Oxitec's GM insects:
Failed in the Field?

GeneWatch UK

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Oxitec is a UK-based commercial company which produces genetically modified (GM) mosquitoes and other insects.[1] In September 2015, Oxitec was acquired by the US-based synthetic biology company Intrexon.[2]

Oxitec's male GM mosquitoes are genetically engineered to express a fluorescent trait and a 'late-acting lethality' trait, which means that most of their offspring die as larvae and do not survive to adulthood to reproduce. Repeated 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. Since 2008, Oxitec has conducted experimental open releases of GM *Aedes aegypti* mosquitoes into the environment in the Cayman Islands, Malaysia, Panama and Brazil. The *Aedes aegypti* species transmits the tropical diseases dengue fever, zika and chikungunya.

Oxitec's business plan is dependent on locking its customers in to repeated payments for ongoing releases of its GM mosquitoes with the aim of keeping the target wild species' numbers low.

Oxitec has repeatedly claimed that its experiments have been successful. This briefing examines these claims and finds they are not supported by the evidence. It includes new evidence recently released as a result of Freedom of Information requests in the Cayman Islands.

Oxitec's claims of success

The August 2015 Press Release announcing Intrexon's agreement to acquire Oxitec claimed "*Open field trials with Oxitec's mosquitoes have taken place in Brazil, Panama, Grand Cayman and Malaysia, with over 90% reduction of the Aedes aegypti pest population reported in each efficacy trial*."[3] In its Press Release announcing completion of the acquisition of the company, Intrexon again stated "*Efficacy field trials in Brazil, Panama, and Grand Cayman have each shown a greater than 90% reduction of the Aedes aegypti population*".[4] Repeating this claim in testimony before the U.S. House of Representatives' Science, Space and Technology Committee in May 2016, Oxitec's then CEO Hadyn Parry stated "*In trials in several countries, we have shown that the population of Aedes aegypti can be reduced by over 90% in around six months*".[5]

In fact, Oxitec did not conduct an efficacy trial in Malaysia, as the trials were abandoned following a small open release experiment to measure flying distances and survival rates.[6] The Health Ministry concluded that "*the method was not practical besides involving high costs*".[7] There are also major problems with how Oxitec interprets its data from the experiments it has taken in other countries (the Cayman Islands, Panama and Brazil) and there is no direct evidence of a fall in the population of biting female mosquitos, which transmit disease. These are discussed further below.

Success in the Cayman Islands?

"*To date all the measures recorded have shown no significant reduction in the abundance of Aedes aegypti in the release area*". MRCU scientist, 4th April 2017.[8]

"*After the commencement of the releases in the treatment area there has been a significant increase in the number of female mosquitoes collected in the treatment area. Since the releases began the mean weekly catch in the treatment area has been 1.72 compared to 1.13 in the untreated area (52% higher)…The most likely cause of the increase in female mosquitoes in the treatment area is the accidental release of female mosquitoes into the area when males are being released*". MRCU scientist, 4th April 2017.[9]

"*We all need to be looking at the data that is being collected; we cannot just take Oxitec's word that it is working*". MRCU scientist, 4th April 2017.[10]

"*I have spent a lot of time analysing the Oxitec data and remain firmly of the opinion that the data does not support a claim of 62% suppression. I do not think MRCU should be making this type of claim as our long term credibility could be at risk. I think we should state that we currently have insufficient data to allow us to reach any firm conclusions on the effectiveness of the technique and further data collection is required*". MRCU scientist, 6th September 2017.[11]

"*Results to date are inconclusive. Any reduction so far seems well below the 80-90% recorded by Oxitec in other release areas and required by MRCU*". MRCU scientist, 15th September 2017.[12]

The first open release trials of Oxitec's GM mosquitoes took place in 2008 to 2010. Trials then stopped but restarted in summer 2016 to 2017. The trials were conducted with the Cayman Islands' Mosquito Research and Control Unit (MRCU).

