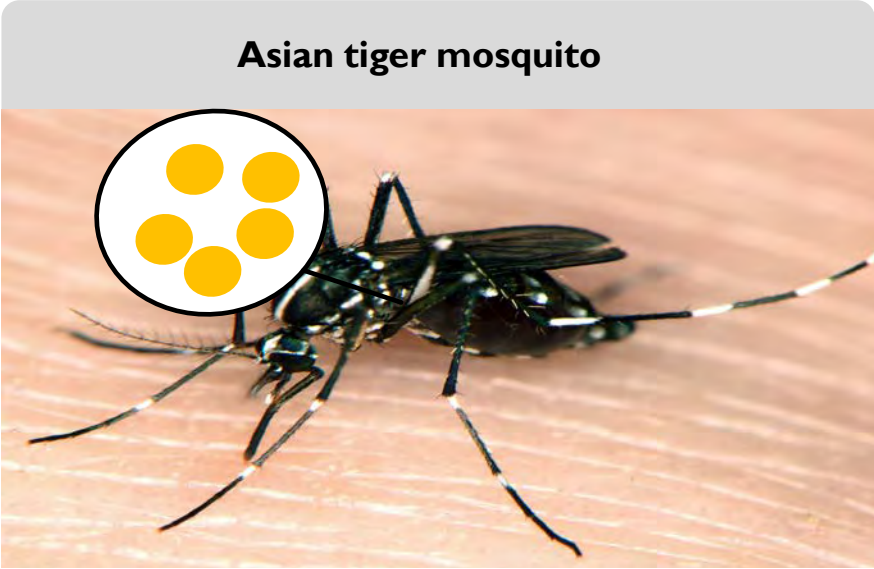
- Wolbachia is a bacterium that is estimated to occur naturally in over one million insect species, including mosquitoes. The bacterium resides within mosquitoes throughout their lifespan, and the mosquito/bacterium combinations are often fixed, i.e., the Wolbachia ZAP strain occurs in the common house mosquito (*Culex pipiens*), while the two wAlbA and wAlbB strains are present in *Aedes albopictus*.
- The presence of Wolbachia can cause reproductive failure in mosquitoes when mating partners carry different strains of the bacterium. When *Aedes albopictus* males carrying the ZAP strain (MosquitoMate product) mate with females that naturally carry the wAlbA and wAlbB strains, the development of their offspring is arrested and they will not reach adulthood.

Oxitec GE Mosquitoes – Oversight of GE mosquitoes for population control is now with EPA.

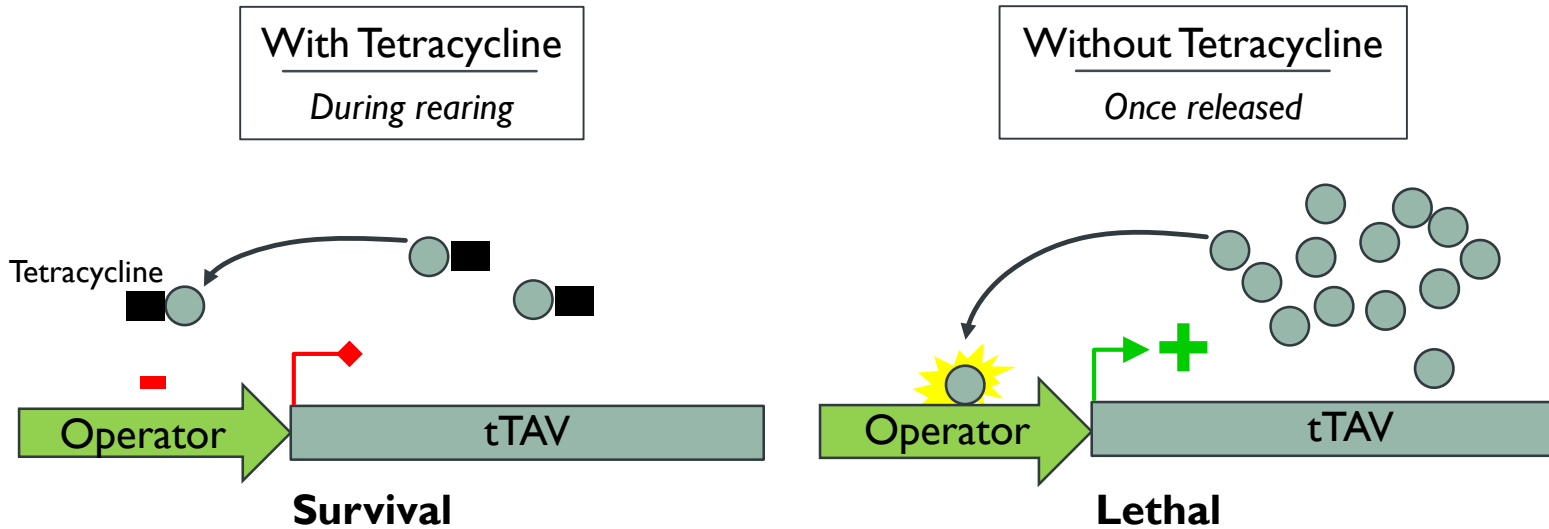
- FDA finalized guidance in October 2017 re: FDA and EPA jurisdiction over pesticide mosquito-related products.
- Male Oxitec GE mosquitoes carry two additional genes, tTAV and DsRed2, which they will pass on to the next generation when they mate with wild-type females. Their offspring then produces so much tTAV protein that it interferes with regular cellular functions and the insects die before reaching adulthood. The male Oxitec GE mosquito can itself only survive because it was reared in the lab in the presence of tetracycline, which strongly reduces the production of the tTAV protein. The DsRed2 protein emits light under certain conditions, and is used as a marker for reproductive success.



