

Ethical, legal and social issues of genetically modified disease vectors in public health

Social, Economic and Behavioural (SEB) Research



The "Special Topics in Social, Economic and Behavioural (SEB) Research" series is a peer-reviewed publication commissioned by the TDR Steering Committee for Social, Economic and Behavioural Research.

For further information please contact:

Dr Johannes Sommerfeld
Manager
Steering Committee for Social, Economic and Behavioural Research (SEB)
UNDP/World Bank/WHO Special Programme for Research
and Training in Tropical Diseases (TDR)
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

E-mail: sommerfeldj@who.int

Ethical, legal and social issues of genetically modified disease vectors in public health

Darryl Macer¹ Ph.D.

¹ Director, Eubios Ethics Institute, Japan and New Zealand
Associate Professor, Institute of Biological Sciences,
University of Tsukuba, Tsukuba Science City,
305-8572, Japan
Email: Macer@sakura.cc.tsukuba.ac.jp

TDR/STR/SEB/ST/03.1

Copyright © World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases 2003

All rights reserved.

The use of content from this health information product for all non-commercial education, training and information purposes is encouraged, including translation, quotation and reproduction, in any medium, but the content must not be changed and full acknowledgement of the source must be clearly stated. A copy of any resulting product with such content should be sent to *TDR, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland*. TDR is a World Health Organization (WHO) executed UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases.

This information product is not for sale. The use of any information or content whatsoever from it for publicity or advertising, or for any commercial or income-generating purpose, is strictly prohibited. No elements of this information product, in part or in whole, may be used to promote any specific individual, entity or product, in any manner whatsoever.

The designations employed and the presentation of material in this health information product, including maps and other illustrative materials, do not imply the expression of any opinion whatsoever on the part of WHO, including TDR, the authors or any parties cooperating in the production, concerning the legal status of any country, territory, city or area, or of its authorities, or concerning the delineation of frontiers and borders.

Mention or depiction of any specific product or commercial enterprise does not imply endorsement or recommendation by WHO, including TDR, the authors or any parties cooperating in the production, in preference to others of a similar nature not mentioned or depicted.

The views expressed in this health information product are those of the authors and do not necessarily reflect those of WHO, including TDR.

WHO, including TDR, and the authors of this health information product make no warranties or representations regarding the content, presentation, appearance, completeness or accuracy in any medium and shall not be held liable for any damages whatsoever as a result of its use or application. WHO, including TDR, reserves the right to make updates and changes without notice and accepts no liability for any errors or omissions in this regard. Any alteration to the original content brought about by display or access through different media is not the responsibility of WHO, including TDR, or the authors.

WHO, including TDR, and the authors accept no responsibility whatsoever for any inaccurate advice or information that is provided by sources reached via linkages or references to this health information product.

Design: Jocelyne Bruyère

Cover design: Lisa Schwarb

TABLE OF CONTENTS

EXECUTIVE SUMMARY	1
1. INTRODUCTION	3
1.1 Ethics of disease prevention	3
1.2 Bioethics and biotechnology	4
1.3 Bioethics and molecular entomology	6
2. THE GENETIC ENGINEERING DEBATE	7
2.1 Growing use of genetic engineering	7
2.2 International systems for consideration of genetic engineering	7
2.3 Codex Alimentarius Commission and the safety of genetically modified food	8
3. MODIFICATION OF VECTORS AND PATHOGENS FOR PUBLIC HEALTH PURPOSES	9
3.1 Methods used for control of insect vectors	9
3.2 Past attempts at introduction of modified pathogens	9
3.3 Development of genetic modification techniques	10
3.4 Modification of other organisms	11
3.5 Modification of human hosts	12
4. ETHICAL AND SOCIAL ISSUES	13
4.1 Reducing the complexity of ethical and social issues	13
4.2 Intrinsic ethical issues of genetic engineering	15
4.3 Animal rights concerns	15
4.4 Consent from trial participants	16
4.5 Consent from broader society on environmental risks	18
4.6 Social consensus building and early cessation of trials	18
4.7 Equality and inequality in access	19
4.8 Ethics of technology choices and knowledge development	20
4.9 Intellectual property rights and technology transfer	20
4.10 Inducement to participants	21
5. PUBLIC ATTITUDES TO GENETICALLY MODIFIED ORGANISMS	23
5.1 Need for public acceptance prior to interventions	23
5.2 Results of public opinion surveys on genetically modified organisms	24
5.3 Wide social and legal discussion of biotechnology	25