The trials began with a small scale release, in 2008-09, the results of which were published in Nature Biotechnology in 2011.[13] Oxitec first announced the success of its technique in field trials in a press release issued jointly with the MRCU on 4th November 2010.[14] This stated that "*A significant reduction in the local mosquito population was observed from August. All of the trial objectives were successfully met, including the main goal of suppressing the local Aedes aegypti population*". Nearly two years later, in September 2012, these results were reported in the journal Nature Biotechnology[15] and Oxitec's Press release stated: "*Oxitec and MRCU report 80% suppression of a dengue mosquito population in Grand Cayman by release of engineered sterile male mosquitoes*".[16] This claim is based on the difference between the ovitrap index (the proportion of ovitraps with one or more eggs after 1 week) in the release area and the control area. The paper says this measure is used because the number of eggs per trap (not reported) was extremely variable (perhaps not showing any reduction). Adult data is not reported, although 24 adult traps were deployed. Because there is no baseline data on mosquito populations at the site there is considerable uncertainty in the results. In particular, the control area is next to the release area and numbers of mosquitoes in the control area increase during the experiment: this could mean that mosquitoes are moving away from the release area rather than actually decreasing. At different times during the experiments, Oxitec moved mosquito traps from one location to another and changed the size of the release site, adding to difficulties in interpreting the results.

No results from the 2016-17 trials in the Cayman Islands have been published in academic journals. However, some information about these trials has been released, largely as a result of Freedom of Information (FoI) requests. A series of documents now available on the CNS Library website in the Cayman Islands,[17] including an MRCU Annual Report on the "Friendly *Aedes aegypti* project in West Bay", published in June 2017 and covering the releases up to 25th June 2017.[18] These documents also include emails between the MRCU and Oxitec, highlighting disputes about costs and revealing that Oxitec is unhappy about the release of the MRCU Annual Report.[19] Subsequently, emails about the Oxitec project sent within the MRCU[20] and between the MRCU and Ministry of Health, Environment, Culture and Housing (HECH)[21], have been released as the result of a further Freedom of Information request. According to these emails: "*The MRCU Annual Report was actually written by Oxitec…*".[22] The emails also show that MRCU scientists are in agreement with concerns raised by GeneWatch about the lack of demonstration of efficacy and the release of large numbers of female mosquitoes (which bite and may transmit disease).[23]

For the first time, the MRCU annual report includes female adult mosquito numbers collected from traps in the published data (rather than just egg traps) (Figure 1B).[24] These show, as discussed in the text (page 6), that no adult mosquito suppression was observed until February (week 7) in 2017, and that the egg traps therefore provide a poor measure of success in supressing the number of adult female mosquitoes (which bite and transmit disease): a concern that has previously been raised in the scientific literature, and which may invalidate Oxitec's claims of success elsewhere, which are largely based on data from egg traps.[25] Further, the graph shows significant increases (spikes) in adult female mosquito numbers (green line) in the release area 5 to 7 weeks after the releases begin, and again 7 to 8 weeks after the releases are increased. These spikes in the adult female population exceed 150% of the comparator population, but their true extent is not shown as the peaks are cut off on the graph.

The emails released more recently as a result of the FoI request highlight "*a significant increase in the number of female mosquitoes collected in the treatment area*", rather than a decrease, which is thought to be due to the accidental release of GM female mosquitoes.[26] The emails reveal a high level of concern about the inadvertent release of GM female mosquitoes from the MRCU scientist with access to the data[27]:
"*I have previously raised concerns about the significant increase in female Aedes aegypti in the West Bay release area during the first few months of the release. As a Quality Assurance measure I have looked at the percentage of female mosquitoes in two pots of 1000 mosquitoes.*
"*In the first pot there were 28 female mosquitoes and in the second pot there were 9. With the target release rate of 500,000 per week this means we could be releasing between 4,500 to 14,000 female mosquitoes per week. I believe that this needs to be addressed as soon as possible*". Although later this issue is claimed to have been resolved[28] another email refers to this and other production problems as not being fully resolved:[29] "*Production issues have not yet been fully resolved; release of high % of females, high adult and larval mortality, mold in rearing unit etc.*" It remains unclear how reliable the sorting method is in general, and whether it could be reliably scaled up for a large-scale programme, without inadvertently releasing very large numbers of biting females which can bite and transmit disease. The emails also highlight the importance of data on the numbers of adult mosquitoes in order to assess the potential impacts on disease[30]: "*Disease is transmitted by adult mosquitoes so I want to see an effect on the adult mosquito population. We do not know how egg counts relate to adult population*."

