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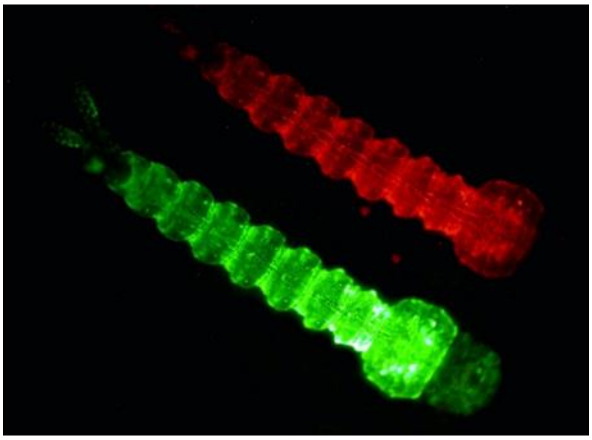
GM Insects and Disease Control



Insects play a critical role in ecosystems, but can also cause economic and social harm by transmitting diseases to humans and livestock, and damaging crops. Genetically modified (GM) insects could be used alongside other approaches to mitigate harms. This POSTnote summarises possible benefits, risks and uncertainties associated with their deployment.

Overview

- Insect-borne diseases impose a large burden on health, with about half the world's population at risk of infection.
- Insect pests cause economic losses through damage to crops and livestock.
- Climate change, changes in land use, global trade and insecticide and drug resistance are exacerbating insect pest problems.
- A potential control method is the genetic modification of insects to reduce the size of populations or replace them with less harmful forms.
- Studies of genetically modified (GM) insect releases are not yet sufficient to demonstrate their risks and benefits.
- Existing regulatory frameworks have been designed for GM crops and are not directly applicable to GM insects.

Background

Insects including mosquitoes, midges and fleas are responsible for the transmission of bacteria, viruses and parasites to humans, livestock and crops. There are currently no vaccines against some of these diseases, and in other cases drug-resistance is making existing treatments less effective. The emergence and resurgence of several insect-borne diseases (Box 1) is driving the search for new insect controls.

Effects of Insect-borne Diseases on Humans

Despite current control measures, the costs of insect-borne diseases such as malaria and dengue remain high (Box 1). There were 207 million cases of malaria in 2012.[1] Annually, there are an estimated 390 million cases of dengue infection in tropical areas.[2] Dengue resulted in an average annual economic loss of $950 million between 2001-2010 in Southeast Asia.[3] Insect-borne diseases have direct and indirect costs. For example, direct costs of malaria include personal and public expenditure on drug treatment, insecticide-treated nets, mosquito control programmes, and education and awareness campaigns. Indirect costs include working days lost and a decrease in productivity. Direct and indirect costs of malaria can decrease gross domestic product (GDP) by 1.3% in countries with high levels and is a barrier to economic development (POSTnote 360).[4]

Globalisation, changes in land use and climate change are factors expanding the geographic and host range distribution of insect-borne diseases. The World Health Organisation (WHO) considers that innovative solutions are needed to meet the challenges posed by such diseases.

Insect-borne Diseases and Livestock

Insect-borne pathogens such as bluetongue virus present a health risk to livestock (sheep, cattle, goats, horses) (Box 1).

Box 1. Potential Risks to the EU/UK

- **Human diseases:** Malaria, dengue fever, chikungunya fever, yellow fever, West Nile fever, Human African trypanosomiasis. Most of these diseases are of significant public health concerns in Africa. Chikungunya is found in Southeast Asia, parts of Africa and the Indian subcontinent. The first European outbreak of Chikungunya was in Italy in 2007.[5] Risk of it spreading in southern Europe are high.
- **Livestock diseases:** Bluetongue, Schmallenberg, lumpy skin disease, African horse sickness, epizootic haemorrhagic disease. Bluetongue virus has been detected in southern Europe and a significant outbreak reported in 2006 in northern Europe.[6] Schmallenberg virus was detected in the UK in 2012 when outbreaks were reported in northern Europe.[7]
- **Agricultural insect pests:** Diamondback moth, spotted wing drosophila, olive fruit fly, Mediterranean fruitfly. Olive fruit flies cause significant damage to olives in southern Europe, North Africa and the Middle East.[8] The Mediterranean fruit fly is a global pest.[9]

The annual global economic loss due to bluetongue is estimated to be $3 billion.[10] A large outbreak in the UK could have a potential cost estimated at £230 million.[11] Direct and indirect costs include mortality, weight loss, drop in milk yield, and trade restrictions on animals and their products.