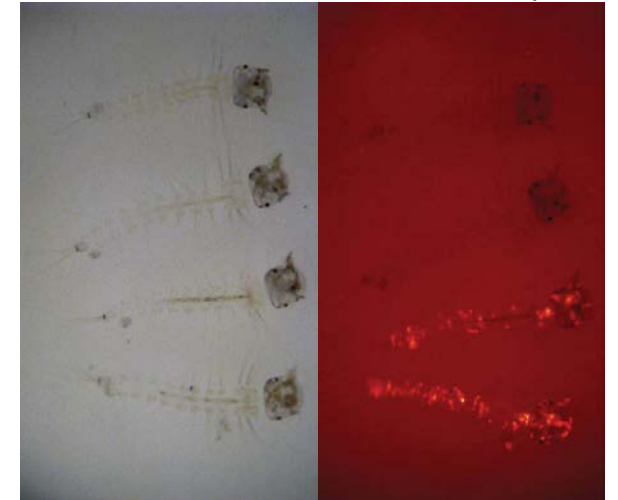
	Wolbachia strains in <i>Aedes albopictus</i>	Mating result
Mating within wild <i>Aedes albopictus</i> population	<p>Male × Female</p>	<p>Mosquitoes reproduce normally</p>
Introduction of ZAP Males into wild <i>Aedes albopictus</i> population	<p>ZAP Male × Female</p>	<p>Mosquito eggs do not hatch, no adult mosquitoes emerge</p>



- Male mosquitoes contain a lethal operator/gene (tetO/tTAV) and a marker gene (dsRed2):
Released males are homozygous
- tTAV protein clutters the transcriptional machinery:
Accumulation of tTAV in the cells causes insect death
- Tetracycline is an antidote to tTAV:
Binds to tTAV protein and blocks transcription initiation



DsRed2 marker identifies OX513A mosquitoes



Source: Oxitec

Commonalities Between MosquitoMate and Oxitec Products

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source: www.oxitec.com

- Release of **live adult male mosquitoes** into the environment
- Offspring of these males cannot develop into adulthood
- Species-specific effect
- Reduces mosquito population by hindering successful reproduction