More fundamentally, the emails released as a result of the FoI question the basis of all Oxitec's claims of efficacy. An internal assessment of the data states: "*To date all the measures recorded have shown no significant reduction in the abundance of Aedes aegypti in the release area*".[31]

In more detail, regarding the ovipots (egg pots), MRCU scientists find: "*Statistical analysis of the ovipot indicies in the untreated and treated areas shows that the reduction seen in the treatment area is not statistically significant*…" and report that the average egg count in the ovipots has increased "*18% in the treated area and 11% in the untreated area*" with the result that "*Statistical analysis of the data shows that since commencement of the release there is no significant change between the egg counts in the treated and untreated areas*…". The emails also state[32]: "*I would like target levels to be calculated as I have discussed with Renaud; i.e. Not use of an average of an average which is mathematically incorrect*". A more detailed explanation is subsequently sent to Oxitec.[33]

The emails also raise concerns about how Oxitec defines the period over which population suppression is measured[34]: "*Oxitec want an undefined period for data analysis but in my opinion this is very unscientific as it allows them to select a time period where control is at its highest. This is very unscientific*". In addition, the emails highlight how Oxitec has changed the target area for the releases during the experiments[35]: "*From the onset of the trial the size of the program was known and in all their previous trials the impact of immigration of wild Aedes aegypti from adjacent areas has been reported and used to justify reducing the treatment area. This effect should have been known about and factored into the design of the trial from the beginning. I am not in favour or* [sic] *reducing the trial area at this stage as I think it would invalidate the results collected so far*". In addition, the emails raise concerns about how Oxitec identifies the GM mosquito larvae, based on the fact they are genetically engineered to carry a fluorescent marker[36]: "*In my opinion it is not accurate and consistently reported extremely high levels of mating success which were not supported by trap data. It is a very subjective measure and very difficult to determine*".

In addition, it should be noted that the trials involved "*an increase in release rates, coupled with insecticide applications*" after the initial releases failed to make an impact on the wild population.[37]

In the emails released as a result of the FoI request, Oxitec makes a much reduced claim for efficacy[38]: "*In the dry season we had reduced the populations by an average of 51%. In the more critical wet season this had increased to 61% and was on a positive trend as reported by Dr. Petrie* [then MRCU Director]. *The setback then occurred in July which is acknowledged as due to logistical/operational reasons unrelated to the effectiveness of the technique*". This email includes weekly data for 2017, based on eggs per trap in the treated area compared to the untreated area. The email states this is "*Oxitec's standard for all its projects*" (although this is not the measure used in the first Cayman Islands' trial, nor in Oxitec's only published paper in Brazil). This reduced claim still goes far beyond the view of the MRCU according to the emails, which is: "*To date all the measures recorded have shown no significant reduction in the abundance of Aedes aegypti in the release area*".[39]

Success in Brazil?

"*To verify those numbers we talked to Danilo Carvalho at the University of São Paulo in Brazil, who helped analyse the data. He tells us the numbers are more like 60 to 70% reduction, not 90, and actually called into question Oxitec's methods and said their analysis*

was below scientific standards." Phil Torres [journalist], TechKnow, Al Jazeera 29th November 2016 (at 12:54).[40]

According to Oxitec, it initially undertook open release trials at three sites in Brazil. These were conducted in Itaberaba and Mandacaru (both in the city of Juazeiro in Bahia, North East Brazil) with the pest control organisation Moscamed and the University of São Paulo (USP); and in Pedra Branca (in the town of Jacobina, Bahia), jointly with Moscamed.[41]

In May 2013, an Oxitec Press Release stated: "*Oxitec report 96% suppression of the dengue mosquito in Brazilian trials*",[42] based on the trial in the village of Mandacaru, Bahia state, Brazil. The press release adds: "*These results follow a previous trial which demonstrated an 80% reduction of a mosquito population in Itaberaba, part of the city of Juazeiro, Brazil. Similar results were also achieved in the Cayman Islands in 2011. The latest evaluation in Mandacaru achieved even greater reduction because it was conducted in a more isolated area and therefore had less immigration of wild mosquitoes from un-treated areas*".

The trials in Mandacaru have never been published in an academic journal.