Insect-borne Diseases and Crops

In the EU, crops such as tomatoes, maize, olives and potatoes are seriously affected by insects and insect-borne diseases. Fruit and vegetable crop yields are vulnerable to insects such as aphids, which transmit plant viruses. Despite the application of pesticides and other approaches, agricultural pests and diseases cause an estimated 40% loss of potential global food produce.[12] Effective control of insect-borne plant diseases is difficult because of distances covered by insects and their ability to colonise fields rapidly before farmers become aware of infestation. The problem is particularly acute in the tropics, where pests are a year-round problem, and supply and cost factors limit access to effective pest control methods. Climate change in other areas may increase the insect breeding period and subsequent losses.

Insect Control Strategies

Insecticides are widely used as a public health measure and for crop protection. For example, two control strategies targeting mosquitoes are indoor spraying of insecticides, such as DDT, and the use of insecticide-treated bed nets. However, synthetic insecticides can adversely affect human health and the environment,[13] which has led to tighter regulation of their use globally, such as by the Stockholm Convention on Persistent Organic Pollutants[14] and the EU Directive on the Sustainable Use of Pesticides.[15]

Alternative Control Approaches

Environmental management is an alternative control method. For example, removing breeding sites around human habitations (tyres, barrels) can be an effective way of controlling mosquito populations in urban areas. However, habitat reduction is not always a practical option such as in rural and agricultural settings (rice fields, wetlands and potable water storage tanks in areas with unreliable supply of potable water). Another approach is to introduce organisms that feed on the disease-transmitting insect, such as introducing larvae-eating fish in permanent natural water bodies to reduce malaria transmitting mosquitoes. However, the effects of such control methods on non-target species needs to be assessed prior to release (POSTnote 439).

Insecticides have been the main method of controlling insects, but their use is limited by factors such as increasing resistance, contamination of land and water bodies and effects on non-target species. It is also becoming increasingly expensive to identify, develop and register new active ingredients for insecticides. Research efforts have increased into alternative control methods for crop protection. For example, biological control methods have been used for the control of a range of pests such as the African armyworm in Tanzania.[16] However, commercialisation has proved difficult.

Sterile Insect Technique (SIT) involves the release of sterilised laboratory-reared male insects over an affected area. They are sterilised with irradiation, genetically or by infecting with a bacteria (wolbachia).[17-19] They compete to mate with wild females in a form of area-wide birth control that may locally eliminate an insect population. The first successful use of SIT was in the elimination of screwworm flies in Curacao in 1954.[20] It is effective when a single dominant insect species is responsible for pathogen transmission and repeated release of sterile males in sufficient numbers are required.[21]

Enhanced Insect Control Strategies

Genetically modified (GM) insects could be used as part of an integrated approach for insect and disease control. They could be of significant value for diseases for which there currently are no drugs or vaccines (human and livestock diseases) or limited effective pesticides are available (crop diseases). GM insects are produced by altering or inserting new genes into the DNA of insects (Box 2). The release of sterile pink bollworm (a pest of cotton) in the USA which was genetically modified to carry a fluorescent marker was the first use of GM insects in a plant pest control programme (POSTnote 360). In April 2014, the commercial release of a GM mosquito (*Aedes aegypti*) to control dengue virus transmission was approved in Brazil.[22] This is the world's first commercial GM insect release for human disease control.

Population Suppression or Replacement

For GM insect control programmes, population suppression or population replacement strategies can be used (Box 3). A population suppression strategy aims to reduce bite rate, which has been shown by epidemiological studies to reduce disease burden. A population replacement strategy aims to reduce an insect's competence to transmit a disease causing pathogen. Under various conditions, computer simulations support both strategies for control of insect-borne pathogen transmission. A population replacement strategy may be most effective for long term prevention of disease but may be more challenging to develop a commercial model for. GM release trials to date have used the population suppression approach. This is self-limiting while providing greater understanding of the risks and benefits of releases.

Box 2. Creating GM insects

Many genes have been identified that determine biology and behaviour of insects. The process of inserting these genes into an insect is called transformation. Once the genes are inserted into the organism they are called transgenes. An insect that has been altered in this way is described as transgenic or genetically modified. By injecting genetic material into insect eggs, genetically modified strains can be created carrying complex arrangements of transgenes necessary for various experimental paradigms. In the future, genome editing may be used. Genome editing is a more precise method for introducing desirable genetic traits compared to transgenic modification approaches (POSTnote 482). A variety of transgenes are used to modify insects:

- Marker genes are used to make the insects fluoresce. These allow researchers to distinguish them from the unmodified variety, which is important for monitoring them in the environment.
- Lethal genes which cause the insect to die, or genes that cause it to be unable to fly or reproduce
- Refractory genes confer resistance to a particular pathogen rendering the modified insect unable to transmit the pathogen.

