Genetically modified insects

A response from the British Ecological Society to the House of Lords Science & Technology Committee

23 September 2015

The British Ecological Society

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The British Ecological Society (BES) is the UK's academic learned society for ecological science and the oldest institution of its kind in the world, established in 1913. The BES has nearly 5,000 members, representing the full scope of ecological research and practice and breadth of ecological careers, from undergraduate students to established professionals.
The Society welcomes the opportunity to respond to the Committee's inquiry on Genetically Modified (GM) Insects and asks it to consider the ecological impacts of the release of GM insects, particularly for gene drive methodologies. There are early models and simulations on the ecological impacts of some GM technologies that make insightful discoveries; further research is needed on these impacts, on a case by case basis.

Introduction

1. The most advanced applied research on genetically modified (GM) insects is being undertaken with the aim to control insect vectors of human diseases such as mosquitos in the spread of malaria and dengue, and to control populations of crop pests, including the diamondback moth, olive fruit fly, and Mediterranean fruit fly. There is potential for GM insects to be used to control insect-borne diseases in livestock including bluetongue and Schmallenberg virus[1], and in wildlife conservation, such as the control of avian malaria (*Plasmodium relictum*) which continues to threaten multiple native species in Hawaii after the introduction of mosquitos in the early 19th century[2].

2. The potential benefits that GM insect control could bring are obvious. This is especially significant in the case of malaria, where parasites are becoming resistant to drug treatments and mosquitos are becoming resistant to pesticides[3], and for dengue where no licensed vaccine or dedicated therapy exists, and prevention and control solely depends on effective vector control measures[4].

3. GM insect control presents numerous benefits when compared with the use of broad spectrum insecticides; it does not rely on the release of toxic chemicals into the environment, and

[1] GM Insects and Disease Control. (2014) POSTnotes POST-PN-483.
[2] The Long Now Foundation, Work Group 1 -Paradise Regained. Eradication of Invasive Mosquitoes and Disease http://longnow.org/revive/case-studies/#workgroup1 [Accessed 19.08.15]
[3] Hemingway J, Ranson H. (2000) Insecticide resistance in insect vectors of human disease. Annual Review of Entomology, 45:371-391
[4] World Health Organisation. Dengue and Severe Dengue Factsheet: www.who.int/mediacentre/factsheets/fs117/en/ [Accessed 18.08.15]

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works well against targets that are difficult to find, and /or difficult to reach by conventional practices[5]. These insects are unlikely to yield direct off-target effects however there may be some indirect impacts on wild populations and communities.

GM Insect Technologies

Gene Drive

4. Gene drive systems promote the spread of genetic elements through populations by assuring that they are inherited more often than Mendelian segregation[6] would predict. Gene drive techniques insert a desired genetic modification into an organism along with DNA that increases the rate at which the change is passed to the next generation. This method has the potential to rapidly modify an entire population, depending on generation times[7].

5. With the recently developed 'CRISPR', a gene-editing technique that allows researchers to make precise changes to DNA, gene drive has become a realistic tool with tremendous potential to address insect vectors of disease. Bier & Gantz (2015) showed that a mutagenic chain reaction which is based on the CRISPR could be used to spread a mutant gene onto both chromosomes in a pair, thereby passing on this genetic modification to nearly all of their offspring. In theory at least, the application of gene drive could mean the spread of a malaria resistant gene throughout an entire breeding population of mosquitos in one season[8].

6. Bier and Gantz joined a host of other scientists in a letter to Science calling for multiple strategies to ensure the safety of gene drive experiments, since the accidental release of gene drive insects for the last could have unpredictable ecological consequences[9]. Some of these consequences are discussed later in the response.

Homing Endonuclease Genes

7. A gene drive system using Homing Endonuclease Genes (HEG) is aimed at population suppression. HEGs are naturally occurring 'selfish genes' or 'parasitic genes'; these are genes that exploit the host cell functions in order to copy themselves into a particular sequence of DNA, again at a higher rate than would be expected in Mendelian segregation. HEGs can be engineered to cut a sequence in the DNA in the middle of an essential gene, therefore disrupting its function. For example, this could be for a gene that is essential for disease transmission but not essential for the host[10 11].

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[5] Alphey L, Nimmo D, O'Connell S, & Alphey N. (2008). Insect population suppression using engineered insects. In Transgenesis and the management of vector-borne disease (pp. 93-103). Springer New York.

[6.] Genes in sexually reproducing organisms normally have, on average, a 50% chance of being inherited. Single-gene functions are usually inherited in one of several patterns depending on the location of the gene and whether one or two normal copies of the gene are needed for the disease phenotype to manifest.

