Early in November, at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) in Atlanta, researchers from the British company Oxitec disclosed results from the world's first genetically modified (GM) mosquito field trials aimed at controlling the carrier for dengue fever. After the presentation at the meeting, *Science* (330, 1030–1031, 2010) published a news story claiming the trials had “strained ties” with Oxitec's collaborator, the Bill and Melinda Gates Foundation. Anthony James, the lead investigator on the Gates team, was also quoted as saying he would “never release GM mosquitoes the way Oxitec has now done in Grand Cayman.” Although some concerns have been raised as to how information about the trial was disseminated, it seems that controversy over the environmental release of a GM organism has been overblown.

Oxitec's plans for transgenic mosquito trials have not been without controversy in the past. They have been criticized by environmental groups, such as Ottawa-based ETC Group and EcoNexus of Oxford, concerned about the risks of releasing an entirely new strain of organism into the environment. Activists warn that transgenic insect releases that reduce wild mosquito numbers might not only create an ‘empty niche’, which other potentially damaging insects might fill, but also affect organisms higher in the food chain that rely on mosquitoes as a dietary source.

The present spat, however, centers around disagreements over the rapid move to an open release of insects and in particular the way in which the existence of the trial was communicated to the community and public at large. Luke Alphey, CSO of Oxitec, concedes that researchers may have differing views on how to plan and execute such field tests; however, he says he hasn't received any complaints from the community nor has he been scolded by his Gates collaborator James, a professor at the University of California, Irvine. When contacted by *Nature Biotechnology*, James declined to comment, but a spokesperson for the Gates Foundation says of a different trial Oxitec is running in Mexico in collaboration with the Foundation says that “we are happy with the way that is going.”

For his part, Alphey says he was “surprised that *Science* chose to present the story the way they did.” If there is a controversy around the way Oxitec prepared for the trials, he says, it has not officially been directed at his company.

Oxitec first commenced the Cayman trials in September 2009. Together with the islands’ Mosquito Research and Control Unit (MRCU), the company liberated about 3.3 million sterile male transgenic *Aedes aegypti* mosquitoes into a region spanning about 16 hectares through 80 releases.
Table 1: Progress in GM mosquito research

The OX513A mosquitoes used in the trial carry the LA513 transposon integrated into their genetic material via a piggyBac helper plasmid (BMC Biol. 5, 1–11, 2007). LA513 encodes the tetracycline-repressible transcription activator (tTA), a protein whose high-level expression is deleterious to cellular development, probably due to transcriptional 'squelching' and/or interference with ubiquitin-dependent proteolysis (Nat. Biotechnol. 23, 453–456, 2005). When expressed, the tTA protein binds to the tetO operator sequence (upstream of tTA) and drives expression of tTA from a nearby minimal promoter, which in turn binds to tetO, creating a positive feedback system. Because tetracycline binds tTA, preventing the activator from interacting with tetO, batches of transgenic mosquitoes can be grown in the presence of the antibiotic (whereas in its absence, transgenic mosquito larvae die). The resultant transgenic Aedes eggs are collected for hatching at a trial site, and the smaller male pupae sorted from females and on maturity released into the field, where breeding with wild-type female mosquitoes results in sterile mating.

Field tests in Grand Cayman were conducted in two stages. The first set of small-scale releases assessed whether transgenic males could survive in the wild and mate with wild females. The presence of transgenic larvae showed that the transgenic males did survive and were capable of finding mates. These results formed the basis for a second trial, which began last year, to test the effect of the transgenic mosquitoes on suppressing the wild population. Adult mosquitoes as well as eggs were monitored using adult traps and ovitraps (black jars containing water and a paddle leading inside, on which mosquitoes lay eggs), respectively. Offspring from transgenic males also carried a fluorescent marker, allowing the transgenic larvae to be easily distinguished from wild counterparts.

According to Alphey's ASTMH presentation, results from the large release showed up to an 80% reduction in the numbers of wild mosquitoes ~11 weeks after the release. This reduction in the population was sustained for a further ~7 weeks until the end of the trial. It is possible that the approach could be even more effective in suppressing wild mosquitoes because in this case the study site was not isolated and surrounding areas contained high densities of wild mosquitoes.

William Black, a collaborator on the Gates project, was impressed by the results; the Cayman Islands trial “went very, very well,” he says. David M. Brown, project manager at the department of microbiology and molecular genetics at the University of California, Irvine, agrees that the results enjoyed a very positive reception at the meeting. “There were [even] a few comments of gratitude,” he says, as the Cayman Islands trial is an important step in pushing GM insect technology against dengue fever forward.

Alphey says preparatory work for the Grand Cayman trial was extensive and meticulous. Elected political representatives were informed and flyers were distributed. MRCU officials were educated and went on foot to answer questions the locals had about the trials. All vehicles and equipment carried phone numbers and clear labels, so any concerned observers could contact the authorities. There was good awareness, he says, “that the project was testing a new genetic method to control dengue using sterile males, that males don't bite, that not all species of mosquitoes would be controlled.”

Even so, some commentators have questioned whether publicity about the trial could have been better handled. For example, many only became aware of the trial's existence after the Cayman Islands government posted a YouTube video announcing the trial (http://www.youtube.com/watch?v=tv6JsC2MQYI)—hardly the traditional forum for publicizing an environmental release of a transgenic organism.
Bart Knols, managing director at K&S Consulting in The Netherlands, says that because the material is now public but has not yet passed through peer review, the trial sponsors have potentially opened themselves up for criticism. According to Knols, public information connected with transgenic insect release trials, at a global and local level, needs to be managed carefully—if not for Oxitec’s sake, he says, then for others, because if bad press did occur, it “may not affect Oxitec itself, it may affect other groups around the world who are working on [GM] insects. And then no one can take advantage of all these new tools that have been developed.”

David Andow, McKnight University professor of insect ecology, at the University of Minnesota in St. Paul, also feels that Oxitec could have done a better job making the research community aware of its work. It is not clear whether the Cayman Islands evaluated the trials according to international standards such as the guidelines laid out in the Cartagena protocol, he says. “Communication would have gone a long way in making it clear to people like me whether or not [Cayman Islands officials] did that,” he says.

Oxitec is continuing talks with the Malaysian government, which is considering releasing transgenic mosquitoes to address its local dengue problem. By comparison, Oxitec has “been good about publicizing the work they’re doing in Malaysia,” says Andow. “They essentially leapfrogged that [step] in the Cayman Islands.” Now, Knols says, the Malaysian government may insist that Oxitec finish its trials in the Cayman Islands before beginning in Malaysia.

What seems to be clear is that the transgenic mosquito release in the Cayman Islands was viewed as a success. Indeed, William Petrie, director of the MRCU in the Cayman Islands, says the sterile transgenic mosquito release technique is head and shoulders above the population control methods currently in place there. Val Giddings, president of the Silver Spring, Maryland consultancy PrometheusAB and a former vice president at the Biotechnology Industry Organization (BIO), says that Oxitec’s strategy, as a first attempt at using transgenic insects, is beyond reproach. Not only did the company pick a relatively isolated trial site and carry out the trials in collaboration with the government following the necessary protocol, it also used a species-specific technique in which the transgene would be extinguished in following generations.

Alphey says Oxitec is moving ahead with other projects using technological lessons learned from the study itself. Meanwhile, company researchers are preparing their data for peer review and publication. “I think what we’ve done is reasonable and appropriate,” says Alphey, “Few people in the field would disagree with the proposition that new tools are required for dengue, and this is a significant step forward.”

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