Oxitec's Genetically Modified Mosquitoes: A Credible Approach to Dengue Fever?

GeneWatch UK

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The UK company Oxitec has conducted experimental open releases of genetically modified (GM) mosquitoes in the Cayman Islands, Malaysia, Brazil and Panama. Oxitec's releases of GM mosquitoes in the Cayman Islands and Malaysia have ceased but open releases in Brazil have continued since 2011 and started in Panama in 2014. Further proposed trials in both countries are currently suspended. This briefing summarises the concerns about the open releases conducted to date.

Oxitec's patented technique for genetically modifying insects is known as RIDL (Release of Insects carrying a Dominant Lethal genetic system). All the company's open field experiments to date involve its OX513A strain of the *Aedes aegypti* mosquito, which is genetically engineered to contain a red fluorescent marker and the RIDL 'conditional lethality' trait. The mosquitoes are genetically engineered to die at the larval stage in the absence of the antibiotic tetracycline, which acts as a chemical switch to allow breeding in the laboratory.

Oxitec's male OX513A GM mosquitoes are intended to mate with wild females and produce offspring which die as larvae. Releases of many millions or billions of GM males, vastly outnumbering the wild male mosquito population, are intended to reduce the total adult population of mosquitoes over time, as many of the GM offspring fail to survive to adulthood. The GM mosquitoes released in the experiments are of the *Aedes aegypti* species, which transmits the tropical disease dengue fever. There is as yet no evidence from any country that releases of GM mosquitoes can reduce the incidence of dengue fever.

Concerns about open releases of Oxitec's GM mosquitoes are outlined below.

Claims about suppression of the wild mosquito population are largely based on unpublished results

Oxitec has published no results from its experiments in Brazil in scientific journals, although it has been conducting these experiments since 2011 and has made frequent claims of success in press releases. Results from the Cayman Islands suggest this technology is very ineffective at reducing wild mosquito population numbers, requiring 2.8 million GM adult male mosquitoes to be released per week to suppress a wild population of only 20,000 mosquitoes (10,000 males).[1] Monitoring of populations has in any case been insufficient to establish whether wild males are simply moving to the control areas surrounding the releases. In the Cayman Islands, the mosquito population was observed to increase in the control area as the population in the release area decreased, and this is also seen in the very limited information available from Brazil.[2,3,4] In Malaysia, the single trial conducted did not examine population suppression as the numbers of GM mosquitoes released were far too small.

Impacts on dengue fever have not been monitored and releases could worsen disease in endemic areas

There has been no monitoring of the impacts on dengue fever of its GM mosquito releases in any country, despite a scientific consensus that assessing impacts on disease is essential

to assess the efficacy of new technologies.[5,6] Oxitec and its research partners in Brazil have both admitted that the experiments there (the largest ones conducted) are inadequate to assess the impacts on disease.[7,8] In February 2014, a dengue emergency was declared in Jacobina, Brazil, one of the areas where Oxitec conducted its experiments.[9]

There are a number of mechanisms through which releasing GM mosquitoes could make the impacts of the dengue virus worse, including:

(i) In areas of high mosquito abundance, where dengue is endemic, reducing the frequency of biting can increase the incidence of the more serious form and often fatal of the disease, dengue haemorrhagic fever (DHF), by reducing cross-immunity to the four different serotypes of the dengue virus, or increasing the incidence of dengue fever (DF) due to age-related effects (known as 'endemic stability'). [10,11]

(ii) Enabling an increase or expansion in territory occupied by the competitor species *Aedes albopictus*, an important vector for dengue and chikungunya in many countries which may be harder to eradicate than *Aedes aegypti*. [12,13,14] Brazilian experts have warned that dengue may mutate so that *Aedes albopictus* becomes a more important dengue vector in such circumstances.[15] The potentially devastating effect of a single mutation in the virus has already been observed with chikungunya.[16] *Aedes albopictus* has been responsible for concurrent epidemics of dengue and chikungunya in some countries and its presence can also extend the dengue season and perhaps introduce new viruses.[17,18,19,20,21,22]

In contrast, a new vaccine is expected to be available shortly which does not provide full protection from all dengue serotypes but which has been shown in clinical trials to reduce the incidence of severe disease (DHF) in vaccinated children by 81%, subject to confirmation by more research which is already underway.[23] Malaysia has abandoned trials of Oxitec's GM mosquitoes and plans to use the vaccine.[24,25,26,27] According to the World Health Organisation, at least five other vaccines are under development, some of which could show improved protection. A wide variety of other research continues, including into treatments.[28]

Poor or missing risk assessments

Oxitec has a poor track record of meeting regulatory requirements, in particular, under European Union (EU) law it should provide a publicly available environmental risk assessment which meets European standards before exporting GM mosquito eggs to foreign countries, yet it has repeatedly failed to do so.[29,30,31] The company has been criticised by independent scientists for the poor quality of its risk assessments for the Cayman Islands and Malaysia and lack of transparency and public consultation.[32]

The UK Department for the Environment, Food and Rural Affairs (Defra) has admitted that Oxitec breached UK and EU regulations implementing the Cartagena Protocol on Biosafety when it failed to provide a risk assessment to the Panamanian authorities prior to exporting GM mosquito eggs to Panama for open release, but Defra says it will not enforce the regulation because Panama did not want the risk assessment.[33] The Department has been warned about the importance of the regulation by the EU authorities.[34] The Gorgas Institute, which acts as Oxitec's partner for its experiments in Panama, has produced a risk assessment, but this is clearly marked "Uso confinado" (confined use) and does not meet EU or international standards for open release of GM insects.[35] Panama has not supplied any risk assessment documents to the Cartagena Protocol's Biosafety Clearing House.

