Genetically-modified insects: under whose control?

GeneWatch UK, Testbiotech, Berne Declaration, SwissAid, Corporate Europe Observatory

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Summary

Plans to commercialise genetically modified (GM) insects, including agricultural pests, would result in many millions of GM insects being released in fields of crops, including olives, tomatoes, citrus fruits, cabbages and cotton. Many millions of GM mosquitoes have already been released in experiments intended to reduce transmission of the tropical disease dengue fever. In future, any insect species, including beneficial insects such as bees, might be genetically modified.

Releases of GM insects are covered by laws and regulations that cover the release of genetically modified organisms (GMOs) and by general requirements for environmental and health protection. However, there is no specific regulatory process for GM insects anywhere in the world.

Regulatory decisions on GM insects in Europe and around the world are being biased by corporate interests as the UK biotech company Oxitec has infiltrated decision-making processes around the world. The company has close links to the multinational pesticide and seed company, Syngenta. Oxitec has already made large-scale open releases of GM mosquitoes in the Cayman Islands, Malaysia and Brazil and is developing GM agricultural pests, jointly with Syngenta.

The European Food Safety Authority (EFSA) is one of several examples showing how industry organises its influence. In EFSA´s GM insects working group, which was established to develop guidance for risk assessment of genetically engineered insects, there are several cases of conflicts of interest, including experts with links to Oxitec who only partially declared their interests. The draft Guidance on risk assessment of GM insects shows some significant deficiencies: for example it does not consider the impacts of GM insects on the food chain. Oxitec's GM insects are genetically engineered to die mostly at the larval stage so dead GM larvae will enter the food chain inside food crops such as olives, cabbages and tomatoes. Living GM insects could also be transported on crops to other farms or different countries. EFSA has excluded any consideration of these important issues from its draft guidance. Many other issues are not properly addressed.

A World Health Organisation (WHO)-funded project has allowed the company to bypass requirements for informed consent for the release of GM mosquitoes. The WHO-funded Mosqguide project, which was supposed to be developing best practice, also allowed the company to gain approval from Brazilian regulators to release 16 million GM mosquitoes before draft regulations on the release of GM insects had been finalised or adopted, without publishing a risk assessment.

Multiple attempts by Oxitec to influence regulation around the world have included:

- Attempts to define 'biological containment' of the insects (which are programmed to die at the larval stage) as contained use, by-passing requirements for risk assessments and consultation on decisions to release GM insects into the environment;
- Attempts to avoid any regulation of GM agricultural pests on crops which will end up in the food chain;
- Avoidance of any discussion of how GM insects can be contained at a site, or products produced using GM insects can be labelled;
- Exclusion of many important issues from risk assessments, including impacts of surviving GM mosquitoes on the environment and health, and impacts of changing mosquito populations on human immunity and disease;
- Failure to follow transboundary notification processes for exports of GM insects correctly;

- Undermining the requirement to obtain informed consent for experiments involving insect species which transmit disease;
- Attempts to avoid liability for any harm if anything goes wrong;
- Pushing ahead with large-scale open releases of GM mosquitoes before relevant guidance or regulations are adopted.

Introduction

Oxitec is a UK company producing genetically modified (GM) insects with the aim of creating a global market in GM insects for open release into the environment. It is supported by the multinational pesticide and seed company, Syngenta. Oxitec's GM insects include GM mosquitoes and GM agricultural pests. Oxitec has already released many millions of GM mosquitoes into the open in the Cayman Islands, Malaysia and Brazil but Syngenta is interested mainly in the market for GM agricultural pests. Other research groups are also working on GM mosquitoes and thousands of other species of insects could be genetically modified in future, including beneficial insects such as bees.

Releases of GM insects are covered by laws and regulations that cover the release of genetically modified organisms (GMOs) and by general requirements for environmental and health protection. However, there is no specific regulatory process for GM insects anywhere in the world.

This briefing examines how Oxitec is seeking to influence regulatory processes for GM insects so that it can commercialise its products.

GM insect species and traits

Oxitec's patented technique for genetically modifying insects is known as RIDL (Release of Insects carrying a Dominant Lethal genetic system).[1] The idea behind this technique is to bring down the number of insects that damage a crop, such as bollworms, or spread a human disease, such as mosquitoes. Many millions of male GM insects with the RIDL trait are intended to be released per week in a commercial programme, vastly outnumbering the wild population of insects, and this is intended to suppress the wild population. The GM males mate with wild females and produce GM offspring which are genetically programmed so that many of them die.