[7] Oye K *et al*. (2014) Regulating gene drives. Science: 345 (6197), 626-628.

[8] Bier E, Gantz V (2015) The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. Science 348 (6233) 442-444.

[9] Akbari O S. *et al.* (2015). Safeguarding gene drive experiments in the laboratory. Science 349 (6251), 927-929.

[10] Burt A (2003) Site-specific selfish genes as tools for the control and genetic engineering of natural populations Proceedings of the Royal Society B 270, 921-928.

[11] Deredec A, Burt A, Godfray HCJ. (2008) The Population Genetics of Using Homing Endonuclease Genes in Vector and Pest Management. Genetics 179(4):2013-2026.

8. The rapid transmission dynamics of a HEG have been shown to work in caged mosquito populations[12], and further, the HEG technique has been used to cut the paternal X chromosome in the malaria vector (*Anopheles gambiae)*, preventing it from being transmitted to the next generation. This technique resulted in fully fertile mosquito strains that produced more than 95% male offspring[13].

Sterile Insect Technique (SIT)

9. The Sterile Insect Technique (SIT) is not classified as genetic modification, but its application and precursor to GM induced sterility merits inclusion here. SIT is a self-limiting, population suppression system whereby radiation-sterilised male insects are released to mate with their wild counterparts, thereby reducing the reproductive potential of the target population.

10. Application of SIT within an area-wide integrated pest management programme (AW-IPM) successfully eradicated New World screwworm (*Cochliomyia hominivorax*) from the USA and Mexico[14], and was successfully used to eradicate the parasite in Libya just four years after it became established in the late 1980s[15]. SIT is also used widely in Florida and California to control populations of Mediterranean fruit fly (*Ceratitis capitata*), and has been used for the control of the pink bollworm moth (*Pectinophora gossypiella*) and the codling moth (*Cydia pomonella*).

11. The application of SIT has been largely restricted to agricultural pests, although it has been used as a component of AW-IPM to create tsetse- free areas within Zanzibar[16]. SIT requires sterilization of a large number of insects, which can greatly impact on their fitness, making them less competitive with wild insects once released. This, along with the costs associated with SIT (i.e. expensive radiation sources and costly security), has limited its application in mosquitos, where few trials have achieved eradiation of diseases like malaria and dengue in the target area, or long term control[17].

Release of insects carrying a dominant lethal (RIDL)

12. The RIDL technique, developed by British biotech company Oxitec is a genetic enhancement of the SIT, whereby transgenic technology is used to insert a lethal gene into the insects. This gene produces a non-toxic, lethal protein (tTAV) that allows larval development, but prevents the offspring of RIDL insects surviving into adulthood[18].

13. RIDL has several benefits over SIT; it has a heritable visible genetic marker so that sterile and wild insects can be distinguished. There is no risk of accidental escapes of fertile, mass-reared pests

[12] Windbichler *et al.* (2011) A synthetic homing endonuclease-based gene drive system in the human malaria mosquito. Nature 473,212–215
[13] Galizi R, Doyle LA, Menichelli M, *et al.*(2014) A synthetic sex ratio distortion system for the control of the human malaria mosquito, Nature Communications 5: 2041-1723
[14] Van der Vloedt A, Klassen W. The development and application of the sterile insect technique (SIT) for New World screwworm eradication. Food and Agriculture Organisation of the United Nations: http://www.fao.org/3/a-u4220t/u4220T0j.htm [Accessed 27.08.15]
[15] Lindquist D, Abusowa M, Hall M (1992), The New World screwworm fly in Libya: a review of its introduction and eradication. Medical and Veterinary Entomology, 6: 2–8.
[16] Vreysen J (2006) Prospects for area-wide integrated control of tsetse flies (Diptera:Glossinidae) and trypanosomosis in sub-Saharan Africa. Rev Soc Entomol Argent 65:1–21.
[17] Scolari F, Siciliano P, Gabrieli P, Gomulski LM, Bonomi A, Gasperi G, Malacrida AR (2011) Safe and fit genetically modified insects for pest control: from lab to field applications. Genetica 139(1):41-52.
[18] Oxitec Ltd http://www.oxitec.com/

as there would be using SIT. There is also a female-specific variant of RIDL (fsRIDL) that produces male-only cohorts of the insects on a large scale[19].

14. Field trials using RIDL male mosquitoes (*Aedes aegypti)* have been undertaken in the Cayman Islands, with the aim of controlling dengue infections. This resulted in a suppression of the wild population by 80% relative to nearby untreated areas [20 21]. There is also evidence of this technology reducing the local *Ae. aegypti* population by 81% and 95% in field trials in Brazil[22].

