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Ethical, legal and social issues of genetically modifying insect vectors for public health

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Abstract

The use of genetically modified (GM) insects for control of human disease can be consistent with common ethical norms of international society to reduce human suffering. This paper considers a range of ethical issues including animal rights, informed consent, community consensus and environmental viewpoints. Each community needs to decide its own priorities for methodology of disease policy guidance for ethical genetic engineering, and to negotiate with neighbouring countries. The approach to genetically modify insects raises few intrinsic ethical issues; however, important environmental and human health concerns need to be assessed before release of any GM insects. The policy that each community adopts should be the product of open dialogue involving all sectors of society. It can be expected that this process will take years and not all communities will endorse genetic control approaches to insect vectors.

Keywords: Genetically modified insects; Bioethics; Animal rights; Environmental ethics; Biosafety; Public health; Informed consent; Public opinion

1. The ethics of disease prevention

There is global support for the efforts to improve existing and develop new approaches for preventing, diagnosing, treating and controlling infectious diseases that cause loss of human life (Macer, 2003). The ethical principle that lies behind the idea of preventing, treating and controlling disease is that human life is something worth saving. There is however considerable ethical debate over the most ethical measures for achieving these goals, including the extent to which risks to human health, damage to the environment and other living organisms, and economic costs are balanced in societies that have a range of worldviews and social structures.

Certain principles basic to resolving ethical dilemmas can help decision makers make more informed policy decisions. The principle that we should love the life given to us (self-love) implies that each person should be given autonomy (self-rule) to work out how to balance the ethical dilemmas and choices themselves. The Universal Declaration of Human Rights of 1948 specifically set as a baseline that all human beings possess equal rights, and should be given a chance to exercise their autonomy. One of the fundamental human rights is a right to health, and working towards giving every person a chance to grow up free of disease is the ethical foundation of public health. If a person does not possess some basic level of health, he/she cannot even face many of the choices commonly accepted as normal. Poverty also restricts the choices of many people (Azevedo and de Moraes Marcilio Cerqueira, 2002), especially in areas faced with infectious insect borne diseases.

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Justice simply means that if we want others to recognize our autonomy, we have to recognize theirs as well. There are at least three different meanings of the concept of justice: compensatory justice—meaning that the individual, group, or community, should receive recompense in return for contribution; procedural justice—meaning that the procedure by which decisions about compensation and distribution are made is impartial and includes the majority of stakeholders; and distributive justice—meaning an equitable allocation of, and access to, resources and goods (Macer, 2003). There are ethical questions about how a society should represent procedural justice when there are major divisions within the society on particular issues. The process of consensus building and reaching common ground may be preferable for many cultures rather than confrontations.

At present there is great inequality between rich and poor nations in the direction and priorities of research, and in the distribution of and access to benefits that might come from this research. Under any ethical theory, the presence of diseases that threaten the lives of not just one but more than a billion people worldwide provides a compelling need for efforts to eradicate the diseases. There is wide diversity in the risks that members of each community face from infectious diseases due to: individual genetic variation in resistance to infectious disease agents; a person's nutritional state and immediate environment; a family's economic situation with respect to providing barriers to vectors and disease; access to both preventative and therapeutic medicines. These variations can be regarded as a type of lottery. Working towards better global equity is a goal that attempts to even out the lottery that people are born into. This is ethically mandated by Rawlsian justice (Rawls, 1971), which argues that efforts should be made to minimize the variation in all social factors because no one knows before they are born into which situation they will be born, so everyone would wish for equal opportunity and equal exposure to risk. All should have a chance to be born and grow up in an environment free of infectious diseases, if that can be achieved.

The ethical principle of beneficence supports the development of science and medicine, and its provision to those who suffer. A universal ideal found throughout human history is that it is better to love doing good things than bad things, and to love our neighbour as ourselves. Humans have used technology in efforts to make their lives easier and better for thousands of years, and the ethical principle of beneficence argues that we should continue to make life better. This ethical principle is based on the general motivation inside people to love doing good rather than harm, and may be expressed as love or compassion (Boyd et al., 1998). Efforts that work for the betterment of others in society have a universal moral mandate.

The ethical principle of non-maleficence, or do no harm, would make us reasonably cautious about premature use of a technology when the risks are not understood. Recently some have advocated a total precautionary principle for genetic engineering, which would mean that no technology with more than 0% risk should ever be attempted (Ho, 1998). This has also entered the Cartegena Protocol on Biosafety, which is an International Legally Binding Agreement that regulates international movement of living modified organisms (LMOs) (CBD, 2000). Because no human action has 0% risk, the principles of both benefit and risk are used to assess technology and are central to any public health program (Callahan and Jennings, 2002).