Oxitec began open releases of GM insects by releasing pink bollworms (a cotton pest) genetically modified to contain a fluorescent marker in open trials in the USA.[2] These releases were made using bollworms sterilised with radiation, not with the genetically modified RIDL trait. The fact that large-scale releases of Oxitec's GM fluorescent bollworms are incompatible with organic standards appears to have led to this programme being halted and not extended to include the use of RIDL.[3]

Beginning in 2006, Oxitec teamed up with multinational seed and pesticide company Syngenta and adopted a new strategy to get its GM insects to market. They chose to try to establish a market and favourable publicity and regulatory processes by first releasing GM mosquitoes with the stated aim of reducing the tropical disease dengue fever. At the same time, Oxitec has worked with regulators to facilitate the release of other GM insects in the future.

All the company's open field experiments with RIDL to date involve its OX513A strain of the *Aedes aegypti* (Yellow Fever) mosquito, which is one of two mosquito species that transmit

the tropical disease dengue fever. Oxitec has made open experimental releases of GM *Aedes aegypti* mosquitoes in the Cayman Islands, Malaysia and Brazil.[4] The male GM mosquitoes are intended to mate with wild females and produce offspring most of which die as larvae. Oxitec is also developing GM *Aedes albopictus* (Asian Tiger) mosquitoes (the other species that transmits the dengue virus). This is a female-flightless trait, in which the female offspring of the GM mosquitoes are unable to fly and therefore die from lack of food.[5] Oxitec has also developed flightless female *Aedes aegypti* mosquitoes.[6]

Oxitec's GM agricultural pests have a female-killing trait: this means male offspring survive to adulthood but females mostly die at the late larval or pupal stage, in the absence of the antibiotic tetracycline (which is used to breed the insects in the lab). Species include the Mediterranean fruit fly[7,8], diamond back moth,[9,10] olive fly[11], tomato leaf miner/borer[12,13]; the Mexican fruit fly; and the red flour beetle.[14] Oxitec recently announced that its Olive fly and Mediterranean Fruit fly strains are ready for national evaluation.[15] The company also plans to begin working on some new species from the Pacific region: the Queensland fruit fly and two species of Oriental fruit fly, native to the Philippines.[16]

Although Oxitec frequently refers to its GM insects as sterile, they are not sterile: they all breed and produce offspring. Most of the females die as larvae in the case of GM agricultural pests (for which Oxitec uses a female-killing approach), or are flightless adults (in the case of GM mosquitoes), but the GM male insects survive to adulthood and a small percentage of GM females are also likely to survive. In the case of agricultural pests, both the surviving GM insects and large numbers of dead larvae are likely to be transported around the world on or in fruit and vegetables. This means they are likely to spread to new environments and enter the food chain. In the case of Oxitec's OX513A GM *Aedes aegypti* mosquitoes, most of the offspring (both male and female) die as larvae although a small percentage will survive to adulthood. Because many millions of GM mosquitoes must be released to mate with the wild population, this can be a large number of surviving GM insects. GM mosquitoes can be easily transported as eggs, larvae or adults anywhere where there are movements of people or of breeding sites (such as tyres): on boats, trucks or trains.

Once GM insects are allowed onto the market, many other GM traits may be developed and other species will be genetically modified. Oxitec and others are also working on so-called "gene drive" systems which will allow scientists to attempt to replace whole populations of wild insects with genetically modified ones.[17] Future GM insects could include dozens of agricultural pests,[18] beneficial insects such as bees[19], silkworms[20] and potentially thousands of other insect species that are now being sequenced.[21]

Commercial interests

Oxitec is a spin-out company from Oxford University.[22] Ex-Syngenta staff who joined Oxitec since 2006 Oxitec include Oxitec's CEO, Regulatory Affairs Manager and Head of Business Development.[23] Oxitec's Chair and one of its other Board members are also ex-Syngenta staff. Oxitec consultants include Colin Ruscoe, former site manager at Syngenta Crop Protection, who is Chairman of the British Crop Production Council.[24] Oxitec's former Head of Business Development (from 2006 to 2010), Ann Kramer, is another ex-Syngenta employee. Kramer evolved Oxitec's strategy to focus on public health and to enter Brazil and led the company's negotiations with the US government.[25]

From March 2009 to June 2011, Oxitec received research funding directly from Syngenta for genetic transformation of *Lepidoptera* (a large order of insects that includes moths and butterflies).[26] Syngenta's interest in the company appears to date from about 2006, when Oxitec developed a method for genetically engineering insects so that their female offspring

die.[27] Oxitec is applying this method to the GM agricultural pests which it is developing for commercial use.

Oxford University is an investor in Oxitec and will profit if its GM insects are commercialised. The company's early venture capital investors were Oxford University and Landon Clay of East Hill Management LLC in Boston.[28] A new round of venture capital funding in February 2012 raised new funds from Asia Pacific Capital and others.[29] W. Gage McAfee, Managing Director of Asia Pacific Capital, joined Oxitec's Board in December 2011, and promised in the company's press release to focus on both GM mosquitoes and GM agricultural pests in China and in India.[30,31] There are also other unnamed investors and shareholders in the company.