The results of the earlier Itaberaba trials were not published until 2015.[43] In July 2015, Oxitec's Press Release stated: "*Releases of the genetically engineered Oxitec mosquito, commonly known as 'Friendly Aedes aegypti', reduced the dengue mosquito population in an area of Juazeiro, Brazil by 95%, well below the modelled threshold for epidemic disease transmission*".[44] The lead author this paper is Danilo Carvalho, who was reported by Al Jazeera in November 2016 as questioning Oxitec's claims and methods (cited above).

The results of the Itaberaba trials have been the subject of a critique published in the Lancet Global Health.[45] As shown in the Appendix to this paper, Oxitec's claim of 95% suppression in this trial is based only on captured adult male, not adult female mosquitoes. This means no conclusions can be drawn about the effect of the releases on the number of adult biting female mosquitoes which transmit disease. The start and end time for the claimed reductions are chosen by Oxitec to give the most favourable results. Further, there is no control area with which to compare the numbers of adult males and, according to the Supplementary material in the Itaberaba paper, the method of monitoring adult mosquito numbers was changed during the experiments. A claim of 78% reduction based on ovitraps is not cited by Oxitec in its press release, and the graphs which purport to show this are missing from the paper. Controls are provided for the egg traps, but there is no buffer zone between the treated area and the control area, meaning adults mosquitoes can move between the treatment and control areas. As in its Cayman Islands experiments, Oxitec reduces the release area during the experiments, and the positions of the ovitraps are also changed.

In its 2014 Press Release, Oxitec stated: "*A project led by Moscamed in the town of Jacobina, Bahia, has reduced the wild population of Aedes aegypti in the Pedra Branca neighborhood by 92%. This project is ongoing and is now being extended to other neighborhoods in the city*." [46] But no results have ever been published from this third trial site.

In 2016, Oxitec began larger-scale trials of its GM mosquitoes in Piracicaba, a city located in the state of São Paulo, Brazil.[47] In March 2017, Oxitec's Press Release stated "*Oxitec's Friendly™ Aedes achieves 81% suppression of wild Aedes aegypti in CECAP/Eldorado, Piracicaba, in second year of project*".[48] Some graphs were included in the press release,

reporting the numbers of wild larvae in ovitraps. However, no results from Piracicaba have been published in an academic journal.

One press article has reported concerns that Oxitec has released less than half of the number of insects considered adequate for Piracicaba to be protected after the end of the releases.[49] If so, this might be a result of similar production problems to those highlighted in the Cayman Islands emails, such as mould in the production facility. The article says that the agreement signed in May 2016 to treat eleven neighborhoods in Piracicaba provides for two years of mosquito releases and two years of monitoring of the area. It reports that documents provided by the Piracicaba Prefecture show that, from May 2017 - when the phase of suppression should have begun in October of the same year, Oxitec released less than half of the number of mosquitoes considered appropriate to have a significant impact on the egg bank weekly in Piracicaba, and in a few weeks they released less than a fifth of this number. The article reports that after discontinuation of releases, reinfestation of the treated area could occur in very short time due to lack of any impact on the egg bank, since eggs can remain viable for about a year after being deposited and the largest number of individuals is always in the egg stage. It also reports that in another document provided by the city of Piracicaba, dated January 11, 2018, Oxitec states that in six districts of the central region (Cidade Alta, Cidade Jardim, Clube de Campo, Nova Piracicaba, São Dimas and Vila Rezende) more than half the population of the treated area - are still "in the initial phase of suppression": the stage that should have started in May 2017.

Success in Panama?

In Panama, open release trials of Oxitec's GM mosquitoes were conducted in 2012. There have been no further trials there since, reportedly due to the high costs.[50]

In January 2015, an Oxitec Press Release claimed: "*Oxitec's genetically engineered mosquitoes in Panama pilot achieve over 90% control of the mosquito responsible for outbreaks of dengue fever and chikungunya*".[51] The Panama results were published in 2015 in the journal Pest Management Science.[52]

This paper reports a sustained reduction in *Aedes aegypti* of up to 93%, based the maximum reduction in larvae that could be identified in the release area compared to the control areas, using ovitrap data. It uses four-week moving averages (criticised by MRCU scientists) and does not provide raw data. No data on the impact of the releases on numbers of adult female *Aedes aegypti* mosquitoes is reported, although ten adult traps were placed at each of the sites. This paper finds that the competitor mosquito species *Aedes albopictus* was increasing significantly year upon year at each of three study sites (one release and one control site) during the experiments.