The ethical issues raised by biotechnology are commonly termed bioethics dilemmas, although when we examine the actual moral questions they may not be so novel and are often related to areas of applied ethics that were debated long before we had modern biotechnology (Comstock, 2000). There are several basic theories of ethics. The simplest distinction that can be made is whether they focus on consequences, actions or motives. Consequential arguments are the criteria applied to assess the ethics of biotechnology applications, i.e. whether they contribute to the greater good by improving the well-being of all. Consequential arguments state that the outcome can be used to judge whether an action was ethically correct or not. An action-based argument looks at the morality of the act itself, so that the actual action to cause harm itself is an unethical action regardless of the consequences or motives. Motive-based theories of ethics, including virtue-based ethics, judge an action based on the motivation of the action. For example, if the act was done with good intentions or not. Another separation that is used is between deontological theories, which examine the concepts of rights and duties, and teleological ones, which are based on effects and consequences. If we use the image of walking along the path of life, a teleologist tries to look where decisions lead, whereas a deontologist follows a planned direction.

The objects and subjects of ethics can be viewed in terms of ecocentric, biocentric or anthropocentric concerns. Ecocentric concerns, that value the ecosystem as a whole, are used when expressing environmental concerns. The reverence for all of life (Schweitzer, 1966) can apply to the whole ecosystem or to every member of it. Biocentric thinking puts value on the individual organism, for example one tree or one animal. Anthropocentric thinking is focused on the human individual. There is a trend for more ecocentric views to be included in recent legislation, with protection of ecosystems for their own value. While it can be useful to isolate distinct issues, as will be done in this report, it is not realistic to separate human/nature and social interactions. This is because almost all of human life is a social activity,

involving many relationships with people and the ecosystem. Different ethics are implied when human activity, e.g. agriculture or urbanization, attempts to dominate nature or to be in harmony with the environment.

Despite the fact that there are a variety of definitions of health, disease, disability, and what is a meaningful human life, working to alleviate disease and empower individuals to reach their potential are universal goals for the progress of humankind. The basic ethical principles of autonomy, justice, beneficence and non-maleficence can be applied to help decision-making in a range of bioethical dilemmas in medical and environmental ethics. There is some debate over whether further principles can always be derived from these over the precise terminologies in each field (Weed and McKeown, 2001), but the general consensus is that these four principles are fundamental in a range of cultures (Beauchamp and Childress, 1994; Macer, 1998; Tsai, 1999). The emphasis on individuals may be questioned more in developing countries. There are also theories of ethics based on community, which argue that individuality, autonomy or rights of a person are not suited to the community structure of society.

2. Bioethics and molecular entomology

This paper examines some philosophical issues over the use of genetic engineering on insects for public health purposes. There is a long history of altering the behaviour of disease vectors so that they cannot transmit pathogens to humans (Spielman and D'Antonio, 2001). Insects have also long been the targets of attention in agriculture as well as in medicine. While there are few intrinsic ethical concerns about killing insect pests, as discussed below, ecocentric approaches to ethics do raise some objections to modification of ecosystem components, and these need to be taken more seriously.

People of all cultures have developed biotechnologies as they live together with many species in the wider biological and social community. A simple definition of biotechnology is the use of living organisms (or parts of them) to provide goods or services. Over five millennia of classical plant and animal breeding have seen the emergence of agricultural societies, and modern biotechnology is built on that. Since the mid-1990s, foods produced from genetically modified organisms (GMOs) have been sold in a growing number of countries (James, 2004). There has been fierce international debate over the environmental and human health aspects of GM foods, but no harmful effects of GM foods on human health have been shown scientifically (FDA, 2001). There is greater concern over the environmental impact of gene transfer in the environment. A number of governments have considered the issues and concerns people have raised about genetic engineering, and there is a wealth of useful material in the reports and submissions made to them (United Kingdom Royal Commission, 1989; New Zealand Royal Commission, 2002). Reports have also been made by independent organizations on the ethical issues (Nuffield Council on Bioethics, 1999a).

New technology has been a catalyst for our thinking about bioethics, and has been a stimulus for research into bioethics in the last few decades. Genetic engineering allows genes to be exchanged in a controlled manner between different species. Since its invention in 1974, it has conjured up images of hope and dread. Public opinion is mixed. With the emergence of genomic sequencing, we now have the DNA sequence of human beings, dozens of pathogens, and some disease vectors, e.g. *Anopheles gambiae* (Holt et al., 2002; Morel et al., 2002). It is therefore not surprising that molecular entomology, the study of DNA and the proteins it encodes in insects, is emerging as a serious scientific approach for insect control (Atkinson et al., 2001; Robinson et al., 2004).

The general approach has global support beyond the dreams of individual scientists. The UNDP/World Bank/WHO Special programme for Research and Training in Tropical Diseases (TDR) has been developing the ideas of genetic control of insect vectors since a 1991 meeting on use of genetically modified (GM) mosquitoes to replace disease vectors. TDR's Steering Committee for Molecular Entomology has outlined a three-pronged effort towards developing GM mosquitoes for malaria control, with similar approaches for dengue fever and Chagas' disease (TDR, 2002). First in the process for each disease is to study host–parasite interaction; second is to develop methods to transform the vector; and third is to look at population ecology and genetics and at how to replace a population of harmful vector insects with a population of non-harmful insects. Social factors need to be carefully considered (TDR, 2000; Macer, 2003).