Oxitec has received significant subsidies for its research via the Oxford University Challenge Seed Fund and grants from the Wellcome Trust, the Biotechnology and Biological Sciences Research Council (BBSRC, a UK government research council), UK Technology Strategy Board (TSB), the European Union (EU), and the World Health Organisation Special Programme for Research and Training in Tropical Diseases (WHO-TDR). The BBSRC has contributed more than £1.5 million in total to the company's research since 2009, mostly via partnerships with Oxford University. Funding from the Gates Foundation appears to have been terminated following Oxitec's controversial experiments in the Cayman Islands (see below).

Oxitec's role in developing GM insect regulation

In 2009, the BBSRC reported that Oxitec's founder Luke Alphey: "*is also working towards developing regulatory frameworks for GM insects internationally and within a number of countries including the USA*".[32]

From 2010 to 2013 Dr Michael Bonsall, of the Department of Zoology, University of Oxford, received a grant from the BBSRC to work with Luke Alphey of Oxitec on mathematical modelling of the risks and benefits of its technology.[33] The grant states that they are "*working with various regulatory and policy-making bodies around the world, and aim to produce a policy document that we hope will form a key part of the information that such stakeholders need to assess the risks and benefits of this new technology*".[34] Bonsall is a co-author on seven papers as a result of this and earlier work funded by the BBSRC and the Royal Society.[35,36,37,38,39,40,41] The papers include an assessment of Oxitec's late-acting lethality approach which claims it is likely to be more effective at reducing mosquito populations than the sterile insect technique (SIT) which uses irradiated insects; and a cost-benefit analysis which claims that Oxitec's genetic control strategy for *Aedes aegypti* mosquitoes could eliminate dengue rapidly from a human community, at lower expense than the costs of the disease. Both these papers are based on unvalidated computer models which make optimistic assumptions about the likely efficacy of Oxitec's approach. Oxitec has never demonstrated that RIDL is more effective than SIT, although this claim is central to the company's marketing materials.[42,43] The calculations also neglect potential harmful effects of poor efficacy on the incidence of severe forms of dengue fever.[44] Other papers co-authored by Bonsall involve computer modelling of the effects of releases of Oxitec's GM insects on the control of agricultural pests. Downsides such as the potential negative impacts due to the partial survival of the GM insects are not discussed.

Regulation in Europe

Oxitec has yet to release GM insects in the European Union, however the company is closely involved in developing guidance about how they should be regulated.

In 2011, Oxitec sought to make open releases of GM diamond back moths (*Plutella xylostella*) under contained use regulations in the UK on the spurious grounds that its RIDL technology is equivalent to "biological containment".[45,46,47,48,49,50,51,52] If it had been successful, there would have been no published risk assessment or public consultation about open releases of these GM insects. However, Oxitec's RIDL technology does not provide biological containment in the sense of the definition in the relevant regulations[53], because its GM male insects are intended to come into contact with and mate with wild females of the same species, which cannot be regarded as limiting their contact with the environment. Further, Oxitec has genetically modified a non-native strain of diamond back moth which is not allowed to be released in the UK under plant pest control regulations. After consultation with the regulators, Oxitec has yet to make an application for release of GM diamond back moths in the UK. It seems likely that any application will be dealt with as a deliberate release for experimental purposes, which will require consultation and review by the Advisory Committee on Releases to the Environment (ACRE).

On 1st December 2007, Dr Michael Bonsall was appointed to membership of ACRE. Dr Bonsall was required to leave the room when Oxitec's proposal to make open releases of genetically modified diamond back moths under Contained Use Regulations were discussed by ACRE.[54] However, he has been closely involved in developing regulatory guidance which will be used to assess any future application to release GM insects in the European Union.

Rather than developing specific legislation to cover releases of GM insects into the environment, the European Commission (EC) asked the European Food Safety Authority (EFSA) to develop guidance for the risk assessment of GM animals, including insects, under legislation which covers the deliberate release of all genetically modified organisms (GMOs) into the environment (Directive 2001/18/EC).

EFSA set up a Working Group on GM insects to develop this Environmental Risk Assessment (ERA) Guidance, which held its first meeting on 6th June 2011.[55] EFSA is a food safety organisation which has no independent expertise in insects, the environment, or the transmission of mosquito-borne disease.