Population suppression is not the same as benefit to health

"*GMMs [Genetically Modified Mosquitoes] must be effective in reducing transmission of the targeted pathogen(s) and not detrimental to the environment and human health if they are used as public health intervention tools. Demonstration of efficacy will be a critical determinant for decision-making about deployment*". World Health Organisation, 2014.[53]

"*The trials we've conducted so far are not on a large enough scale to be able to show any sort of dengue control*". Derek Nimmo, product development manager at Oxitec.[54]

"*There is only a loose correlation between a reduced number of mosquitoes and a reduced number of dengue cases*". Dr. Phil Lounibos, University of Florida.[55]

"[Dr. James] *suggested that these genetic tools might not be the best strategies for ZIKV* [zika virus] *given that at this point there seem to be multiple vectors not only at the species but also at the population level. The current genetic technologies would not be appropriately applied to such complex systems*". Zika Symposium, 2016.[56]

"*Technologies for controlling mosquito vectors based on genetic manipulation and the release of genetically modified mosquitoes (GMMs) are gaining ground. However, concrete epidemiological evidence of their effectiveness, sustainability, and impact on the environment and nontarget species is lacking; no reliable ecological evidence on the potential interactions among GMMs, target populations, and other mosquito species populations exists; and no GMM technology has yet been approved by the WHO Vector Control Advisory Group*". "Transgenic mosquitoes – fact or fiction?" Journal paper, 2018.[57]

"*The ecology of GMMs is not completely understood, and their supposed interaction with particular biomes and nontarget species is mostly theoretical... Environmental and ecological variations may alter the expected outcome of suppression strategies based on GMM release, possibly resulting in failure to suppress targeted mosquito vector populations*". "Transgenic mosquitoes – fact or fiction?" Journal paper, 2018.[58]

"*Nontarget species are often vectors themselves and therefore epidemiologically important. For example, suppressing Ae. aegypti populations could affect the population dynamics of Ae. albopictus*". "Transgenic mosquitoes – fact or fiction?" Journal paper, 2018.[59]

"*The Vector Control Advisory Group (VCAG) of WHO is responsible for assessing new tools for vector control. However, it is likely that only a few will be proven effective and safe to be included under the IVM* [Integrated Vector Management] *framework. In this context, other mosquito control strategies are closer to being utilized in the field compared to GMM release, such as attractive toxic sugar bait (ATSB) and the incompatible insect technique (IIT). Moreover, a recurring issue of GMM-based strategies is the lack of epidemiological evidence showing their safety and effectiveness and their failure to be accepted and supported by local communities*". "Transgenic mosquitoes – fact or fiction?" Journal paper, 2018.[60]

Even if suppression of the wild population of *Aedes aegypti* mosquitoes is (at least temporarily) successful, this might not lead to a reduction in the harm caused by tropical diseases. There are several important issues:

(i) Disease transmission thresholds are not well known and even a small number of mosquitoes may still lead to transmission of disease;

(ii) More than one species can transmit zika, dengue and chikungunya. Non-target species, such as *Aedes albopictus*, will not be reduced by the releases and might possibly increase due to reduced competition, particularly in the longer term;

(iii) There is a complex relationship between human immunity and infection, so in some circumstances reducing infection can lead to reduced immunity and hence a rebound in cases of disease;

(iv) There are several mechanisms through which the technology could become less effective over time (for example, if the GM mosquitoes evolve resistance to the killing mechanism), making a rebound in disease more likely.

There has been no monitoring of the impacts on dengue fever, zika or chikungunya of Oxitec's GM mosquito releases in any country, despite a scientific consensus that assessing impacts on disease is essential to assess the efficacy of new technologies.[61,62] 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.[63,64]

Oxitec has claimed that the World Health Organisation (WHO)'s Vector Control Advisory Group (VCAG) has "*issued a positive recommendation in support of Oxitec's self-limiting mosquito (OX513A)*".[65] However, the relevant VGAC statement in fact says: "*Full-scale programmatic deployment is not currently recommended for any of the five new potential tools reviewed by VCAG. However, the VCAG recommended the carefully planned pilot deployment under operational conditions of two tools (Wolbachia-based biocontrol and OX513A transgenic mosquitoes) accompanied by rigorous independent monitoring and evaluation*".[66] More specifically the VCAG states that Randomised Controlled Trials (RCTs) "*with epidemiological outcomes should be carried out to build evidence for routine programmatic use of OX513A Aedes against Aedes-borne diseases*". This advice is at odds with Oxitec's claims that its technology is already ready for deployment.