In Brazil, the risk assessment included in the documents when GM mosquitoes were exported for open release was produced by Oxitec's partner the University of São Paulo, not by the exporter, and omits most of the issues required to be covered prior to export under

EU law. [36] This is also in breach of UK and EU legal requirements. Brazil supplied risk assessment documents to the Cartagena Protocol's Biosafety Clearing House only in August 2014, more than three years after starting open release experiments.[37] The summary risk assessment relates to the decision by Brazil's biosafety regulator CTNBio to approve commercial releases, although commercial releases have yet to be approved by Brazil's health surveillance authority, ANVISA. A brief dissenting opinion is included, highlighting the lack of consensus on some issues, and the Brazilian Public Health Association, ABRASCO, has also criticised Oxitec's approach.[38] Attempts to continue releases in Brazil without ANVISA's approval have been suspended.[39]

It is widely recognised that fully informed consent from the public is needed for releases of genetically modified mosquitoes.[40,41] However, in the absence of a comprehensive published risk assessment, participants in GM mosquito experiments cannot be fully informed about the risks.

Release, survival and spread of GM insects, including biting females

There are a number of mechanisms through which Oxitec's GM mosquitoes can survive and spread, including by feeding in areas contaminated with the antibiotic tetracycline, which is widely used in medicine and agriculture. In the laboratory, 3% of the offspring of Oxitec's GM mosquitoes survive to adulthood, even in the absence of the antidote tetracycline.[42] When GM mosquitoes were fed cat food containing industrially farmed chicken, which contains the antibiotic tetracycline, the survival rate increased to 15-18%. Oxitec originally hid this information[43] but later admitted to an 18% survival rate of larvae fed on cat food in a published paper.[44] Oxitec claims that this survival rate will not happen in the wild because the GM larvae will breed only in clean water. However, a number of studies have found that *Aedes aegypti* mosquitoes can breed in septic tanks where there can be high levels of contamination with antibiotics such as tetracycline. [45,46,47,48,49,50] *Ae. aegypti* also commonly live in areas where discarded takeaways are likely to contain meat contaminated with tetracycline.

It is also inevitable that some biting female GM mosquitoes will be released and others will survive and breed. In the Cayman Islands, mechanical sorting led to about 5,000 biting female mosquitoes in every million males (additional sorting was then performed by hand before release).[51] In Brazil, Oxitec report that female contamination was on average 0.02% i.e. about 200 biting female GM mosquitoes were released in every million males. [52] The percentage of surviving GM insects, including biting females, could also increase if resistance to the genetic killing mechanism evolves over time: for example, genetic mutations in the insects which allow the GM insects to survive and breed successfully could be rapidly selected for during mass production.[53,54]

Potential toxic or allergic effects, impacting humans, animals or wildlife

In addition to the risk of being bitten by GM female mosquitoes, journalists have reported that in Brazil "…*it's impossible to talk during the liberation sessions without accidentally swallowing a few*…" due to the very large numbers of GM mosquitoes released to try to swamp the wild population.[55] Risk assessments in Panama and Brazil have included claims that the proteins produced in the GM mosquitoes do not cause toxic or allergic reactions when eaten and are not expressed in the mosquitoes' saliva, so can't be passed on by biting by those female GM mosquitoes that are accidentally released or survive to adulthood. However, there is little public information to support these claims and Oxitec has provided no data to demonstrate that the tTA protein expressed by its GM mosquitoes will not be harmful to humans or animals. Signs of toxicity[56] and neurotoxicity[57] have been reported in mice expressing the tTA protein, yet these papers are not cited in the risk assessments. In Spain, Oxitec has withdrawn an application to release GM olive flies while it undertakes further testing demanded by the regulators, including tests of toxicity to other species that might eat these insects.[58]

Spread of antibiotic resistance into the environment

The use of tetracycline to breed the GM mosquitoes in the lab or in factories for large-scale production carries the risk of spreading antibiotic resistance, which could pose a major risk to human and animal health.[59] Insect guts are reservoirs for antibiotic resistance genes with potential for dissemination.[60,61] Insect production in factories exposed to antibiotics could lead to drug resistance in their microbiota so that the insects disseminate antibiotic resistance when released into the environment.[62,63] For example, swallowing or being bitten by GM mosquitoes might transfer antibiotic resistance from bacteria in the insect's gut or salivary glands into bacteria in human or animal guts or bloodstreams which cause disease. If these bacteria become resistant to tetracycline as a result, some human or animal diseases may become difficult to treat. This issue has not been considered in risk assessments in either Panama or Brazil.

Use of non-native strains

Oxitec's GM mosquitoes have been developed from a non-native strain. In the Cayman Islands, the OX513A insertion in *Aedes aegypti* (originally developed from a Rockefeller strain[64]) was introgressed into a Mexico-derived genetic background by five generations of back-crossing;[65] it appears that this same strain was then used in Brazil and probably also in Panama. Oxitec has not published any information about the origins of the Mexican strain and it does not appear to have tested the back-crossed strain for insecticide-resistance or disease transmission properties. If the genetically modified strain is a more effective vector of disease than the established strain where it is introduced, this could pose a risk.

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