The declaration of interests of members of the EFSA working group and its advisors are listed on the EFSA website.[56] As a member of the working group, Michael Bonsall includes his collaboration with Oxitec in his declaration of interests but states incorrectly that Oxford University receives no financial benefit from its relationship with the company: the University is in fact a major investor in Oxitec. Luke Alphey of Oxitec also acts as an advisor to the panel. He declares his role as Chief Scientific Officer at Oxitec and that he has investments in the company and patents on its technology, but the minutes of the meetings state that his role at Oxitec was "*not deemed to represent a conflict of Interest*".[57] Bonsall and panel member Jeff Bale are both members of the UK Advisory Committee on Releases to the Environment (ACRE), where they will presumably both comment on the Guidance they have drafted. Bonsall admitted to the Sunday Times that there was pressure from the biotech industry to get the EFSA guidance adopted.[58] It is unclear why Dr Bonsall was required to leave the room when Oxitec's genetically modified diamond back moths were discussed by ACRE whilst he was allowed to play a central role in drafting EFSA's guidance for the same GM insects. The EFSA minutes do not record any discussion of his conflict-of-interest.

Other members of the EFSA working group on GM insects also have close links to Oxitec. Panel member John Mumford declares his role in the risk assessment project Mosqguide for GM mosquitoes, but does not mention that Oxitec is a partner in this World Health Organisation (WHO)-funded project (see below). Mumford (and his wife Mary Quinlan) are co-authors on three journal papers with Oxitec.[59,60,61] Working Group member George Christophides declares his role in the EU-funded FP7 INFRAVEC project, but does not mention that Oxitec is a partner in this project; Romeo Bellini is also a partner in the

INFRAVEC project (undeclared) and a co-author on a journal paper with Oxitec's Luke Alphey.[62] INFRAVEC (Research Capacity for the Implementation of Genetic Control of Mosquitoes) is a four year research infrastructure project, which has been awarded €8.5 million in EU funding from 1st September 2009 to 31st August 2013.[63,64] Iztvan Kiss is a co-author on a paper with Mike Bonsall and Oxitec's PhD student which models the genetic control of pest insects.[65] Two other members of the Working Group, Sait and Malacrida, work for International Atomic Energy Agency (IAEA)'s programme on the use of GM insects to improve the sterile insect technique. Working Group member Ester Kok has previously been criticised for conflicts-of-interest in developing the risk assessment process for GM plants, due to her work with the food industry body the International Life Sciences Institute (ILSI), which established an industry task force to deal with biotechnology in 2004.[66] EFSA's GMO Panel has also been involved in drafting the guidance and will be responsible for amending and adopting it: members of this panel include Vice Chair Gijs Kleter, who has also worked with ILSI.[67]

Major problems with the draft European guidance on GM insects developed by the EFSA Working Group include[68]:

- describing GM insects intended to be used for the suppression of wild insect populations as "sterile" more than 20 times, despite the fact that most of Oxitec's GM insects survive to the late larval or pupal stage and many survive to adulthood;
- as a result of the misleading use of the term "sterile", failure to consider how GM insects may spread in the environment and the potential consequences;
- failure to consider risks of eating GM insect larvae which die in or on vegetables or fruit;
- failure to consider fully the ecosystem effects of suppressing wild insect populations; including the potential for other pests to increase in numbers.

A major problem for Oxitec/Syngenta is the large numbers of GM insects likely to enter the food chain if its approach is ever implemented for GM agricultural pests. This may be a particular problem for olives, tomatoes and citrus fruits, where millions of female GM larvae may die inside the fruit. It is also likely to be an issue for GM larvae which die on the surface crops such as cabbages and broccoli, and for surviving GM eggs and larvae (mainly males) which will be transported with the crops when they are harvested and sold.

Rather than dealing with this issue the EFSA working group has explicitly excluded the risk of people eating GM insects from its draft guidance, which refers instead to earlier guidance on GM animals in food and feed, which in its turn explicitly excluded GM insects. This approach appears to be consistent with Oxitec's desire to treat the presence of GM larvae in food crops as "technically unavoidable" for the purpose of the regulatory process.[69] In the EU, food and feed products which contain a proportion of GMOs of less than 0.9 % of each ingredient are not labelled as containing GMOs on the condition that the presence of the genetically modified organism is adventitious or technically unavoidable. However, it is unclear how this applies to GM insects which have been deliberately released knowing they will enter the food chain and remain on crops. It is also unlikely that this will be acceptable to retailers or consumers in the EU or in other countries.

Regulation in North America

In 2002, the US National Academy of Sciences published a report on GM animals which stated that aquatic organisms and insects present the greatest environmental concerns, because their mobility poses serious containment problems, and because they easily can become feral and compete with indigenous populations.[70] The report expressed concerns about gaps in regulation. The Pew Initiative on Food and Biotechnology published a report in 2004 on gaps in the regulatory system for GM insects in the USA, and a report of a

workshop on the issues.[71,72] A central finding of the report was that there are gaps in the regulatory framework in place to review the many issues raised by the potential introduction of GM insects into wild populations. There is no specific regulation on the release of GM insects, no law that clearly covers all the risks and all of the types of GM insects and no single regulatory body: the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) could all play a role.