While there is debate over the use of funds to combat infectious disease using genomics and biotechnology as opposed to implementing practical measures to curb vectors and pathogens in the field (Curtis, 2000), it is widely agreed that the former approach will be a major strategy in the future (Hoffman, 2000; James et al., 2001). A common way to insert DNA for genetic transformation of insects is to use transposons or viruses (O'Brochta and Atkinson, 1998). A number of papers in this issue of the journal describe the advances that are being made in this field. Most attention has been given to efforts to genetically transform insects in the laboratory, and to test their behaviour before releasing them into the environment. A mechanism that would safely spread the gene among vectors in the wild is the

objective of these studies, except for the approach using sterile insects.

Transposable elements can contribute to genome evolution in nature, but the way they invade the genome and are regulated remains one of the major questions in population genetics. Effector molecules must be identified that will induce the anti-pathogen phenotype in the vector, and mechanisms are needed to drive the effector system into the vector population (Beaty, 2000). The latter step raises more ethical issues about the safety and desirability of changing the entire vector population, and possibly related species.

3. Intrinsic ethical issues of genetic engineering

The conclusions of studies of ethical issues inherent to the process of genetic engineering compared to traditional methods of animal and plant breeding, are that the only significant differences in the process are the more precise control of genetic engineering and whether the DNA involves cross-species gene transfer that does not occur in nature (Nuffield Council on Bioethics, 1999a; Comstock, 2000; Macer, 2003). One of the key questions is whether there is an intrinsic value of genetic integrity at an organism and ecosystem level that humans should not change. In the attempt to prioritize issues given in Table 1, it assumes that there are some persons in the community that place intrinsic value upon native fauna including insects. One way to consider this question is to note that cross-species DNA transfer does occur in nature between all species, even of different kingdoms, and that the genomes of insects are subject to genetic flux in nature. In this sense, because the DNA change can be precisely designed, an actual targeted genetic change through genetic engineering should be safer than a natural change because it is more under control. Given the results of public opinion surveys that find opposition to cross species gene transfer (Macer, 1994; Macer and Ng, 2000), if the DNA change is made using DNA within the same species entirely, then this concern can be removed. In this way of thinking there may not be any new intrinsic ethical dilemma from the modification of DNA structure in genetic engineering as it simply mimics the natural ways organisms use to change genetic structure. However, the scientific details of the targeting process, and the intentional nature are important for some persons.

Another argument used in these discussions concerns the telos (purpose) of an organism. A teleological explanation describes phenomena by their design, purpose, or final cause. Teleology is the branch of moral philosophy dealing with the cause and effect of an action, the belief that there is purpose and design in nature, and consequently, with the belief in the existence of a Creator. There are concerns that the ability to alter the telos of an animal has profound implications (Munro, 2001). If one believes that every organism has a purpose, then the telos is an intrinsic concern, and genetic engineering alters the telos or 'being-ness' of an organism. However, it is debatable whether changes and control through genetic engineering are significantly different from changes made by humans to animals and plants in farming and modern life. It is basically an issue of human control of nature, and there is debate over the extent to which humans should control nature (Reiss and Straughan, 1996; Bruce and Bruce, 1998; Comstock, 2000). If we consider this issue in a historical context, we see that humans in many affluent cultures have controlled nature in significant ways, e.g. by concrete river banks, irrigation and sanitation projects. However, especially in some developing countries, limited resources have meant that control of nature has been less. However, sociological evidence has found that a number of people object to human control of nature, regardless of whether it poses a risk (Macer, 1994).

4. Animal rights concerns

Another concern in ethics when discussing animals is their capacity to suffer or feel pain. If insects do not feel pain or sense feelings, then the most prevalent ethical approach for animals would argue that there is nothing intrinsically wrong in manipulating them (Singer, 1976). However, if we consider the idea of making so-called vegemals, animals that do not feel pain, we are still manipulating life for human purposes without considering the interests of the animal (Macer, 1989). The concern is that living organisms should not merely be treated as a means to the ends desired by humans. Animal rights concerns about the genetic modification of higher animals, e.g. mammals or birds, mean there is more ethical concern about modifying sentient animals, and more public concern, than if insect vectors were engineered. In addition to so-called intrinsic concerns (pain, sentience, consciousness), there are also extrinsic values placed on some animals by human society. For example, some animals are national symbols and people have greater concern about harming them. There are also biodiversity concerns about endangered animals, some of which are expressed in the Convention on Biological Diversity.