6.	REGULATIONS	27
6.1	General basis for regulation	27
6.2	Cartagena Protocol on Biosafety	28
6.3	National and regional regulations	29
7.	RECOMMENDATIONS FOR KEY AREAS TO ENSURE ETHICAL INTEGRITY IN THE USE OF GENETICALLY MODIFIED VECTORS AND PATHOGENS	31
7.1	Establish safety and international standards before field trials	31
7.2	Information access and local communities as partners	32
7.3	Group consent	33
7.4	Environmental assessment	33
7.5	International cooperation	34
7.6	Further next steps in consultation on ethical, legal and social issues	34
	ACKNOWLEDGEMENTS	37
	ABBREVIATIONS	38
	REFERENCES	39

EXECUTIVE SUMMARY

Consistent with its implicit ethical mandate to reduce human suffering from disease, TDR has outlined a three-pronged effort to develop genetically modified (GM) mosquitoes for control of tropical diseases such as malaria. The approach to genetically modify vectors or their symbionts and/or pathogens for disease control raises few intrinsic ethical issues; however, important environmental and human health concerns need to be assessed before release of any genetically modified organism (GMO). Each country needs to decide its own policy guidance for ethical genetic engineering of microorganisms, plants, animals and ecosystems, and to negotiate with neighbouring countries; this policy advice should be the product of open dialogue involving all sectors of society. However, given the broad acceptance of use of GMOs for specific purposes, as endorsed by specialized international agencies including the United Nations Development Programme (UNDP) and United Nations Food and Agriculture Organization (FAO), the question is not so much whether to release GMOs but rather how to release them and what type are safe and effective enough to enter field trials.

Part of the process is for society to set values for consensus 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. In developing model guidelines, this report recommends examining the following issues:

- 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 TDR auspices 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.
- To avoid any suspicion by the public that could result in public rejection of the approach, TDR and member governments should not involve partners in the projects from any military research establishments.

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, and TDR is called upon to take a lead in elaborating and developing ethical and scientific standards for research in this area.

1 INTRODUCTION

1.1 Ethics of disease prevention

The ethical mandate of TDR is to improve existing and develop new approaches for preventing, diagnosing, treating and controlling infectious diseases that cause loss of human life. The ethical principle that lies behind the idea of preventing, treating and controlling disease is that human life is something worth saving. Certain principles basic to resolving ethical dilemmas (Engelhardt, 1986; Gillon, 1986) need to be considered before proceeding to examine the topic of genetic engineering for public health.

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, 2002).

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. 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 based on a direct referendum, as is sometimes used in Switzerland. These issues are discussed below, given the controversies surrounding GMOs.

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 Cartagena Protocol on Biosafety (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 programme. Few papers have considered the ethics of public health (Callahan and Jennings, 2002). 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 (Veatch, 1989), and 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; Tsai, 1999).

In different societies there are debates over whether principlism is the most suitable form of ethical theory for decision-making; however, it is the most widely accepted in modern bioethics. 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. Community advocates argue that societies need a commitment to general welfare and common purpose, and that this protects members against the abuses of individualism, which can be equated with selfish pursuit of liberty. The question is what community we talk of, whether the individual family, the village, the state, country, region, or global community. MacIntyre (1984) argued that Aristotle considered local community practices and their corresponding virtues should have primacy over ethical theory in normative decision-making. These practices include parenting, teaching, governing, and healing.

Despite the fact that there are a variety of definitions of health, disease, disability, and meaningful human life, working to alleviate disease and empower individuals to reach their potential are universal goals for the progress of humankind. This report seeks to examine how these goals may be accomplished considering the use of genetic engineering for public health purposes. Before we do this, we will consider more the ethical theories that people use and the rise of biotechnology.

1.2 Bioethics and biotechnology

Recent developments in biotechnology have made people re-examine the ethics of life. The term **bioethics** has emerged as a term to summarize the ethical issues associated with human attitudes to life, the environment, use of natural resources and biotechnology. Much recent attention has focused on medical ethics and human health questions, but the concepts of bioethics have also long included environmental ethics. Bioethics is a broad concept linking many traditional academic fields (Beauchamp and Childress, 1994; Reich, 1995; Macer, 1998, 2002). Central to the concept is recognition of the autonomy of patients and the subsequent need for informed consent in medicine (Ramsey, 1970).