The Cayman Island emails point out[67]: "*The pilot trial in West Bay has been monitored and evaluated by Oxitec and as such does not meet with the VCAG recommendations*". The latest published VCAG minutes also make clear that the relevant studies have not been conducted: "*Results from epidemiological trials remain the primary missing information for assessment of the public health value of this product. Epidemiological studies must be carried out to assess the public health value of reducing vector populations through the application of OX513A*".[68]

Despite the VCAG recommendations, Oxitec recently took Brazil's national health agency ANVISA to court to try to force it to allow commercialisation without evidence of efficacy. The Federal Judge authorised commercialisation and is reported as writing in the decision that "*by searching through the World Wide Web, I have accessed several publications mentioning the success of the planned release of transgenic mosquitoes in the city of Piracicaba*".[69] ANVISA is appealing the decision: stating that it first needs to assess the safety and efficacy of the use of Oxitec's GM mosquitoes as a public health measure to control dengue, zika and chikungunya.[70]

Oxitec claims that an approval it received from Brazil's biosafety agency CTNBio in 2014 should be sufficient to receive a commercial licence.[71] However, the Opinion published by CTNBio includes a Dissenting Opinion from two experts regarding the risks of the technology[72] and also states: "*Pursuant to provisions of Law no. 11105 and Ruling Resolution no. 05, CTNBio is in charge of assessing risks, limited to the direct biologic risks resulting from releasing a GMO in the environment. Accordingly, this opinion does not focus issues of technology efficacy, costs and advantages/disadvantages as against other technologies of Aedes Aegypti population control. Finally, questions directly linked to dengue control are not a CTNBio concern, since the matter is under the Brazilian Health Ministry and State Secretariats that may select adopting the technology to control this endemic disease*". ANVISA granted Oxitec a temporary registration in 2016 to allow it to proceed with its trials in Piracicaba,[73] however it has been clear that the technology also must be regulated and assessed as a public health intervention before it can be used commercially.[74,75]

Costs, cost-effectiveness and opportunity costs

"…*the monetary feasibility and cost–benefit of releasing GMMs should be assessed; identifying the actual direct and indirect costs of developing, producing, and releasing GMMs is key for its successful inclusion under the IVM* [Integrated Vector Management] *framework*". "Transgenic mosquitoes – fact or fiction?" Journal paper, 2018.[76]

"*CI* [Cayman Islands] *Government should not be expected to pay for a technology that has a*[sic] *yet failed to deliver any significant results*". MRCU scientist, 4th April 2017.[77]

"*For MRCU to proceed without the recommendation from this WHO advisory group* [the VCAG] *is (in my opinion) very unwise. Not only could it divert much needed resources from our own control efforts but it could lead to other countries following our example and investing their own vector control resources in an unproven technique. This could have severe negative consequences for Public Health in the region as a whole*". MRCU scientist, 4th August 2017.[78]

"*I was always led to believe Oxitec's rhetoric that they would 'eliminate' Aedes aegypti. I wonder why that has been diminished within the contracts?*" MRCU scientist, 31st August 2017.[79]

In 2011, Oxitec published a paper claiming that its technology is cost effective at preventing dengue.[80] The computer modelling in this paper was conducted before any experimental results were published and is therefore out of date. Further, there have been no studies of the impact on disease. The numbers of GM mosquitoes that would be needed to prevent a single case of disease remains highly speculative due to the problems discussed above, and (at best) appears to be much higher than Oxitec originally supposed, even if disease prevention is achievable (which is still unknown). In addition, large numbers of GM females have been released during the experiments, which may have made the situation worse.