While perhaps only followers of the Jain religion in India regularly refrain from killing insects that are human pests, there are still some people who may object to killing mosquitoes. It is not known if manipulating the insects so that they would not be a human pest would be more acceptable to persons with these ecocentric world views than traditional methods of insect control that attempt to eradicate a whole insect population.

Table 1
Ethical priorities in community engagement over genetic methods of vector control

Expected benefits	Negative concerns	Autonomy/justice
(1) Prevent human disease.	(1) Risk of damage to the environment from ecological changes under ecocentric and/or biocentric views.	(1) Regulatory systems for oversight need to find proper balance between expected benefits and precaution.
(2) Less health and environmental damage compared to insecticides.	(2) Possibility of horizontal transfer of the transgene(s) to non-target organisms.	(2) Education materials and process, after a 2-way development process.
(3) Less environmental change compared to civil engineering approaches to vector control.	(3) Modification of one ecosystem component, altering the telos (purpose) of an organism.	(3) Whether consent is required from every individual, including children.
(4) Development of social consensus process that can be applied to other public policy.	(4) Indigenous persons place higher value on the unmodified the native fauna.	(4) Options for those who refuse to be involved, e.g. alternative insecticide protection methods.
(5) Emergence of informed choice and empowerment of individuals leading to greater personal responsibility for health choices.	(5) Human control of nature.	(5) Inequality in access to the modified mosquitoes.
(6) Sites of field trials could be promised to be beneficiaries of more permanent use.	(6) Greater concerns over mobile genetic elements compared to "sterile" vectors.	(6) Roles of external persons, e.g. activists, media, NGOs, commercial actors.
(7) Modified mosquitoes would not be killed, so the vector species would remain alive.	(7) Unforseen consequences on human health.	(7) Payment mechanisms for trials, and insurance for accidents.
	(8) Intellectual property issues.	(8) Sustainability of intervention.

Note: This summary table includes issues under the three headings in an order suggested for most endemic countries, with a component indigenous population that has a non-industrialized and non-Western scientific worldview, but the priority for each community could be found after community engagement, which may also identify new issues.

Those who subscribe to an ecocentric viewpoint might argue that the ecosystem as a whole would benefit from an intervention that left the mosquitoes in the ecological community, with the elimination of the disease-causing pathogen from the vector, if the alternative was eradication of the vector species. In this case the total number of species affected by this type of genetic modification of vectors would be significantly less than the number of species affected by use of insecticides (Macer, 2003). However, there are still those who believe there should be no human modification of the ecosystem. This actually should argue that there should be no direct or planned modification of an ecosystem by humans, since human activity modifies almost all ecosystems, including those where humans are not directly a component member.

5. Consent from trial participants

Recognition of the ethical principle of autonomy means that all participants need to give informed consent to an intervention that has a reasonable risk of causing harm (Annas, 1989). There are significant difficulties in obtaining individual informed consent in some developing countries (Ekunwe and Kessel, 1984; Angell, 2000; Alvarez-Castillo, 2002), but by adequate investment of time and provision of suitable materials, it should be possible to obtain informed consent from individuals at direct risk, even though the exact cultural interpretation of the informed consent process may vary between countries (Nuffield Council on Bioethics, 1999b). There are risks of direct or indirect harm to human beings from the original pathogen-transmitting vector, so a trial needs to be done to show that there is greatly reduced risk of harm from the modified vector. This is the whole purpose of the project to create modified vectors, to reduce risks. Until a trial is made we cannot be sure that there will be no risk and that the whole enterprise has been successful.

The risks may not just be those that arise directly from the ability of the vector to carry the target pathogen. There could be a negative impact on human health by altering the behaviour of blood-feeding insects. In the case of insects that cannot be confined to a particular population, whether they fly or float to new places, notions of "human subject" and "informed consent" need to be extended. There are basic ethical issues involved in vector collection and studies in the field. Firstly, many such studies have relied on a researcher waiting for the vector to land on a human host, and then capturing it hopefully before the vector has transmitted the pathogen to the "bait". In fact, any field studies in which human beings are exposed to the pathogens raise the question as to why some other intervention is not used in that area.

The approach developed for population genetics studies may be useful where the community and local authorities are involved in the decision-making process. Informed consent requires information to be provided, so disseminating information about the plans and progress of the project, and obtaining the consent of any person potentially affected by the release of transgenic insects, is important for the ethical conduct

of research trials, whether or not national guidelines require this, or even exist. Other lessons show us that people who lack the means to express their preferences may have been abused by the lack of individual or community consent for research in anthropology (Fine, 1993; Kleinman, 1999) and epidemiology (Capron, 1991; Dickens, 1991; Gostin, 1991; Chee et al., 1996).