There are at least three ways to view bioethics:

- **Descriptive bioethics** is the way people view life, their moral interactions and responsibilities with living organisms in their life.
- **Prescriptive bioethics** is to tell others what is ethically good or bad, or what principles are most important in making such decisions. It may also be to say something or someone has rights, and others have duties to them.
- **Interactive bioethics** is discussion and debate between people, groups within society, and communities about descriptive and prescriptive bioethics.

Developing and clarifying descriptive and prescriptive bioethics, usually through a process of social interaction, allows us to make better choices, and choices that we can live with, improving our life and society. The choices that need to be made in the modern biotechnological and genetic age are many; they extend throughout life, from before conception to after death. The timing of reproduction, contraception, marriage, are not new choices, but when we consider these issues it is clear that not all people can exercise choice to the same degree, and that the limits to choice are determined by family, culture and laws which change over time. In order to inform prescriptive bioethics, we need to describe the bioethics that people have followed in the past and the bioethics that they have today, so that we can have a bioethics that better reflects what people in society actually desire (Macer, 1994).

The theories of ethics

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 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. Given the international mandate of the World Health Organization (WHO), there needs to be more work on world views of ecocentric and biocentric thinking if the WHO and United Nations Development Programme (UNDP), and the guidelines for use of genetic engineering, are to represent the broad values of humankind.

Bioethics is built upon the long tradition of ethics, and it is actually difficult to draw a sharp distinction between the two, except to say that bioethics deals with the choices associated with the environment, biology and medicine. However, the ethical issues raised by biotechnology are commonly termed bioethics dilemmas (Macer, 1990), 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).

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. Efforts to find medicinal compounds in nature reach back even further into human history, while use of medicinal plants is observed in other primate species (Huffman, 2001). 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, and is reviewed below. 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, as discussed in section 3.3 below.

1.3 Bioethics and molecular entomology

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 (section 4 below).

TDR's Steering Committee for Molecular Entomology has outlined a three-pronged effort towards developing genetically modified mosquitoes for malaria control. A similar approach can be envisaged in the near future for other disease vectors, e.g. those of dengue 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. This work has been developing since a 1991 meeting on use of genetically modified (GM) mosquitoes to replace disease vectors. Studies have shown that, among the 4000 known species of mosquitoes, only about 50 carry human *Plasmodium* and only a quarter of these are good vectors for the parasite. In fact, most species of mosquito are not anthropophilic (human-liking). It is predicted that, within several years, an *Anopheles* mosquito resistant to malaria may be made and that, by the end of the decade, the population genetics and ecology of these mosquitoes will be understood enough to use them for public health purposes to prevent malaria. The technology has been developing rapidly, and it has also been predicted that similar approaches will be useful for preventing other diseases of high priority to TDR (TDR, 2002). In all these approaches, social factors need to be carefully considered (TDR, 2000[a]).

For the future, we can also imagine genetic modification of the pathogens themselves, and even of the human host, as methods for resistance to disease. The emphasis of this report is on the ethics of introducing GM vectors, especially insects, for disease control. The following section will review the history of modification of insect vectors, and section 4 will examine the ethical issues.

2 THE GENETIC ENGINEERING DEBATE

2.1 Growing use of genetic engineering

The licensing of the proteins insulin and human growth hormone made from genetically engineered bacteria in 1982 signalled the beginning of the practical use of genetic engineering (Macer, 1990). Several hundred biologicals have now been produced using genetic engineering and are in clinical use around the world. Since the mid 1990s, foods produced from genetically modified organisms (GMOs) have been sold in a growing number of countries (James C, 2001[a], 2001[b]).

There has been fierce international debate over the environmental and human health aspects of GM foods, which has led to threatened trade wars between Europe and the USA. In general, no harmful effects of GM foods on human health have been shown scientifically (FDA, 2001) and the careful choice of non-toxic substances and avoidance of allergy-inducing proteins should mean that human health is not affected. However, since it is always possible that someone will become allergic to GM food, labelling is important. There is greater concern over the environmental impact of gene transfer in the environment, which is discussed below. A wide range of information is available from all sides of the spectrum (FAO, 2001; CAC, 2002; USDOE, 2002).

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 (e.g. United Kingdom Royal Commission 1989; Catenhusen and Neumeister, 1990; New Zealand Royal Commission, 2002). Some of the major issues are discussed in this report. Reports have also been made by independent organizations on the ethical issues (e.g. Nuffield Council on Bioethics, 1999[a]). Despite this widespread debate, the future of food production is tied to the use of varieties of plants and animals made from genetic engineering, especially for developing countries that face food shortages (UNDP, 2001).