In Malaysia, the ministry estimated a cost of RM100 million ($25.7 million) to implement the GMO mosquito project in four selected states in the country and cited costs as one reason for abandoning any plans to use Oxitec's technology.[81]

In 2014, the release of 300,000 GM mosquitoes in Panama was reported to have cost $620,000 (more than $2 per mosquito).[82] Oxitec proposed undertaking subsequent releases at a reported cost of $4.5 million, but Panama did not agree to pay these costs.[83]

The Cayman Islands emails, released as a result of a Freedom of Information request, reveal that Oxitec planned to charge US$8 million to roll out its GM mosquito releases across Grand Cayman over a three year period beginning in 2018.[84,85] An email from Oxitec refers to "*commitments to our contractors of US$400k-500k a month going forwards*" for preparations for the proposed roll out of GM mosquito releases across the island.[86] The emails also repeatedly refer to an additional CI$336,000 (US$409,749) payment for an extension of the 2016/17 trials, which is disputed due to the lack of signing of the contract.[87,88,89] In October 2017, the MRCU's Acting Director states: "*The 2016-17 West Bay Pilot was not meant to cost anything to CIG* [Cayman Islands Government]. *It was only with the "deployment extension" May-Dec which was never agreed/signed, that Oxitec states costs were incurred*…".[90]

The Cayman Islands emails further highlight that the inadvertent release of female mosquitoes (which bite and may transmit disease) is only one of a number of "production

issues":[91] "*Production issues have not yet been fully resolved; release of high % of females, high adult and larval mortality, mold in rearing unit etc.*" Such issues will also add to costs.

In Brazil, Oxitec's new GM mosquito factory in Piracicaba, which commenced construction in June 2016, was expected to cost £2.5m to £3m according to the company's 2015 accounts[92] but was reported to have cost £5 million to date in its 2016 accounts.[93] The factory aims to produce 60 million GM mosquitoes per week[94] although there are press reports that the numbers released may have been inadequate (perhaps due to production problems).[95] Prices are not given and Oxitec's 2015 and 2016 accounts both state that it may be *"some time before the Company's investments in Brazil lead to a self-sustaining cash flow*".

In October 2016, Science reported: "*The Piracicaba expansion will cost the city roughly $1.1 million over 2 years—some $10 per person in the treated area—about half of which will come out of the existing mosquito control budget. Oxitec itself is paying even more than that, says Slade, but it's too early to tell how much the mosquitoes will cost if they are reared on a much larger scale. "It's only when you roll up your sleeves and build a factory that you know what your costs are."*". In the Cayman Islands emails, an MRCU scientist states: "*My main concern now is value for money. $0.42 /head/month in Brazil compared to $39/head/month in Cayman*".[96] It is possible that this much higher cost is closer to the likely commercial rate which Oxitec needs to make a profit.

Costs and cost-effectiveness are not the only issue: there are also opportunity costs when operational and R&D budgets are spent on Oxitec's technology. The Cayman Island emails highlight that the MRCU scientist with access to Oxitec's data is disappointed that MRCU has signed a $400,000 extension of the project as "*an as yet unproven technique*" and that in his view this could have funded 13 staff for one year "*which would have allowed us to treat all problem yards across the island on a once weekly basis*"[97]. A further email expresses concerns that "*Our established and proven control methods are being neglected and it appears we have put all our eggs in one basket and see Oxitec as the only solution*".[98]

Any costs for commercial releases of Oxitec's GM mosquitoes are likely to be an addition to existing mosquito control budgets. This is because Oxitec's approach is not a stand-alone technology (the Cayman Island experiments combined it with insecticides). Existing control measures, many of which focus on controlling other species, would in any case need to be maintained, and may even need to be supplemented with other measures (due to other species such as *Aedes albopictus* becoming more of a problem). Oxitec's former Chief Scientific Officer, Luke Alphey has recently stated: "*Since Ae. aegypti and Aedes albopictus are known to compete…it is possible that the successful implementation of* …[GM mosquito] *gene drives could lead an existing Ae. aegypti population to be displaced by Ae. albopictus where it would not otherwise have been. This would likely hamper efforts to eliminate viruses such as dengue since Ae. albopictus are also competent vectors*...".[99] In fact, in its application to release GM *Aedes aegypti* mosquitoes in the Cayman Islands, Oxitec assumes that future releases of GM *Aedes albopictus* will also be needed.[100] Oxitec's GM *Aedes albopictus* have never been tested in open air releases, so it is unclear whether this approach would work, or how much it would cost.