If a study involves humans, oversight by an ethics committee or institutional review board (IRB) is necessary. In an increasing number of countries, such committees are established by law and are charged with certain legal responsibilities, typically about the conduct of research or clinical practice at local or national level. An IRB is a group of persons from a range of disciplines who meet to discuss the ethical issues of particular submitted procedures and review the benefits, risks and scientific merit of the application. The IRB usually requires that each human subject in a medical trial gives informed consent to be involved in the project. Model ethical guidelines on the establishment and procedures for an IRB have been produced by an international consultative committee for TDR (WHO, 2000). These guidelines however are not sufficient for the broad question of how to obtain informed consent for a public health intervention involving thousands of persons where the benefits are not demonstrated.

Ethics or bioethics committees include groups of people set up to adjudicate about bioethical matters. An IRB is in a sense an institutional ethics committee, but a typical IRB works through a large number of applications and often excludes the broader social discussion and representation that is seen in a regional or national bioethics committee. There are also national variations in the laws to define membership and scope of work, and terms used. The project to introduce transgenic insects will need an ethics committee with a broad overview, and specific regional ethics committees to consider the local issues.

To consider the issue at a local level, as required for obtaining appropriate informed consent, it is essential that a local ethics committee (and/or IRB if associated with an institution) open to the communities involved is established. There are cultural differences in the way informed consent should be taken (Levine, 2001; Alvarez-Castillo, 2002). The accepted norm in international ethical guidelines is seen for example in the modified Helsinki Declaration (World Medical Association, 2000) and the draft Council for International Organizations of Medical Sciences (CIOMS, 2001) guidelines. In cases involving bilateral research collaboration, the most stringent ethical standards of the two countries should be applied. This creates problems for non-literate populations, and for populations whose common sense social assumptions are different. It is desirable that internationally agreed standards are applied, and that there are few points of difference between these standards even for simple clinical trials of drugs. The ultimate decision procedure should be decided by the local ethics committee, but international consistency and guidance will be essential.

Although the control population for the study may continue to face the same high risk of contracting the disease, recent trends in research ethics debate whether we can leave control groups without any treatment. Therefore, ethically there may need to be some other vector reduction measures given if making any interventional study in an area. While those designing ethical guidelines on placebo-controlled trials (e.g. Helsinki Declaration) were thinking of placebo controls on clinical trials of potential medical drugs, we can ask the ethical question whether researchers have an obligation to the local population to use the best available means of disease control whenever they enter an area for a study. This practically means that, as well as studying the new method, a researcher may ethically be compelled to also provide the best available proven alternative to the study population. There may be times when the provision of the proven alternative to the area of study alters the dynamics of the disease so that the results of the vector field trial differ from what the results would have been had no established alternative been provided.

Before and during the intervention, there may be privacy concerns when questionnaires are administered and personal data are stored. For public health purposes, it is essential that all information about individuals involved is linked to other data, but to ensure privacy, the data should only be identifiable to a specific person by a coding frame that is not in a computer linked to a network.

Children are therefore one of the targets of public health interventions, with presumed consent from the therapeutic imperative that they want to be involved in programmes that will avoid disease. Some compulsory vaccination programmes have faced criticism that consent is not obtained even from the surrogate decision-maker, the child's parents. In each family there may several adults, and more children, which raises questions of whether consent is required from every individual. The local cultural norms need also to be considered. However, an appropriate mechanism may be one in which the views of everyone of reproductive age (let us call this the level of adult maturity) are gathered, and consent sought from these persons both as individuals and as a family. The agreement and understanding of children in the community should be sought through suitable materials. However, children should not be exposed to direct risk from therapeutic trials unless there is no alternative. In the case of a child living in a community that was involved in a GM vector trial, no direct risks to the human population would be expected so the consent issue is not a major hurdle. On a

more positive note, children in fact could be a very powerful means to involve the community in a process of community engagement through schools. Since children are at higher risk from many of the diseases in question, they stand to benefit more, and most parents may want to be involved in the trial because of the potential benefit to their children rather than themselves.

6. Environmental risks and public consensus

The human community also needs to consent to the environmental risks of a trial as these represent potential harm to other members of the biological community as well as other members of the human community. Globally people vary in the importance they ascribe to the environment, or parts of it. Especially in areas where more traditional world views are found, we may see greater value given to parts of the environment that are forgotten in the modern industrial mindset (Table 1). We also see variations between persons in all cultures as to their images of nature and what is life (Macer, 1994). Some people are willing to sacrifice themselves for the environment. Examples such as the preservation of sacred groves in India for thousands of years, even during times of severe crisis and human death (Gupta and Guha, 2002), show that in some cultures almost all people are willing to die rather than damage that part of the environment they cherish. This behaviour is often linked to religious beliefs in the afterlife.

A variety of potential broader ecological, environmental and health risks are associated with the release of GMOs. Environmental risks can be considered from both anthropocentric and ecocentric-based approaches. The risks identified include the possibility of horizontal transfer of the transgene to non-target organisms, and possible disturbance of insect ecology (Hoy, 1995; Nuffield Council on Bioethics, 1999a). There have also been concerns expressed in some cultures, e.g. New Zealand, over the need to value the native fauna and flora, which is considered by many in the Maori community to be something not to modify (New Zealand Royal Commission, 2002). While human beings cannot consent for other organisms to be modified, very few persons suggest that any consent is required except for possibly sentient animals.