Some drought-stricken countries in Southern Africa, e.g. Zambia, have recently taken decisions to reject food aid because it may contain GM food, the same GM food which is common in North America and some other major exporting countries e.g. Argentina. Some developing countries, however, accept the use of GM food and crops. China was among the early developers of GM crops, while India accepted the use of GM cotton in 2002, after several years of internal political debate over whether genetic technology was safe and whether the technology would make farmers dependent upon foreign imported seed and technology.

2.2 International systems for consideration of genetic engineering

A formal emphasis on ethical issues has only recently been considered in the UN system, despite major work in academia and nongovernmental organizations (NGOs) in the 1980s (Macer, 1990). For example, the 1991 Food and Agricultural Organization (FAO)/World Health Organization (WHO) Conference on Food Standards, Chemicals in Food and Food Trade recommended that the terms of reference for the Joint FAO/WHO Expert Committee on Food Additives be expanded to include biotechnology, but that this body should "only consider scientific issues regarding health, safety and technical concerns and should not be involved with socioeconomic, ethical or like issues which properly should be addressed in other fora" (Macer, 1999). In the Codex Alimentarius Commission (CAC), the joint FAO-WHO Intergovernmental Commission to set food standards (discussed in section 2.3), ethical issues are often shuffled between committees for political purposes as there may not be international consensus. In fact, safety is based within the ethical principle of non-maleficence or "do no harm".

In over 100 interviews conducted by Macer (1999) on the ethical issues of food and agriculture at the responsible UN agency, the Food and Agricultural Organization (FAO), the issues raised by GMOs and GM food were cited more than any other single ethical issue. Although a wide range of ethical issues

exists in traditional practices and social systems, the new technology of genetic engineering is a catalyst for people to think about ethical issues. Member countries need guidance, including expert technical guidance, not only on the narrow issues and implications of selected genetic technology but also on the broader issues that many are concerned about e.g. the intrinsic ethical issues of genetic engineering, intellectual property, and economic control of genetic resources and agriculture in general. In 2001, FAO released a brochure on the ethics of GMOs; United Nations agencies are, in general, supportive of the use of genetic engineering to help people in every country (UNDP, 2001).

Despite this largely technical work, there is still a need to look at the underlying ethical issues that make genetic modification a concern. The holistic definition of health as represented by the WHO definition of health as a "state of complete physical, mental, and social well-being and not only the absence of disease and infirmity" is consistent with consideration of the broader social and ethical issues as part of technology assessment.

2.3 Codex Alimentarius Commission and the safety of genetically modified food

The issue of food safety is not directly relevant to the question of use of GM disease vectors in public health, but because of its central importance in the public attitude to genetic engineering in general, international mechanisms for its regulation are of interest. Also to be considered is that, by genetically engineering a trait in a crop plant, it might be possible to complement vector control, e.g. by using plants to release insecticidal toxins that inhibit the breeding of vectors.

In 2000-2001, WHO (WHO, 2001) convened a series of expert consultations to address the safety of foods derived from biotechnology. The consultations addressed overall aspects of the safety assessment of genetically modified foods of plant origin and of foods derived from genetically modified microorganisms (GMMs), as well as the potential allergenic effect of foods derived from biotechnology. There were technical papers on the concept of substantial equivalence and GMO products, and other documents produced by the Organization for Economic Cooperation and Development (OECD) for the G8 summit meeting in Okinawa in 2000. FAO (1997, 2001) has also released reports on the theme, and promotes safe use of biotechnology.

Human health aspects of GM food are specifically reviewed by the Codex Alimentarius (CAC) Ad hoc Intergovernmental Task Force on Foods Derived from Biotechnology (established by the 23rd CAC, June 1999). This Task Force has developed model risk assessment guidelines for genetically modified foods in general, as well as those from GM plants and microorganisms, as strategies for dealing with emerging food quality and safety issues (CAC, 2002), and has produced a number of reports e.g. Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology, Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants, Proposed Draft Guideline for the Conduct of Food Safety Assessment of Recombinant-DNA Microorganisms in Food. The role of this Task Force in the management of ethical controversies is discussed in section 4 below.

3 MODIFICATION OF VECTORS AND PATHOGENS FOR PUBLIC HEALTH PURPOSES

3.1 Methods used for control of insect vectors

A biological method that has been shown to be effective in the field for area-wide control of some insects is the sterile insect technique (SIT), which involves raising large numbers of insects that are then sterilized by irradiation before being released in the field (Lachance, 1974). If sufficient numbers of competitive male insects are released, most wild female insects mate with these and thus produce no viable offspring. There have been some successful programmes in different areas since the 1970s, e.g. for eradication or suppression of Mediterranean fruit fly (Mansour and Franz, 1996), screw-worm in Central America (Krafsur and Lindquist, 1996), tsetse fly from Zanzibar, melon fly from Okinawa, and medfly from Mexico (Krafsur, 1998).