The USDA's Animal and Plant Health Inspection Service (APHIS) initiated oversight by issuing permits for contained experiments and then open releases of GM bollworms containing a fluorescent marker trait in the USA.[73] There were 14 US government-funded field trials over a nine year period, beginning in 2002. The world's first environmental impact statement (EIS) on GM insects was produced by APHIS in 2008.[74] Drafting of the EIS started in 2006 and it includes consideration of the RIDL trait in fruit flies and pink bollworms, as well as the fluorescent trait. The distribution list for the document includes Ann Kramer, Oxitec's Head of Business Development from 2006 to 2010, who states on her website that she led led the company's negotiations with the US federal government at this time.[75] The EIS was found to be "scientifically deficient" when reviewed by scientists at the Max Planck Institute.[76] They report that the document reverses an earlier more cautious view published by APHIS in 2001, without providing the substantial body of evidence required to back up its assertions.

A pink bollworm eradication programme using large-scale releases of bollworms sterilised with irradiation has been in operation in the USA since 2002, building on an earlier programme begun in California in 1968, and has been successful in largely eradicating the pest.[77] Based on its 2008 EIS, APHIS issued a Record of Decision in May 2009 which stated that "integration of genetically engineered insects into programs, is also the environmentally preferable alternative". However, GM bollworms (or any other GM pest) are not actually in use in the USA, due to concerns about contamination of organic crops and other issues. Further, RIDL was never seriously considered as part of the pink bollworm eradication programme, because the programme was effective using irradiated bollworms. Despite a long collaboration between the National Cotton Council, the USDA and Oxitec, open field trials were made only with the GM fluorescent trait. The history of the joint research is reported on US researcher Miller's website[78] and in a paper published in 2007 in which he states: "*There is a chance the pink bollworm will be eradicated from the Western USA and northern Mexico before a transgenic pink bollworm is approved for use in the field*" and claims that the regulatory process has stifled the new technology.[79]

Oxitec's Ann Kramer attended the US National Cotton Council's Pink Bollworm Action Committee's meeting in October 2009, where she made a presentation about using Oxitec's fluorescent GM bollworms (known as "DSRed") in the programme (as an alternative to dyed bollworms) at a cost of $225,000 a year.[80] She also offered to make Oxitec's RIDL bollworms (which she describes as "genetically sterile") available at a cost of $400,000 a year. Kramer reported that Oxitec had worked in collaboration with USDA in Phoenix since 2002, when Dr. Staten and Dr. Miller initially invited them to join a cooperative program, but they had focused on the development of the fluorescent marker strain since 2006. In addition to questions about the technology (such as the need for expensive microscopes to view the fluorescent marker), the discussion highlights problems with the National Organic Program's rules which would prevent the sale of crops as organic in the area where the GM bollworms were used. The minutes state that: "*Dr. Staten strongly encourages that we keep the pressure on by continuing to go after the permit for general release"* and note that a 5-year permit request had been submitted by Miller at APHIS.

Although RIDL is not being used in the USA, Oxitec uses APHIS' 2009 statement that its technology is "*the environmentally preferable alternative*" in all its presentations and

submissions to regulators overseas. Oxitec's regulatory affairs manager, Camilla Beech, has even used this statement as part of a teaching exercise at a WHO-TDR workshop in 2010.[81]

In 2011, the USDA Office of Inspector General issued a report arguing that USDA APHIS' controls over GM insect research were inadequate and that regulations needed to be strengthened.[82] The report also criticised APHIS' Center for Plant Health Science Technology (CPHST) for spending about $550,000 on developing GM plant pests such as the pink bollworm, the Mediterranean fruit fly, and the Mexican fruit fly without any formal process for selecting which projects will receive funding. APHIS' collaborative work with Oxitec on these pests was funded by CPHST. The report's recommendations were accepted by APHIS, requiring it to clarify its role, draft specific GM insect regulations, and make more transparent research funding decisions.

In 2012, the Food and Drug Administration (FDA) decided to review a controversial proposal from Oxitec to release millions of genetically modified mosquitoes in Florida, based on an application that had been originally submitted by Oxitec to APHIS.[83] This decision appears to have been made because, unlike pink bollworms, mosquitoes are not plant pests and thus not the responsibility of APHIS. The FDA regulates GM animals under the Federal Food, Drug, and Cosmetic Act and FDA's Center for Veterinary Medicine guidance document, "Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs", issued on January 15, 2009.[84] The rationale for treating GM animals as veterinary drugs is based on the idea that the proteins they express will affect the animals and humans that eat the meat or fish in a similar way to a drug. The limitations of this approach have already been highlighted in addressing an application to market GM fish, but the problems with GM mosquitoes may be even more difficult, since many potential impacts arise as a result of complex interactions between the insects, humans and the environment.