One of the main concerns of releasing GMOs is environmental risk (FAO, 2001; Aultman et al., 2000). This risk has been successfully controlled in over 10 000 international field trials of GMOs (USDA, 2002). Whilst the methods used for monitoring field trials are argued to be inadequate by those campaigning against GMOs, to date there has not been a significant adverse event from GMO release for the health of any non-target organism, including humans, in the ecosystem (Comstock, 2000). New ethical issues about GM arthropod vectors and their symbionts and/or pathogens should be subject to extensive open discussions and forums.

Any risks to the agricultural systems of rural communities also require assessment, as animal diseases transmitted by vectors are important to farming families. In addition, there may also be risks to wild animals in surrounding areas, which in some ecocentric environmental views have more intrinsic rights to be left undisturbed than farm animals (Rolston, 1994). This calls for broad ecological understanding of the impact, beyond public health. There is also the possibility for GM vectors to spread to areas beyond the initial expectations, which needs to be considered when planning the geographical extent of information and communication programs.

In the year 2001, the first US field test of a GM pink bollworm, a cotton pest, was conducted. It followed very soon after the development of methods to transform the bollworm (Peloquin et al., 2000), suggesting that some researchers may go to field trials within 1–2 years of transforming an insect species. About 3600 moths were studied in a field enclosure of more than one hectare, after being modified with green fluorescent protein (GFP) as a tracing gene. This was based on the idea that a lethal gene can be introduced to kill the progeny of both engineered moths and moths which breed with them (Dalton, 2001). In the short term however, the presence of GFP means that the sterile insects can be readily distinguished in the field. This itself is a significant advantage because currently farmers may have to release up to 60 times the number of sterile insects in the field to control bollworm, but these numbers might be brought down 12-fold if the sterile insects can be easily identified in the field. This type of trial had an important consequence of preparing regulatory systems for oversight of GMOs/LMOs, but still most countries in the world have not established systems for oversight of GM insect field releases (Pew, 2004).

Although there have been numerous public opinion surveys on the release of different GMOs, there have been few surveys asking people their views on introducing GM vectors or pathogens for disease control. One general feature of the surveys is that GM plants are considered less threatening than GM microbes, animals and humans. In a 2003 national sample in Japan, one third thought it would be acceptable to use genetic engineering to make mosquitoes unable to be a vector for human diseases like malaria or Japanese encephalophy, and only 16% said it would not, while half said they did not know. There was 54% approval for environmental release of mosquitoes that do not transmit human disease, which is the same as the support for release of GM disease resistant crops, with 19% disagreeing (Inaba and Macer, 2003).

Although knowledge is important for acceptance of biotechnology, it is not a predictor of acceptance. In surveys of scientists and the public in Japan in 1991–2000, for example, well-educated scientists were often just as sceptical of biotechnology as the general public, and shared the same types of concerns (Macer and Ng, 2000). The failure of the government authorities in public health has led to higher public trust in NGOs, including environmental groups. The media has also disproportionately reported negative aspects of genetic engineering because these appeal to people (Durant, 1995). Thus the late 1990s saw a dramatic drop in public support for biotechnology in every country surveyed. It is therefore important that scientific knowledge be accurately shared with all, that this process be open, and that all opponents are involved in discussion.

If the trial covers an area with a local population of 100 000 persons or more, it is unrealistic and unlikely that informed consent can be given by all people in the area. There will always be some people who are against any proposition, no matter how much others value it, but the opponents cannot be moved from their houses for the period of the trial. So a procedure that is neither paternalistic nor paralytic needs to be developed. After the process of consultation and dialogue to seek informed consent, there still needs to be a procedure to supply relevant information to all persons in the area so that the minority who disagree with the trial have the option to leave. In developing countries, many may not realistically be in either a position to achieve social consensus or for persons to actually leave the area. Other options may be to provide additional insecticide resources to households that object to the study and are afraid of the GM insects presence. The mechanisms for social consensus in biotechnology are not well understood in the affluent countries that have been debating GMOs, and even less is known in developing countries. Public opinion studies suggest that people may respond differently to theoretical and real situations.

Recognizing the autonomy of people as a group demands that we apply the consent model to more than isolated individuals. The introduction of GM vectors and pathogens requires community consent, so a process for seeking group consent needs to be developed for each community (Kleinman, 1999). The question of whether every citizen has to consent to public health interventions is not a new one (Kass, 2001), but with the current social transition from a paternalistic society to informed consent and informed choice, this key concern is appearing in all societies, although at different speeds.