15. The United States Department of Agriculture Environmental Impact Statement on the use of genetically engineered fruit fly and pink bollworm in plant pest control programs concluded that the sterile insect technique using RIDL, was the 'preferred alternative' to radiation-based SIT, and state that 'the greatest potential impacts occur with the no action alternative, in that potential pest risks are not static and continue to increase with expanding trade and travel'[23].

Ecological impacts of GM Insects

16. The ecological impacts of GM insects (both direct and indirect) will vary according to the methods used, and the reproductive behaviour, habitat, life cycle and ecology of the insect and the geography of the target population. Therefore the ecological consequences of the release of GM insects should be ascertained on a case by case basis. The ecological considerations of gene drive, a self-sustaining GM technology, are distinct from the self-limiting release of sterile males; in SIT and RIDL, impacts will largely depend on the number of insects released. With gene drive, one release could be sufficient to change an entire population. In both cases, the change in population is likely to have further indirect impacts on inter and intra-specific competition within the community. An understanding of the ecological consequences of gene drive technologies should therefore be made an urgent priority if we are to gainfully utilise its potential.

Number of insects released

17. Suppression technologies such as SIT and RIDL require flooding local populations with transformants. For RIDL, it has been modelled that a constant release may require between 1.5 and 2.2 times more insects to achieve local elimination[24]. This mass release of insect populations into a target location is likely to have ecological implications, some of which are discussed below.

Incomplete SIT/ RIDL releases

18. The radiation methods used to sterilise males in SIT can result in a small proportion of fertile males; release of these incompletely sterilized males does not reduce the population as efficiently.

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[19] Slade G, Morrison N. (2014) Developing GM insects for sustainable pest control in agriculture and human health. *BMC Proceedings*. 2014;8(Suppl 4):O43.

[20] Harris A, Nimmo D, *et al.* & Alphey, L. (2011). Field performance of engineered male mosquitoes. Nature biotechnology, 29(11), 1034-1037.

[21] Harris A, Nimmo D, *et al.* & Alphey, L. (2012). Successful suppression of a field mosquito population by sustained release of engineered male mosquitoes. Nature biotechnology 30 (9), 828-830.

[22] Carvalho DO, McKemey AR, Garziera L, *et al*.(2015) Suppression of a Field Population of *Aedes aegypti* in Brazil by Sustained Release of Transgenic Male Mosquitoes. Olson KE, ed. *PLoS* Neglected Tropical Diseases 9 (7):e0003864.

[23] Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs United States Department of Agriculture Marketing and Regulatory Programs Animal and Plant Health Inspection Service Final Environmental Impact Statement—October 2008 https://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf [Accessed 05.09.15]

[24] Bonsall, M., Yakob, L., Alphey, N., Alphey, L. (2010) Transgenic control of vectors: the effects of interspecific interactions. Israel Journal of Ecology & Evolution, Vol 560 353-370.

In the case of mosquitos, the release of males does not increase bite rate (only female mosquitos bite), but a larger release of transformant insects is needed to collapse the population[24].

19. The incomplete penetration of the lethal gene in RIDL is also feasible. However in this case, it would still mean that a proportion of the transgenic offspring that survive to adulthood would retain the transgene – therefore enhancing the overall suppressive effect of RIDL[25].

Interspecific competition

20. The interplay of interspecific and intraspecific competition dictates the coexistence of species and plays a major role in the structure of ecological communities. Bonsall *et al*. (2010) modelled the effects of SIT and RIDL control strategies on coexistence and exclusion in two vectors (e.g. two species of mosquito) [24]. This linear study showed that conventional and transgenic control techniques can affect the local existence or exclusion of vector species, and can allow the coexistence of species that would not otherwise necessarily occur; that is although we would expect a competitor to move in to the empty ecological niche after the end of a successful control programme, this study showed that the competitor may be able to *before* the existing occupant was removed. This may have important consequences for the persistence of disease, depending on if the competitor is a competent vector, or is much less competent than the species that is the focus for control. Again, this should be investigated on a case by case basis. For instance, malaria is transmitted by several species of mosquito, whereas *Aedes aegypti* is the principal dengue vector in most of the world (*Aedes albopictus* is a vector in some regions). GM transformants may need to be developed and released for several species in the locality.

21. The outcome of interspecific competition depends on the larval habitats and development times of wild and transformant vectors, which will vary according to season and location. Therefore there is a need to understand the effects of individual demographic characteristics – survival, fecundity and development- to predict community interactions and vector control. Further research is needed on these types of ecological interactions.