NAPPO is the North American Plant Protection Organisation: member countries are Canada, the US and Mexico. Its aim is to protect plant resources against plant pests at a regional level and globally as part of the International Plant Protection Convention (IPPC). Luke Alphey of Oxitec has been a member of the NAPPO Expert Working Group on RSPM 27 ("Importation and Confined Release of Transgenic Arthropods in NAPPO Member Countries") since 2006.[85] Transgenic "sterile" insects are referred to in Guidance on "Confined Field Release" of transgenic arthropods issued by NAPPO in 2007[86], written with assistance from Oxitec.[87] The Guidance defines "confined field release" to include not only physical confinement, such as caged releases, but also releases where establishment and spread of GM insects is restricted by "*biological, temporal, or geographic mechanisms*". The NAPPO guidance and the use of the term "sterile" appears to be part of an attempt by Oxitec to claim that its insects have "biological containment" and therefore that open releases of the insects should not count as open releases of GMOs for the purpose of regulation (despite the facts that they mate with wild females; and that some of the transgenic insects will survive).

Caged trials of Oxitec's flightless female *Aedes aegypti* were conducted in Chiapas Mexico in 2008, working jointly with US researchers funded by the Gates Foundation.[88] Mexico's national regulations on transboundary movement (import/export) and contained use of GMOs entered into force in July 2011.[89] Mexico also has legislation on GMOs for use as food and feed but no specific laws or regulations on GM insects.[90]

The World Health Organisation

Oxitec's Luke Alphey has been a member of the World Health Organisation (WHO) Scientific Working Group on Dengue since 2006.[91] Alphey contributed to the WHO's 2009 technical consultation meeting on GM mosquitoes, run jointly with the US Foundation for the National Institutes of Health (FNIH).[92] The main recommendation of the meeting was that a working

group be charged to produce a guidance framework for the evaluation of GM mosquitoes for malaria and dengue control. The WHO/FNIH working group is supposed to propose quality standards for assessing safety and efficacy and also address ethical, legal, social and cultural issues during the design, conduct, recording and reporting of all phases of GM mosquito field trials prior to deployment. In its report WHO-TDR states: "*The guidance framework is intended to foster standardization of procedures, comparability of results and credibility of conclusions with regard to independent testing (without conflicts of interest) of various GMM* [GM mosquito] *strategies*". A guidance framework working group was established, which held its first meeting in April 2010, and draft guidelines were published for consultation in late October 2012.[93]

In April 2008, WHO-TDR began to support an international consortium to engage with countries where dengue and malaria are endemic about the use of GM mosquitoes. The MosqGuide project was set up to develop best practice guidance relating to the range of requirements for deployment of genetically modified (GM) mosquitoes to control mosquito-vectored disease, specifically malaria and dengue. Oxitec's head of Regulatory Affairs, Camilla Beech, is joint project manager for the Mosqguide project[94] and Beech and other Oxitec staff are co-authors on the project's publications, alongside others such as Margareth Capurro, who is running Oxitec's experiments on behalf of their partners at the University of São Paulo (USP) in Brazil.[95,96] In an update from the project Beech reports that Brazil was used as an example in the original Mosqguide paper for the steps it had taken to draft a new regulation that covers GM insects, but that the regulator CTNBio did not wait for this regulation to be completed before approving releases of Oxitec's GM mosquitoes in 2010.[97] The approval followed a 2007 meeting in London, organised by UK Trade and Investment (UKTI), where it was agreed that Oxitec and the Ministry of Health's scientific institute Fiocruz should initiate a collaboration to evaluate Oxitec's technology in the field in Brazil, with a view to commercialising it, and that "*Brasil's current GM regulations are unlikely to hamper or slow down this step*".[98] The risk assessment for the releases was kept secret on the request of Oxitec's partner Margareth Capurro.[99] The WHO-funded Mosqguide project has not explained why abandoning the regulation and not publishing the risk assessment as a result of a trade agreement between the UK and Brazil should be considered by the WHO to be "best practice" in engagement.

In April 2012, the Final Project Report for MosqGuide was submitted to TDR: however, only parts of the report will be made public[100].

An application was made to CTNBio in July 2012 to conduct further large-scale releases of Oxitec's GM mosquitoes in Brazil.[101] A decision on this application has not yet been reported.

Oxitec was strongly criticised for failing to seek informed consent for its releases of GM mosquitoes in the Cayman Islands, for choosing a country with no biosafety law to conduct its first experiments, for not publishing a risk assessment for consultation, and for the poor quality of the risk assessment that was ultimately released after the experiments had been completed as a result of a parliamentary question in the UK.[102] Subsequently, the company has claimed that public relations exercises conducted under the auspices of the Mosqguide programme are sufficient to inform the public. These include a jingle claiming that Oxitec's GM mosquitoes are "the solution" to dengue.[103] Although Oxitec reports only positive reactions, the Brazilian press has reported criticism both from local people and from scientists.[104,105] Prior to its collaboration with Oxitec, the WHO was clear that fully informed consent is needed for releases of GM mosquitoes into a community[106,107] and the new draft WHO/FNIH guidance also emphasizes the importance of informed consent. Yet, under the Mosqguide programme the WHO seems happy to endorse a PR exercise as if this were "best practice".