Any initial trial may be subject to the philosophy "not in my backyard". Socially powerful persons are generally more effective at preventing trials they perceive to be risky in their area, or, conversely, at attracting social resources towards themselves and away from weaker persons in the community. Ethically it is important that risks and benefits are shared equally, and one way to ensure this would be a commitment to the local community that, if the trial is successful, the full-scale intervention would include them from the beginning. In this way, any risks borne by a local population would subsequently be rewarded by that population being the first group to benefit from the knowledge gained when the full-scale safe and effective control programme is implemented. The field trial must therefore come with a commitment to the local community that financial resources will be available and that sustainable use of the control tool will be affordable.

7. Ethics of technology choices

Issues include the ethics behind research into, and later financing of, technological products that attempt to "fix" a problem rather than invest in increasing the ecological knowledge base to "prevent" the problem. There is considerable preference for deterministic science over "softer" educational systems like flexible learning. It is clear that not all local communities will share the modern scientific world view that technical healing is better for them, so there needs to be flexibility in the approaches available to eradicate disease. In the past, paternalistic interventions were taken on the behalf of citizens; however, civil rights movements have empowered people to take these decisions themselves.

A number of ethical issues have been raised in international debates over the morality of patents, and there have been strong calls against the patenting of medical innovations. Laws on intellectual property vary between countries, despite attempts to harmonize these laws among industrialized countries and members of the World Trade Organization (WTO). A number of developing countries are not members of the WTO, and often the major controversies over whether a country will join WTO is related to intellectual property rights (IPR).

Practical guidance for ethics committees needs to be clarified on public health interventions. One key problem is identifying who is specifically at risk, and what the particular risk is. In vector release studies, everyone in the area may be at risk. These complex questions are made more manageable through breaking down the concerns people have into manageable areas. Defining a minimum standard of protection for research participants in trial and control populations for GMO interventions is the key point. This issue is not specific to GM vectors and pathogens, but it is crucial to consider the benefit/risk equation.

Most concerns can be the subject of better information and education. Gathering satisfactory scientific data by conducting field trials, and understanding ecological issues (Scott et al., 2002), are the main

criteria required prior to release for most people. The remaining concern, and one which is also found in scientists as well as the public, is that genetic engineering is somehow unnatural. This is an issue that needs greater social discussion. However, if presented with the threat of contracting disease, most people have few concerns about using other "unnatural" remedies such as pesticides and medical drugs. Given that most mosquitoes do not transmit disease to humans, it is, arguably, not unnatural to change a mosquito that does transmit diseases into one that does not. There is a need for public opinion studies in the communities before the release, during the process of community engagement, and after the study, if we wish to really understand the opinions and concerns that people have.

8. Regulation

The internationally accepted principles of risk assessment for GMOs take into account: relevant technical and scientific details of the recipient or parental organism, the donor organism(s), the vector, the insert(s) and/or characteristics of modification, the GMO, and the methods for detection and identification of the GMO including specificity, sensitivity and reliability; as well as information relating to intended use, information on location and geographical, climatic and ecological characteristics, and the foreseen health impact of the intervention (Macer, 2003). The ethical principle of non-maleficence is the underlying basis for attempting to avoid harm and the regulation of human activity.

What is a particularly relevant point in the development of GM insect vectors unless it is based on sterile insect methods (Alphey et al., 2002; Robinson et al., 2004), is that in order for a vector programme to be successful, the modification must spread throughout the wild population of a vector. This means that deliberate infection with the transgene may be the target of introducing the GMO. In order to define the parameters associated with the speed and extent of spread of the genetic modification under real conditions, extensive trials are necessary. Some vectors may transmit more than one pathogen, so any intervention programme may have complicated effects on the distribution of disease.

Concern over possible safety and environmental risks raised by biotechnology prompted the WHO, United Nations Environment Programme (UNEP) and United Nations Industrial Development Organization (UNIDO) to identify and study the various safety issues involved. As a result, a UNIDO/UNEP/WHO/FAO Ad Hoc Working Group was formed in 1990 to work out practical guidelines through a series of consultations with international experts and scientists from developing countries. In 1991, the UNIDO/UNEP/WHO/FAO Working Group on Biosafety brought out a Voluntary Code of Conduct for the Release of Organisms into the Environment. The code sets out general principles and a framework and guidelines to be adopted at national, regional and international levels to facilitate the safe application of biotechnology. The scope of this document covers "GMOs at all stages of research, development, use and disposal, while focusing on release to the environment. It covers, but is not limited to, GM plants, animals (including for example, insects, molluscs and fish), and microorganisms and their products and by-products" UNEP, 2002.

The International Centre for Genetic Engineering and Biotechnology (ICGEB) provides assistance in biosafety training for the development of genetic engineering in many countries (ICGEB, 2002). Some issues also relate to the proposed Code of Conduct in Biotechnology being developed under the Commission on Genetic Resources for Food and Agriculture (CGRFA). UNDP (2001) and FAO generally support the development of genetic technology while considering the benefits and risks of the organisms. The capacity of countries to establish committees to adequately address ethical, social and scientific concerns needs to be strengthened.