The SIT has been used mainly in agriculture. Although at the start of the 1970s entomologists began to switch from reliance on chemical pesticides because of concerns over pollution and the problem of resistance to pesticides, trials of SIT against rural mosquito populations in villages in India and Central America have encountered problems due to immigration of females already inseminated with fertile sperm. Other insect control measures that are more widely used include biological control, pheromones and biological pesticides. In the case of human disease, physical barriers such as bednets are very important (D'Alessandro et al., 1995). However, even in the year 2000, WHO argued that DDT was still essential as a mosquito control agent, despite its withdrawal from agricultural production systems because of health concerns. This meant that DDT for vector control was exempted from the Stockholm Convention on Persistent Organic Pollutants agreed upon in December 2000 (UNEP, 2002).

3.2 Past attempts at introduction of modified pathogens

The drawback of the SIT is that it is not really applicable to mosquitoes over large areas because of the numbers involved. A method that modifies insects in situ (in both urban and rural settings) is needed to target a disease vector that is spread over a large area. This is where genetic engineering may be useful.

Successful agricultural products based on modified pathogens were introduced more than a decade ago. The World's first commercial pesticide based on a live genetically engineered organism was licensed for sale in Australia in March 1989 (Wright, 1989). It is *Agrobacterium radiobacter* var K1026 (Nogall), and it protects stone fruits, nuts and roses from crown gall disease. This "pesticide" consists of a harmless strain of the disease-causing bacterium that lives on the same leaves as the disease-causing strain and produces an antibiotic which kills the latter. The gene for the antibiotic is placed on a plasmid which has been engineered so it will not transfer to disease-causing bacteria and make them resistant to the antibiotic. There was an eighteen-month trial prior to the commercial release of Nogall.

In the year 2001, the first US field test of a genetically modified 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 one to two 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 twelve-fold if the sterile insects can be easily identified in the field.

A further area is to attempt biological control of disease vectors by introducing specific pathogens (Lacey and Kaya, 2000). Genetically modified pathogens will be more selective and/or more efficient at killing their vectors. These concerns have to be considered in view of alternative methods of killing insect vectors, such as with pesticide impregnated physical structures that fool insects into attacking them (News report in Science, 2001). The species specificity of such structures is one ecological concern; however, they may be more predictable than purely ecological methods. One strategy would be to genetically modify the vectors so that they are attracted to bait or physical structures as a method to kill them.

3.3 Development of genetic modification techniques

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). Genetic engineering can be defined as the modification of genetic material by recombinant DNA techniques, including the deletion, modification, or insertion of genetic material in a genome. For example, a new gene may be added to a genome to add a new function or make a new enzyme. This gene can be from any species, as all organisms use the same DNA coding system.

A common way to insert DNA for genetic transformation of insects is to use transposons or viruses (O'Brochta and Atkinson, 1998; Lewis et al., 1999). Naturally occurring arboviruses (which do not infect vertebrates) can be modified to express and silence genes in mosquitoes so that determinants of vector-pathogen interactions and other important vector phenotypes can be characterized rapidly (Olsen et al., 1996; Johnson et al., 1999), while mosquito-specific viruses could also be engineered to increase or enhance their biopesticide capability (Ward et al., 2002). Other systems of gene modification may also be developed, given the large amount of attention to genetic engineering in medicine and agriculture. 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. There is a significant hurdle to engineer genes into mosquitos in the wild even if this can be accomplished in the laboratory. There is still a major problem about how to effectively drive genes into vast wild populations after they have been engineered into a few laboratory mosquitos.

Transposons, also known transposable elements, facilitate their own excision and re-integration into another site in the genome using enzymes called transposases. Transposons can be constructed to include any gene combination, and they are microinjected into insect embryos for integration into DNA. 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 (Ladeveze et al., 2001). Over the past twenty years there has been much research on transposable elements in *Drosophila* (the fruit fly), while a dozen other insect species have been genetically modified by using transposons (Atkinson et al., 2001).