Box 3. Population Suppression and Population Replacement
Population suppression is used to reduce the insect population to an extent that pathogen transmission is no longer sustainable. It is carried out by genetically engineering insects so that when they mate with wild type individuals, no viable offspring are produced. The genetic change is unable to be passed on to subsequent generations (self-limiting). Population replacement is used to reduce insect-borne pathogen transmission and is carried out by engineering insect DNA so as to stop the pathogen replicating. Through mating, this genetic change is introduced into the insect population, resulting in reduced or eliminated pathogen transmission. The genetic change is passed on indefinitely through the insect population (self-sustaining).

GM Release Trials
A UK company, Oxitec engineered GM mosquitoes for suppressing the mosquito species transmitting dengue virus. Field release trials were carried out in the Cayman Islands in 2009, Malaysia in 2010-2011, Brazil in 2011-2012 and Panama in 2014. Although, it will take a few years to determine the efficacy in dengue control, the recent release in Brazil will serve as a precedent for future commercial releases. The release trial of GM olive flies in Spain is being reconsidered by the Catalan government and the Spanish National Biosafety Commission following further studies.

Limitations of Technology
The current technology used for GM insect control has technical limitations including:
- not all species can be mass reared in the laboratory
- laboratory bred insects may not survive in field conditions
- full genomic information of most insect species is absent
- GM insect approaches are only likely to be successful if there is one main species transmitting a given pathogen.

Research and Development
There are a number of organisations funding research including the Bill and Melinda Gates Foundation Grand Challenges in Global Health initiative, the World Health Organisation Special Programme for Research and Training in Tropical Diseases, Biotechnology and Biological Sciences Research Council and the UK Technology Strategy Board. Research consortiums such as Infravec have been set up to facilitate knowledge sharing, resources and technology between different EU countries on developing new control measures for insect-borne diseases.[23] As with vaccines and insecticides, successful research and development of GM insects requires follow-up funding, such as venture capital, for the transition to commercialisation. However, direct financial returns from GM insects are uncertain and opposition to genetically modified organisms (GMOs) in some countries has discouraged investment in their development. Uncertainty over timelines from GM insect field release studies to commercialisation may also discourage investors. Currently, only small biotechnology companies are involved in GM insect development, limiting implementation.

The Benefits and Risks of GM Insects
Possible Benefits
Proponents of GM insects consider them a useful tool in a tool kit used to control insect-borne pathogen transmission. There are difficulties in implementing conventional strategies on large scales with limited resources and increased insecticide resistance. Possible benefits of GM insects include:[24]
- fewer effects on non-target species than pesticides
- wide coverage and the targeting of insect populations inaccessible to conventional insect control methods; for example, GM male insects will disperse and seek out females without human intervention
- a possible reduction in the amount of insecticides and any associated toxic residues in the environment
- independence from socio-economic status or requirements for behavioural changes in the release area.

Possible Risks
Some environmental NGOs, such as GeneWatch UK, have highlighted possible risks of GM insects such as:[25, 26]
- the development of resistance in the insect or pathogen, for example, a replacement strategy could select for more virulent pathogens
- the elimination of one species may give rise to the establishment of another insect species
- the newly introduced gene may transfer into another species (‘horizontal gene transfer’)
- the unknown effects of GM insect larvae in crops on human health and the environment
- the damage caused to ecosystems may be irreversible.

Mitigating Possible Risks
The release of GM insects to control disease is controversial. Some academics suggest more studies to provide appropriate regulatory comparators to ascertain environmental impacts and unintended effects on other organisms before a GM insect release is permitted in the EU. Researchers developing GM insects acknowledge the need to proceed cautiously. However, they argue that any significant ecological harm would be detected during trial releases and horizontal gene transfer into other species is limited by the species barrier and by mechanisms that inactivate foreign genetic material.

Regulation of GM Insects
The Deliberate Release Directive (2001/18/EC) provides details on the procedures to be followed in the EU for the evaluation and authorisation of release of GMOs. Existing legislation was designed to govern all GMOs, but its implementation has so far been focused on the regulation of GM crops; described as the ‘plant paradigm’. However, a number of scientific working groups have released guidance on GM insects (Box 4).