The leader of the Mosqguide project, John Mumford of Imperial College, is a member of the WHO/FNIH working group on GM mosquitoes, as well as the EFSA working group on GM insects (see above).[108] Other members of the WHO/FNIH working group listed in the draft guidance include Michael Bonsall (responsible for the biosafety section) and John Mumford. Luke Alphey of Oxitec is listed as a contributor. Although other groups are producing guidance on risk assessment, the WHO/FNIH Guidelines are the only means through which the efficacy of releasing GM mosquitoes is supposed to be assessed i.e. whether or not they can be successful in achieving their objective of improving public health. Many scientists have expressed doubts about whether Oxitec's approach will really work for mosquitoes[109,110,111] and there is also a possibility that it could actually increase the risk of more severe forms of dengue fever if it is only partially effective.[112] It is therefore a serious concern that open release experiments of GM mosquitoes have been supported by the Mosqguide project before the WHO/FNIH guidelines have been agreed.

WHO-TDR's Capacity Building Programme, led by Dr Yeya Touré, has conducted courses in biosafety in relation to GM mosquitoes in regional training centres in Africa, Asia and Latin America for 148 participants from 51 countries.[113] Touré was aware of Oxitec's Cayman Islands trials but apparently did not regard them as problematic, despite one of Oxitec's research partners stating that he would "never" release GM mosquitoes the way the company did.[114,115] He is also a member of the WHO/FNIH working group.

The Cartagena Protocol on Biosafety

Oxitec's Regulatory Manager, Camilla Beech has represented the company in an open-ended online forum on specific aspects on risk assessment (including GM mosquitoes), convened under the Cartagena Protocol on Biosafety (CPB), an international treaty under the UN Convention on Biological Diversity.[116] This has provided input into the work of the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management under the CPB, which has produced draft risk assessment guidance for GM mosquitoes (but not for other GM insects).[117] The AHTEG subgroup on living modified mosquitoes is led by Dr. Eliana Fontes of the Brazilian biotech research organization Embrapa, together with biosafety experts from Cuba and Malaysia and an observer from the European Biosafety Association, who works for Bayer Crop Science.[118,119,120] The draft Guidance was not adopted at the 2012 meeting of the parties to the CPB but the AHTEG will continue with its work.

The CPB covers the transboundary movement of living GM organisms from one country to another. Parties to the CPB are required to notify the Biosafety Clearing-House (BCH) of decisions to import or release living modified organisms into the environment (Article 20 of the Protocol). Malaysia did this and submitted a summary of its risk assessment, as required, but Brazil simply ignored this requirement and the Cayman Islands were not covered by it as they are not a Party to the agreement.

More detailed requirements apply to the export of GM mosquito eggs from the UK because the European Regulation which implements the CPB includes a requirement for a transboundary notification to non-Parties such as the Cayman Islands, and requirements for notifications, including risk assessments, to meet European standards and to be copied to the UK and EU authorities and to be made available under environmental information laws. Oxitec did not follow these requirements. There were considerable delays in access to their risk assessments, which were subsequently criticised by independent scientists and NGOs, and no European standards yet exist because there is no guidance.[121]

Thus, the requirements of the CPB have to date made no practical difference to Oxitec's releases of GM insects, except in Malaysia, where the authorities did publish a summary of the risk assessment on the Biosafety Clearing House and accept comments on it.

United Nations Development Programme (UNDP)

Oxitec and the WHO Collaborating Centre for Vectors based at the Institute for Medical Research (IMR) in Malaysia conducted three intensive workshops on risk assessment of GM mosquitoes attended by delegates from Oxitec and the IMR and experts from the UK, Malaysia and India and later Thailand, USA, Zambia and Zimbabwe (in 2007, and July and November 2008). [122,123,124,125] A report of the Malaysia workshop, on which Oxitec's Camilla Beech is the lead author[126], was used as part of the process of obtaining regulatory approval for Oxitec's trials in Malaysia (where about 6,000 GM mosquitoes were released in early January 2011). A further workshop on Risk Communication on Transgenic Insects was held in Malaysia in March 2010, led by Oxitec's Seshadri Vasan.[127,128,129] The Malaysian experiments were controversial and the risk assessment has been criticised by scientists at the Max Planck Institute.[130] To date, proposed further trials have not taken place.