The Scientists' Working Group on Biosafety of the Edmonds Institute (1998) in Washington, DC, USA, recommended that field trials of vectors genetically engineered to reduce disease should be small scale in terms of the area of dispersal of the vector. "In the case of an anti-malaria or anti-dengue intervention, such a field trial could involve a single village or an isolated cluster of adjacent villages. No large-scale release should be attempted until the effectiveness is shown in the first trial". Thus, while there is general international consensus in the UN system that selected use of GMOs should proceed, there are groups within society that continue to be cautious. There are also countries whose political regimes do not accept GMOs, and these attitudes depend on political elections, including the principle of democracy. National sovereignty should of course be respected, but GM vectors may spread beyond a national border.

The Cartagena Protocol on Biosafety to the Convention on Biological Diversity is an advance informed agreement procedure on the safe transport, handling and use of LMOs resulting from modern biotechnology that specifically focuses on transboundary movements of LMOs. The parties to this protocol agreed to ensure that "the development, handling, transport, use, transfer and release of any LMOs are undertaken in a manner that prevents or reduces the risks to biological diversity, taking also into account risks to human health". It was also noted that "the parties are encouraged to take into account, as appropriate, available expertise, instruments and work undertaken in international forums with competence in the area of the risks to human health"

(CBD, 2000). In the Cartegena Protocol, "a living modified organism means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology. Modern biotechnology means the application of either in vitro nucleic acid techniques, including the recombinant DNA and direct injection of the nucleic acid into cells or organelles, or the fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection". This definition of a LMO is now accepted in international law in general because of the Protocol. The actual term "LMO" is still not as widely used as "GM organism", the term that has been used for two decades in academic and media debates.

One useful development of the Cartegena Protocol umbrella is the establishment of biosafety clearing houses, which are contact points in each member country. The Protocol also includes risk assessment and risk management once agreement is reached, as well as development of capacity building in biotechnology research. Many developing countries do not have the economic or scientific capacity needed to examine the products of modern biotechnology (Chinsembu and Kambikambi, 2001). Information related to GM vectors should be linked to the same biosafety clearing houses.

The United States Department of Agriculture (USDA) has reported the results and approval procedures for six trials of GMOs. These include field trials of transgenic mites, nematodes, flies, spruce budworm, and pink bollworm, as discussed above (USDA, 2002). The field trials of transgenic nematodes and predatory mites were intended to study the risk to the environment of these transgenic organisms and the stability of the transgenes under controlled conditions. The genetic modifications did not affect infectivity of the nematodes, however the field performance of the transgenic mites (in Florida) was dramatically different to in the laboratory due to differences in relative humidity, and the field experiment was terminated after 3 weeks because populations of both predatory mites and prey spider mites declined rapidly. Few individuals in the population contained the transgene. At the end of these field trials, all the transgenic organisms and hosts were destroyed. The American Committee of Medical Entomology has also produced guidelines (ACME, 2002).

9. Conclusion

There are a variety of ethical issues that are raised from the use of GM insects (Table 1), but the most challenging may be the process of informed consent for individuals and communities. Each community or society needs to be given a chance to set consensus values on risk assessment. A universal minimal standard of risk assessment applicable to disease vectors needs to be defined, as diseases cross national and continental borders.

Before field release of transgenic insects, researchers must assess all the scientific and social issues associated with GM vectors and develop safety precautions to address potential risks. The scientific and social risks should be minimized through careful design of the vector system, relevant laboratory experience, and careful choice of the site including considering appropriate social and cultural factors. Even if there are not perceived to be any realistic risks, a procedure for their evaluation should be set up so that new information can be gathered and interpreted. This procedure may involve establishing a specialized ethical review committee under the auspices of an international body such as TDR to offer advice to researchers on the ethics of projects.

There should be prior environmental, medical and social studies for site selection, and the most appropriate site chosen on the basis of these data. Information should be exchanged as broadly as possible with community leaders, members of the local community, and the mass media. Consent should be obtained from the communities involved. Specific mechanisms to obtain individual and group consent need to be developed for public health interventions. A contingency plan for aborting a field trial needs to be developed.

Commitment to the local communities involved in field trials should be made such that they will be the first beneficiaries of more permanent use of a GM vector should results indicate that this is appropriate. Intellectual property concerns should not be barriers to implementing public health measures using GM vectors or their symbionts and/or pathogens. Prior negotiation, including possible involvement to allow access to the latest technology, is preferable to confrontation. The data should be made available to all in order to benefit from global expertise and develop international consensus. There is a need for an ongoing and active process of ethical analysis, through a variety of forums, that will provide us with the conclusions about where it is ethical to conduct these type of studies.

Ethically, we have to consider what are core ethical values for modification of nature for human needs. The ethical principle of beneficence demands action to eliminate hunger and disease. We must do this while preserving the environment for the future.

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