Transient dynamics

22. Bonsall *et al*. also discuss 'Allee effects' introduced by SIT and RIDL control strategies; Allee effects are a phenomenon whereby there is a decline in individual fitness when population densities are low, resulting in a further decline in abundance[24]. While in the case of SIT and RIDL, this can lead to local extinction of the focal control species; it also introduces stable and unstable coexistence points among competing vectors. Bonsall *et al*. call for an awareness of these types of transient dynamics when monitoring the emerging results of control programmes.

Migration

23. Yakob *et al.* (2008) model the potential risk of inadvertent population increase through release of SIT and RIDL for the control of *Aedes aegypti*; the vector for dengue[25]. They explain that survival from the larval to the adult stages of the mosquito is severely restricted by resources, therefore a reduced density of pre-adult stages may actually result in an increase the in the adult population. This effect may be seen in SIT control, since it acts by lowering the number of offspring (larvae) in the next generation. This effect would be unlikely where there are isolated areas with

[25] Yakob L, Alphey L, Bonsall M (2008) Aedes aegypti control: the concomitant role of competition, space and transgenic technologies. Journal of Applied Ecology 45:1258-1265.

high proportions of sterile males, but would become a problem where sterile males migrate from the target area to neighbouring areas.

24. Yakob *et al*.'s theoretical study showed that there was indeed an *increase* in wild vectors throughout all non-target areas into which the sterile males had migrated. The magnitude of this increase declined with distance from the release site. This result was not evident in simulations based on the use of RIDL, which acts after the density dependent processes. With RIDL, all neighbouring wild vectors re-stabilise at lower populations compared to the pre-control level. They also stabilise at this lower level more quickly than with SIT[25].

The food chain

25. The local eradication of insects may have an impact on organisms at higher trophic levels that rely on them as a food source; however there is little evidence available on which to establish exactly what these impacts would be for transformant insects. One study that monitored the environmental impact of a 90% reduction in mosquitoes in Germany (through non GM technologies) showed that while there has been a reduction in mosquitoes 'to a tolerable level', the 'ecosystem as a whole has not been damaged'. Other insects continued to develop in the absence of large mosquito populations, providing a 'food resource for birds, amphibians and bats'[26].

26. Eradicating mosquitos in the Arctic may impact on the diets of migrating birds (although few show up in bird stomach samples), and on the migratory routes of caribou. Elsewhere, the absence of mosquito larvae in water pools may impact on the diets of fish and other animals, and mosquitoes also act as a pollinator for thousands of plant species (although few which humans depend on as a food source). Expert opinion differs, but there is some consensus view that these 'services' would be filled, in the majority of cases, by other organisms that would inhabit the empty ecological niche[27].

27. Investigation of the wider impacts of the long term SIT control of the Mediterranean fruit fly (*Ceratitis capitata*) in Florida and California may also help to shed some light on these types of interactions within the food chain.

28. Under this theme it is pertinent to note that the ecological impacts of insecticides (the current most widespread insect control mechanism) and the subsequent detrimental accumulation of toxins throughout the food chain are well documented[28 29].

Disease free wildlife

29. Nagel & Peveling (2005) summarise the impact of the eradication of screwworm on white-tailed deer in the United States; overall, both domestic and wild animals, including some endangered deer species benefited enormously, however the surge in deer numbers in turn caused an increase in the deer parasitising Gulf Coast tick, which then went on to infect cattle. The release of predator species from disease will also have an impact on prey species. These kinds of interactions again will differ according to ecosystems[30].

[26] Becker N (1997) Microbial control of mosquitoes: management of the Upper Rhine mosquito population as a model programme. Parasitology Today 13 (12): 485-487.
[27] Fang J. (2010) Ecology: A world without mosquitoes. *Nature News*, *466*(7305), 432-434.
[28] Brown, Anthony William Aldridge. *Ecology of pesticides*. John Wiley & Sons 1978. Sánchez-Bayo, Francisco. *Ecological Impacts of Insecticides*. INTECH Open Access Publisher, 2012.
[29] *Ecological Impacts of Insecticides*. INTECH Open Access Publisher, 2012.
[30] Nagel P, Peveling R. Ch 5. Ecological Consequences of Eradication in Dyck, V. Arnold, Jorge Hendrichs, and Alan S. Robinson. *Sterile insect technique*. IAEA, 2005.

Resistance

30. There is potential for an evolutionary response to GM technology, such that resistance develops to the modified gene. This can be monitored effectively, and is seen in other control methods including insecticides. A more hazardous risk is the evolution of more virulent strains of the pathogen following GM control[31]. There is very little research published on this issue, but examples can be found; for instance Medlock *et al*. (2009) model the evolutionary impact of different GM mosquito strategies on dengue virulence in both humans and mosquitoes[32]. Their model suggests that control strategies which raise mosquito mortality pose less of a risk of causing increased virulence to humans than strategies that block the transmission of the disease, or reduce mosquito biting. More research is needed to test such models.