Only female mosquitoes bite



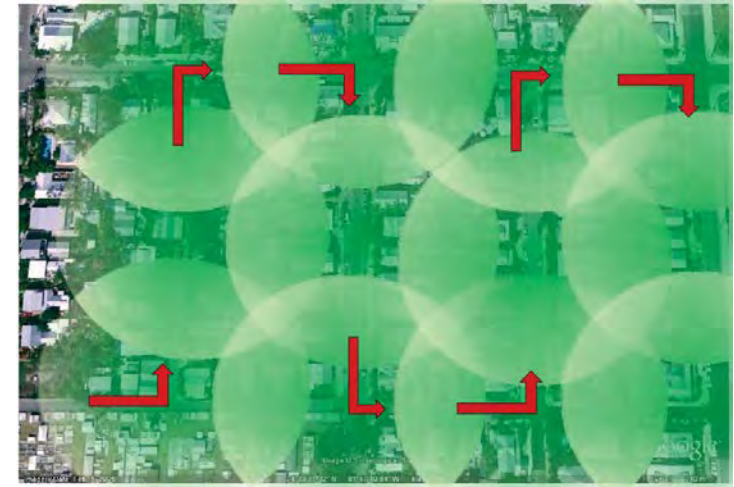
source: www.mosquitomate.com

Individual larvicide placing

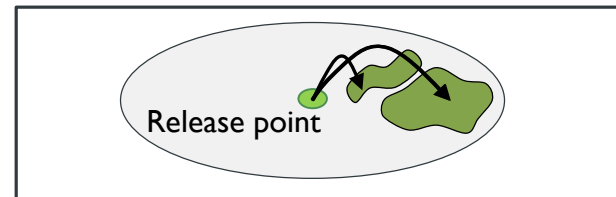


Source: Oxitec

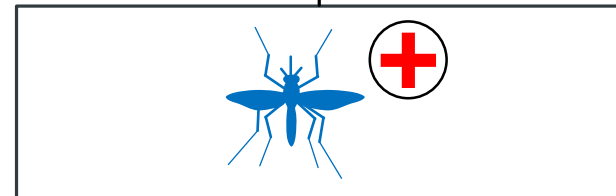
Mosquito-related biopesticide release points



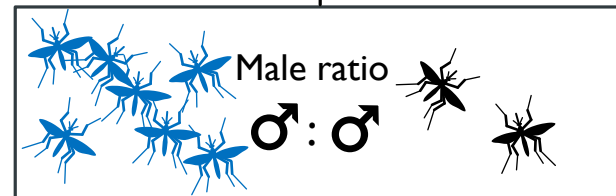
Dissemination is mosquito dependent



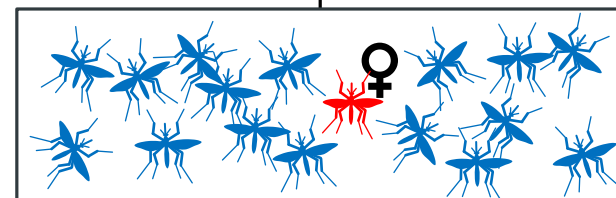
Health of released mosquitoes



Density of existing wild mosquito population



Accidental female release



- Release point \neq treatment area
- Efficacy testing and claims unique among mosquito control products.
 - **Can get where other products can't.**

- Age of mosquitoes at time of release
- Handling conditions during shipping
- Fitness cost of new trait

- Adjust release numbers according to population density

- ID mosquito species (species-specific)
- Human health risk considerations

- EPA issued a registration in November 2017 for the *Wolbachia pipientis*, ZAP Strain in infected *Aedes albopictus* ZAP Males® for 5 years in Washington, D.C., California, Connecticut, Delaware, Illinois, Indiana, Kentucky, Massachusetts, Maine, Maryland, Missouri, New Hampshire, New Jersey, Nevada, New York, Ohio, Pennsylvania, Rhode Island, Tennessee, Vermont, and West Virginia.
- EPA has issued EUP and EUP amendment/extensions that allow experimental field testing and releases of wAlbB-Strain infected *Aedes aegypti* male mosquitoes until December 31, 2018 in Florida, Texas, and California and of the *Wolbachia pipientis*, ZAP Strain in infected *Aedes albopictus* ZAP Males® in Florida, Hawaii, Texas, and Virginia until December 31, 2019. Field efficacy data is needed to support label claims for registration.
- Oxitec has submitted both an experimental use permit and a registration application to EPA. Both are currently under review. The EUP Federal Register Notice of Receipt comment period is being reopened for another month to allow more time for public comments.