These workshops were sponsored by the United Nations Development Programme (UNDP) as part of its Biosafety programme.[131]

A UNDP-sponsored risk assessment workshop on GM mosquitoes in India, attended by Oxitec, included a representative of the Entomology Research Unit, Maharashtra Hybrid Seed Company Ltd (Mahyco)[132], which commercialises pest-resistant GM cotton (Bt cotton) in India in a joint venture with Monsanto. Oxitec's commercial partner in India is Gangabishan Bhikulal Investment and Trading Limited (GBIT), which created Mahyco.[133] There has previously been criticism of Oxitec's decision to export GM mosquito eggs to India in 2008 in collaboration with a different private sector institution, the International Institute of Biotechnology and Toxicology (IIBAT).[134] Monsanto may be interested in using GM bollworms as a means to try to stop the spread of pink bollworms which have developed resistance to the Bt toxin in its GM cotton.[135] Pink bollworms were first reported in India in 1842 when the British brought in new varieties of cotton to replace native cotton plants that must have had natural resistance to the pink bollworm.[136] The larvae of the pink bollworm bore into cotton bolls and feed on the seeds, which are a major source of vegetable oil, and pink bollworms also feed on okra. This means the presence of dead GM larvae in the food supply could be a major problem.

Guidance for the risk assessment of GM insects, including both GM mosquitoes and agricultural pests, is now being developed by the Department of Biotechnology in India.[137] It is unclear what role other departments and regulators will have to play.

Evolving resistance to Bt toxins in GM crops has also been reported in pink bollworms in China.[138] Oxitec has stated in some of its presentations that it is collaborating with SIPPE in China (the Institute of Plant Physiology and Ecology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences).

Although GMOs are regulated in both India[139] and China[140], neither country has any specific laws or regulations to cover the open release of GM insects into the environment or food chain.

Consequences of Oxitec's infiltration of the regulatory system

Oxitec's infiltration of the regulatory system has led to:

- The apparent abandonment by the WHO of any requirement for fully informed consent before making open releases of genetically modified mosquitoes;

- Open releases of GM mosquitoes and GM fluorescent bollworms without any specific regulation or guidance to cover GM insects;
- Failure to publish full risk assessments for consultation before any of the company's open releases of GM insects;
- The omission of many important issues from risk assessments and draft regulatory guidance.

Oxitec chose a British Overseas Territory with no biosafety law (the Cayman Islands) as the site for the first open releases of GM insects in the world. Its risk assessment for Brazil was withheld from public scrutiny and releases were made before a draft regulation on GM insects was finalised or adopted. The company has also made two attempts to class open releases of its GM insects as "contained use" (based on misleading claims of "biological containment" made at NAPPO and in the UK): if it had been successful there would be no public consultation or public risk assessment in North America or the UK.

Planned WHO/FNIH Guidelines are supposed to cover efficacy as well as safety, but these have only recently been published as a draft. This means that there are no guidelines for assessing the claimed benefit of releasing GM mosquitoes on the tropical disease dengue fever, despite the fact that this claimed benefit is highly controversial amongst scientists. For other species such as olive flies the efficacy of Oxitec's approach has also been questioned by experts in the press.[141]

Liability

Oxitec works in partnership with local institutions, including universities and government-run labs. Whilst the company argues that this allows it to be more responsive to local conditions, this approach also raises important questions about who will be liable if anything goes wrong. In Brazil, for example, the local partner USP submitted the risk assessment to the regulators and is responsible for running the experiments. This means liability for any problems caused by errors or omissions in the risk assessment, or for failure to obtain informed consent, may fall on the partners rather than on Oxitec itself.

Conclusions

The biotech industry, with the involvement of Syngenta, is planning to commercialise GM insects around the world. Thousands of species could be genetically modified in future, including a large number of agricultural pests and several species of mosquito, as well as beneficial insects such as bees and ladybirds. The leading company working in this area, Oxitec, has received a grant from Syngenta and most of its management and consultants are ex-Syngenta staff. Syngenta has effectively taken over the management of Oxitec, beginning in 2006, when it began to seek to influence regulatory processes for GM insects around the world. These have included:

- Attempts to define 'biological containment' as contained use, by-passing requirements for risk assessments and consultation;
- Attempts to avoid any regulation of GM agricultural pests on crops which will end up in the food chain;
- Avoidance of any discussion of how GM insects can be contained at a site, or products produced using GM insects can be labelled;
- Exclusion of many important issues from risk assessments;
- Failure to follow transboundary notification processes for exports of GM insects correctly;

- Undermining the requirement to obtain informed consent for experiments involving insect species which transmit disease;
- Attempts to avoid liability for any harm if anything goes wrong;
- Pushing ahead with large-scale open releases of GM mosquitoes before relevant guidance or regulations are adopted.

Regulatory processes will not adequately protect human health and the environment if vested interests are allowed to continue to set the agenda. Society must have more say about whether GM insects should be released into the open and, if so, which species under what conditions.

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