In order to easily identify and select genetically transformed insects from those not transformed, a marker is used. A universal marker that is used to follow gene transfer in any species is GFP from the jellyfish. So far, GFP has been used in flies, mosquitoes and beetles (Berghammer, 1999). Enhanced green fluorescent protein (EGFP) has been transferred to *Anopheles stephensi* mosquitoes (Catteruccia et al., 2000). Use of luciferase as marker gene has also been reported (Johnson et al., 1999).

To genetically manipulate disease vectors, transgenesis systems must be developed (Alphey et al., 2002). 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 (Beatty, 2000). The latter step raises more ethical issues about the safety and desirability of changing the entire vector population, and possibly related species, as will be discussed in the following section.

Apparently stable, germ-line transformation has been achieved in mosquito species that transmit yellow fever, dengue, LaCrosse encephalitis and malaria, using varying techniques and DNA delivery vectors (McCullough, 2001; Lycett and Kafatos, 2002). However, the efficiency of genetic transformation needs to be improved from the under 10% at present. Researchers have genetically manipulated a mosquito, using a Sindbis virus expression system, to express antibodies against the malaria parasite, and this has reduced the number of parasites in the insect's salivary glands by 99.9% (Capurro et al, 2000). Ito et al (2002) reported that they had generated a strain of *Anopheles stephensi* mosquitoes which carries a piece of DNA that induces the production of a peptide (SM1) after blood feeding which blocks transmission of the parasite. These are important steps towards the genetic modification of mosquitoes that transmit malaria to humans (Enserink, 2000).

Some efforts are focused on genes that enhance insect immunity to pathogens. In *Aedes* mosquitoes, expression of a gene has been controlled with a regulatory sequence (promoter) that is activated by a blood meal, since disease agents are spread in mosquitoes after the ingestion of infected blood (Moreira et al. 2000). *Aedes aegypti* is important for transmission of dengue fever in Latin America and elsewhere. Resistance to dengue virus transmission was one of the first reports of genetic modification of mosquitoes (Olsen et al., 1996).

Genetic transformation in *Anopheles* has not progressed as far as in *Aedes* because of the greater difficulty of manipulating the more fragile *Anopheles* embryos. In 2000, scientists working in the UK, Germany, Greece and Brazil achieved transformation of *Anopheles gambiae* cells, the major malaria vector in Africa, and *Anopheles stephensi* embryos, the major malaria vector on the Indian subcontinent (Catteruccia et al., 2000). Once the hurdle of genetic transformation is overcome, almost any target gene can be modified and many approaches can be attempted.

Another potentially useful system is a so-called "terminator" gene, constructed in the *Drosophila* system (Heinrich and Scott, 2000). This gene is, under certain conditions, lethal to transgenic females but otherwise has no effect on either male or female viability. It is considered especially useful for sterile insect release programmes, when only males are released because transgenic females would be killed.

An alternative approach to transforming insects for disease control is to transform the bacterial symbionts living within the insect (Beard et al., 1998). This paratransgenesis approach has been utilized to explore means of preventing transmission of American trypanosomiasis (Chagas disease) from triatomine bugs and of African trypanosomiasis (African sleeping sickness) from the tsetse fly. Bacteria that populate the guts of these insects, necessary for parasite development, may be altered to prevent pathogen development. A potential method for field dispersal of GM bacteria to control Chagas disease transmission has been developed and is being prepared for field testing.

3.4 Modification of other organisms

One option is that a plant, such as corn, could be genetically modified to express specific insecticidal toxins from *Bacillus thuringiensis* (Bt). These toxins would be carried by the wind into mosquito breeding areas as a larvicide (Spielman and D'Antonio, 2001). In the past, large areas were sprayed with Bt spores, but now Bt is widely used in genetically modified corn and other agricultural crops. Microbial control agents like Bt have been established as a commercially viable and promising alternative to conventional pesticides. They have high efficacy and good environmental safety (TDR, 2002). However, resistance to Bt has developed in several target species, and given its importance in agriculture, study of the ecological implications of this type of approach may prove to be equally complex as direct modification of the vectors themselves.

The use of beneficial organisms for the control of mosquitoes was first recognized in the 19th century, when attempts were made to introduce predators such as dragonflies (Lamborn, 1890). However, mass breeding and successful introduction of predators such as hydra, flatworms, predacious insects or crustaceans, often bring a range of problems. Such problems did not occur, or to only a limited extent, with the use of fish such as the mosquito-eating fish *Gambusia affinis*, which was successfully intro-

duced into many countries to control mosquito larvae in the early 1900s (Legner, 1995). *Telapia* fish have been introduced in the Phillipines. In these cases, people eat the fish, so there is potential benefit in introducing them in integrated pest management of agricultural production systems. However, concerns have been expressed because some of the fish may eat other species of animals (Laird, 1997; Service, 1995), and this may be one reason for the declines seen in amphibian populations.