For a non-commercial release of GMOs, the Department for Environment, Food and Rural Affairs (Defra) makes a decision in consultation with the Advisory Committee on Releases to the Environment (ACRE). For a commercial release, Defra performs an initial evaluation of the application with ACRE’s input. It is then sent to all EU member states with the European Food Safety Authority (EFSA) providing a scientific opinion. Member states must then reach a qualified majority (255 votes out of a total of 345) to approve any release. This has resulted in GM approval requests being blocked for several years.[27] The EU Parliament Committee on Environment, Public Health and Food Safety has proposed amendments to new authorisation rules on the cultivation of GM crops negotiated by the EU Council of Ministers (that do not apply to GM insects), which will be voted on November 2014 (POSTnote 482). Commentators suggest that the amendments will make approval of any commercial releases unlikely.

Regulations outside the EU

The EU regulates the process of genetic modification but an insect with the same traits generated by other means, such as by using radiation, is not regulated. Outside the EU, some countries regulate the organism produced rather than the process producing it (Box 5). Internationally, the Cartagena Protocol on Biosafety applies to the transboundary movement, transit, handling and use of all GMOs that may "have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health". The extent and nature of regulations vary between countries outside the EU. The African Union has drafted the African Model Law on Biosafety and recently individual African countries, have created legislation regulating release of GMOs, such as the Kenyan 2009 Biosafety Act. The ability of insects to cover long distances and cross international borders means regulation of transboundary movement is required, particularly in the case of a self-sustaining, population-replacement strategy that could spread over continents.

Risk Assessment

Risk assessments undertaken in accordance with the Cartagena Protocol form the basis for EU decisions. Risk assessment involves hazard and exposure identification, hazard characterisation, exposure characterisation, risk characterisation, risk management and the overall evaluation of risks. In the EU, applicants only assess the risks to human health and the environment of a GMO. Risk assessments used for the recent release of GM insects has been criticised.[28] Some policy analysts and academics have suggested that when considering GM insects, the benefits and risks could be equally evaluated. A risk benefit analysis (RBA) involves the assessment of beneficial and adverse effects. It also compares the benefits and risks of proposed products or technologies with that of other alternatives and status quo. For example, the benefits of GM insects may include the elimination or reduction of disease occurrence or a reduction of environmental harm.

Box 4. Guidance on the release of GM insects

- WHO, in collaboration with the US Foundation for the National Institutes of Health, has published guidance on "safety, efficacy, regulation and ethical, social and cultural issues" surrounding the release of GM mosquitoes.[29]
- European Food Safety Authority has published guidelines for the environmental risk assessment of GM insects for commercial use in the EU.[25]
- An Ad hoc technical expert group on risk assessment and risk management under the Cartagena Protocol on Biosafety published guidance on GMOs which includes a section on GM mosquitoes.[30]
- The Daegu Protocol is an international effort to develop guidance on regulations related to agricultural pests and insects of human disease.[31]
- The North American Plant Protection Organisation (NAPPO) guidelines on the importation and Confined Field Release of Transgenic Arthropods in NAPPO member countries.[32]
- The WHO-TDR project called MosqGuide (2007-2013) gave guidance on the potential deployment of GM mosquitoes in endemic countries and has informed the WHO/FNIH guidance.[33]

Public Perception of GM Insects

In the EU, public perception of GMOs has been largely defined by the GM crop debate (POSTnote 211), which led to a 12 year de facto moratorium until March 2010 on the approval of GM crops. Polls have shown an increase in positive responses to GM technology for health benefits but not GM foods.[34] The regulation of GMOs in EU countries is based on technical risk assessments, but most public concerns relate to non-risk dimensions of GMOs, such as ethical issues. Proponents of 'responsible innovation' contend that the governance of GMOs needs to be revised to address this gap in regulatory approaches. In developing countries, public attitudes are poorly investigated, but many communities may be distrustful of government or commercial interventions using GMOs.[35]

Public Engagement and Dialogue

Academics and small biotechnology companies emphasise the importance of dialogue between public health authorities, citizens groups, academics and industry for the effective management and allocation of funds for development and release programmes. WHO guidance on GM mosquitoes (Box 4) recommends communication and public engagement as part of the process from lab to final release, with affected communities engaged before the technology is deployed.[36]

Box 5. Alternative frameworks for Approval of GMOs

- USA: Commercial GMOs are regulated based on composition, intended use and environment.[37] Risk assessments analyse risks and benefits of the GMO.
- Canada: The novelty of the product rather than the process used for product generation is regulated. Genetic traits introduced by selective breeding or genetic modification will be regulated.[38,39]
- New Zealand: Risks and benefits of the proposed technology are assessed and evaluated to make a decision. The product is approved if the benefits outweigh the risks associated with the product (Hazardous Substances and New Organisms Act 1996).[40]
- Australia: Australia maintains a GM record that can be easily accessed by the public to gain information on GMO and GM products being used in Australia.[41] Australia has a gene technology regulator which uses a qualitative rather than probabilistic risk assessment to guide decisions.[42]

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