Research funding

31. While there appears to be some funding available for the technical development of these technologies within the lab (i.e. through BBSRC, Wellcome Trust and the Bill & Melinda Gates Foundation), securing funding for field trials is extremely difficult. Comprehensive applied projects may require funding for several deliverables, including a lab component, a modelling component and a field component, interacting with each other to address knowledge gaps. This requires sufficient interdisciplinary funding and a range of expertise, including a good understanding of the ecology of vector populations.

32. Traditional funders require the delivery of a project within a defined timescale, which cannot be guaranteed due to uncertainties in the regulatory system of this technology. Conversely, regulators are unable to provide permits for research which is not yet funded. As such, field trials to date have been exclusively funded by risk capital to a private sector entity. EU funding could play a part here, but in practice the negative perceptions of GMOs in some European countries makes this funding extremely difficult to secure.

33. This problematic funding landscape is amplified for non-commercial GM insect projects, including conservation applications such as the control of avian malaria, which is unlikely to provide attractive financial returns to a commercial developer. This issue is also applicable for any target with relatively small potential market; the species-specific nature of GM insect technologies means that there are many more examples of beneficial applications with small markets than large ones.

Regulatory Framework

34. In the EU, applications to release GM insects are assessed under Directive 2001/18/EC[33] and are bolstered somewhat by the European Food Safety Authority (EFSA) guidance on the risk assessment of GM animals[34]. There are international guidelines for the release of (non GM) insects which should also be considered when regulating the mass release of GM insects[35].

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[31] Alphey L. (2014) Genetic control of mosquitoes. Annual Review of Entomology 59, 205-224.
[32] Medlock J *et al*. (2009) The impact of transgenic mosquitoes on dengue virulence to humans and mosquitoes. The American Naturalist 174.4: 565.
[33] Deliberate release of genetically modified organisms (GMOs) http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV:l28130 [Accessed 05.08.15]
[34] EFSA Panel on Genetically Modified Organisms (2013) Guidance on the environmental risk assessment of genetically modified animals. EFSA Journal 2013;11(5):3200, 190
[35] International Standards for Phytosanitary Measures No 3 (2005) Guidelines for the export, shipment, import and release of biological control agents and other beneficial organisms.

35. The current regulatory framework has numerous limitations in its application for GM insects. There are a number of risks that have a greater prevalence in GM crops than in GM insects; gene flow for instance is less of a risk in insects due to their breeding specificity. However other issues, such as 'receiving environments' and dispersal of GM organisms presents a more complex picture for GM insects.

36. A report by the Advisory Committee on Releases to the Environment (ACRE) on GM Insects[36] explores some of these issues and calls for a more holistic approach than is currently provided by the Directive which includes a consideration of the risks of alternative control methods (such as insecticides) and the risks of inaction (continued and increasing disease prevalence as insects develop resistance).

37. As stated above, the ecological risks and hazards associated with the release of GM insects is 'product' specific; i.e. the GM technology, species, lifecycle, locality, and time of year, will all impact on the ecological consequences of its release. A broad-brush approach to regulation is therefore not appropriate in this context. Assessments should be made on a case by case basis, taking into account both the benefits and the risks of the release.

Management regimes

38. The application of GM insects should be undertaken within an integrated pest management system, closely monitored with supplementary management practices. Lessons can be learnt from the good and bad management practices of herbicide resistant GM crops[37][38]. For human disease vectors, the implications of control mechanisms (both GM and non GM) on human herd immunity, and the possible effects on human health when insecticide application is terminated after GM insect release should be carefully monitored.

Further information

The BES is happy for our response to be made available publicly. If you have any questions about the content of this response or about the work of the BES, please contact Jackie Caine, Policy Manager on policy@britishecologicalsociety.org or 0207 685 2510.

[36] Advisory Committee on Releases to the Environment (ACRE) Report on the ACRE information gathering workshop on GM insects (2010) London: Advisory Committee on Releases to the Environment, DEFRA.

[37] Frisvold G & Reeves J (2010) Resistance management and sustainable use of agricultural biotechnology. Journal of Agrobiotechnology Management and Economics 13: 343-359.

[38] Tabashnik B, Gassmann A, Crowder D, Carriere Y. (2008) Insect resistance to Bt crops: evidence versus theory. Nature Biotechnology 26: 199-202.