A further possibility would be to release a transgenic predator of the vector species, e.g. genetically modified mosquito-eating fish. Use of modified animal hosts in agriculture will provide some lessons on the ecological success of such an approach. For example, research has been carried out to make sheep resistant to blowfly strike, which causes the deaths of many domestic animals in New Zealand and Australia (Scott, 2001). Genetically modified blowflies have been made, and an objective of the research is to develop a system that is lethal to the flies under certain conditions only. The immediate plan is to develop the project through use of the sterile insect technique, but the future target is to modify the sheep. In Australia, genetic modification of European carp, an invasive species of fish, is being tested to eliminate the pest through daughterless gene transformation (Nowak, 2002).

3.5 Modification of human hosts

In vaccination, modified pathogens may be used as immunogens to develop resistance to the pathogen in the host. We can also consider developing genetic vaccines by modifying the host rather than the pathogen. Immunization has few ethical dilemmas unless there are substantial risks to those being vaccinated. Human genetic modification has been the subject of extensive ethical reflection (Macer, 1990), and the general consensus is that vaccination of individuals is ethically justified when proven effective and safe. However, because pathogens often mutate rapidly to develop resistance to immune defences, the prospect of making vaccines for all human diseases cannot be relied on.

4 ETHICAL AND SOCIAL ISSUES

4.1 Reducing the complexity of ethical and social issues

One of the reasons why there is such confusion over the use of genetic technology is the failure to deal with ethical and social issues in an organized manner. Perceived complexity has also been a barrier to progress in regulations covering the environmental release of genetically modified organisms. While natural science attempts to tackle problems in a systematic manner by controlling variable factors to allow experiments, ethical dilemmas are not normally dealt with in a systematic framework. Often scientists consider that ethical issues are too complex to discuss rationally, and debate on genetic engineering is spoilt by the failure to clearly identify specific moral questions that need to be answered. After looking at what type of framework might be needed, the section below considers a number of social and ethical issues.

As discussed in the introduction, there are several ways to approach bioethics: descriptive, interactive and prescriptive. These aspects are included in the TDR mandate. Each aspect is related to the other, but a collective approach needs to be thorough. The United Nations Development Programme (UNDP) and WHO have duties to all member countries, which they fulfil by gathering and sharing information, a descriptive function. A further function, that may extend to being prescriptive at times, is as a centre of excellence at international level. WHO and UNDP are intergovernmental forums that have a unique role for interactive ethics. They also host a variety of informal technical meetings, receive expert consultations, support symposia, and provide expert technical advice on policy, some of which relates to ethical choice between different technologies based on concerns beyond raw productivity. A unique role at intergovernmental level for WHO and UNDP is to consider how ethical values can be incorporated into policy beyond the economic efficiency arguments that may be more dominant in the economic analyses discussed by national governments, when trade principles have highest priority.

These complex issues need to be dissected so that they can be easily identified and incorporated in policy, planning and action. The ethical, legal and social issues identified have been separated into several categories, as outlined below.

(a) Opportunities and problems that can be addressed on an ongoing basis if appropriate mechanisms are introduced and maintained

Some issues may be resolved to the extent that they do not need ongoing management or review, and monitoring mechanisms can minimize any conflicts between parties and safety problems. All partners of TDR, UNDP, World Bank and WHO may need, however, to develop new infrastructures and training to deal with component ethical issues as they arise in rapidly emerging areas such as biotechnology. This will help supplement the legal guidelines that have been produced in some member countries to cover some applications of biotechnology, and international undertakings such as the Cartagena Protocol on Transboundary Movement of Live GMOs (CBD, 2000).

Specific opportunities can be identified and incorporated in policy, planning and action. TDR is called on to take a stand (for, against, or no comment) on issues that relate to WHO's unique international mandate to promote health for all, including for the future of humankind, and to be involved in areas where it can be a productive partner in achieving the general goals for member countries. Taking a stand may e.g. be to say that a given technology is good or bad in a given case; it could also mean taking a decision not to comment.

One of the main concerns of releasing GMOs is environmental risk (FAO, 2001). 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 (Ho, 1998), 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). There are concerns over

unknown long-term effects, which could call for ongoing monitoring of farming systems. In fact, the long-term effects of using living organisms in general, not just GMOs, is a useful area of study that could potentially benefit humankind and ecosystems much more than the use of one particular GMOs. Although the environmental release of GM insects may require an extra level of containment, the system falls within this first group of ethical issues because any specific issues can be dealt with in a systematic manner by designed experiments.