Questions about transparency, independence and due diligence

"*Whilst Oxitec and MRCU are making public statements proclaiming major reductions in the Aedes aegypti population in the treatment area the data I have seen does not support this*". MRCU scientist, 4th April 2017.[101]

"*My thoughts on this are as follows; sooner or later we will have to release the results of the West Bay trial to the public. The questions about the effectiveness of the release are just not going to go away. Judging by Kevin's* [at Oxitec] *response to my proposal for the data analysis we appear to have reached an agreement on how we will report the results for the upcoming trial. Why don't we apply the same method of interpreting the results to the previous results and release the data to the public? We should also request that Oxitec apply the same method of analysis to all previous trial data (Brazil, Panama, Cayman etc) so we can see exactly what results have been achieved using the agreed method of analysis*". MRCU scientist, 23rd February 2018.[102]

"*In the past CARPHA* [The Caribbean Public Health Agency] *have stated to me that one of the reasons they do not promote the Oxitec technique is that they have not seen the raw data from previous trials*". MRCU scientist, 4th August 2017.[103]

Oxitec's claims of significant reductions in wild *Aedes aegpti* numbers as a result of their open release experiments have been widely cited in the press and in public information. These claims have likely influenced decisions by public agencies and private investors, as well as members of the public living where these experiments have been conducted.

For example, the Oxitec and MRCU public leaflet used in the Cayman Islands states "*Each area* [where GM mosquitoes have been released] *achieved a reduction in mosquitoes of more than 90%*" and shows a map with the Cayman Islands (96%), Panama (93%) and three trials in Brazil (Itaberaba, 93%, Mandacaru 99%, Pedra Branca 92%).[104] In Brazil, Oxitec's public engagement includes a jingle claiming that Oxitec's GM mosquitoes are "the solution" to dengue, despite the fact that there is no evidence to that effect.[105]

In the Cayman Islands, Oxitec was unhappy about the release of the MRCU Annual Report, stating "*this data should not have been given out without Oxitec consent, even in response to an FOI request*.[106] An article in the Cayman Compass on 25th October 2017 subsequently reported the claimed 62% suppression rate from this MRCU report, with a statement from Oxitec's project manager that the results were in line with what was expected and the effect would increase over time with the continued release of genetically modified males.[107] The emails released as a result of the FoI request reveal the response within the MRCU to be that the information given in this article is "*incorrect*"[108] and state "*The MRCU Annual Report was actually written by Oxitec and we remain divided upon the level of suppression achieved. It is unfortunate that it has been used for this newspaper story*"[109] and "*Targets where* [sic] *not set for the release and therefore no targets were achieved. MRCU was expecting to see a reduction in the region of 90%+ as had been reported in all other Oxitec releases. This was not achieved and the figure of 62% reduction is also not accepted by MRCU*". [110] However, MRCU's acting Director states, "*There is one caveat here: while apparently Oxitec contributed in large part to the MRCU Report referenced, at the end of the day it is an MRCU Report so we cannot tell the public that Oxitec authored it*".[111] The same problem arises later in response to a request for information from a Brazilian journalist: "*I do not agree with the responses we are giving this journalist. I do not agree with the 62% reduction claimed*" [112] and (in response from the acting MRCU Director) "*That 62% was in the report*".[113]

Thus, not only did Oxitec initially object to the release of results it did not regard as favourable, subsequently journalists were given the impression that these results had been checked and confirmed by the MRCU, when in fact that was not the case. This has major implications for mosquito control units elsewhere, who may be at risk of making decisions to

invest in experiments or even make commercial use of Oxitec's technology without any independent information about its efficacy.

Oxitec was originally a spin-out company from the University of Oxford and the main early-stage investors were the University, Oxford Capital Partners and East Hill Management.[114] In September 2015, Intrexon acquired Oxitec for $160 million (paid in a mix of cash and stock).[115] As noted above, claims of "*over 90% reduction of the Aedes aegypti population*" featured heavily in press releases made by the two companies at the time.[116,117] If these claims are not supported by the evidence, this raises serious questions about due diligence and about whether Intrexon's investors are properly informed.

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