(b) Controversial issues considered at global level but not resolved

The GM food debate has been an extremely controversial area of science and technology, and is one that WHO and FAO have constitutional mandates and moral obligations to consider under the themes of food security and food safety of the Codex Alimentarius Commission (CAC, 2002). The Codex Alimentarius Ad hoc Intergovernmental Task Force on Foods Derived from Biotechnology (established by the 23rd CAC, July 1999) is currently developing a strategy for dealing with emerging food quality and safety issues (CAC, 2002). It is hoped these issues will soon move into group (a), if an international mechanism can be agreed upon. However, other legitimate issues for the GM debate, e.g. ethical and social concerns beyond food safety and traceability, are likely to remain in this group of unresolved issues for some time.

The international movement of live GMOs between member countries is covered by the Cartagena Protocol on Biosafety under the Convention on Biological Diversity (CBD, 2000). This convention created a set of biosafety clearing houses in member countries that identify responsible persons in each country, as will be discussed below (regulatory section). However, the issue of environmental release of GMOs, and trade in food produced from GMOs (not live GMOs), continues to be vigorously discussed and remains a public controversy.

While the food crisis is well documented, when UNDP (2001), in its Human Development Report, supported the use of GMOs to provide food to developing countries, there were many opposing voices. Opinion surveys in which people have voiced more fears about insects and animals than plants, allow us to predict that any release of insects will be controversial. Public concerns have already been expressed about agricultural trials of GM insects (Union of Concerned Scientists, 2001).

The approach to resolving these issues will be to move components of controversial issues into manageable areas (of type [a]). Specific controversial issues as given above should be defined scientifically, analytically and rationally, and discussed with the intention of shifting them into manageable areas within the framework rather than being broadly debated, when they often don't get resolved.

(c) Controversial issues not considered

New ethical issues about GM arthropod vectors and their symbionts and/or pathogens should be subject to extensive open discussions and forums. Some of the new technical possibilities need to be assessed for the ethical and social issues they raise. TDR policy decisions are required as to whether TDR should play a major role in any of these areas, but especially in the field of opening up new areas for public discussion. Should the role be to stimulate other organizations to take effective action to work towards resolution of emerging issues? TDR is called to respond to all issues within its mandate and, even if it is not to reach a stand on a particular issue, TDR does have a role to play as the most appropriate intergovernmental forum for discussion of these issues.

As discussed below, 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.

4.2 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 (Macer, 1990; Nuffield Council on Bioethics, 1999[a]; Comstock, 2000).

One of the key questions is whether there is an intrinsic value of genetic integrity at an organism and ecosystem level which humans should not change. 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 (Macer, 1990). 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. Therefore, there is no 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.

One 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 (Macer, 1990; 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.

4.3 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 per-

sons with these ecocentric world views than traditional methods of insect control that attempt to eradicate a whole insect population.

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 less than the species affected by the use of pesticides. 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.

4.4 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; Alvarez-Castillo, 2001). 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; American Anthropological Association 1998; Kleinman, 1999) and epidemiology (Capron, 1991; Dickens, 1991; Gostin, 1991; Chee et al., 1996). Recent examples include the collection of genetic samples from persons in China by US researchers without any informed consent, or with forged informed consent documents. This shows us that even institutions that claim to have high ethical standards abuse research participants (Lawler, 2002).

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 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.

One of the ethical traditions in TDR is the effort to free children from the burden of often forgotten tropical infectious diseases. 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.

4.5 Consent from broader society on environmental risks

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. 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 GM organisms. Environmental risks can be considered from both anthropocentric and eco-centric-based approaches. The risks identified include the possibility of horizontal transfer of the transgene to non-target organisms, and possible disturbance of insect ecology (Tiedje et al. 1989; Hoy, 1995; Nuffield Council of Bioethics, 1999[a]). 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.

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.

4.6 Social consensus building and early cessation of trials

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. How can we resolve the conflict between not being paternalistic (which means asking all citizens for their consent) and the impracticality of waiting for every single person in a community to agree?

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 a position to achieve social consensus. The mechanisms for social consensus in biotechnology are not well under-

stood in the affluent countries who 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. There is therefore a need for further research in parallel to the trials, so that realistic cases can be faced by a community and the process followed.

It is possible to imagine the rumours that would arise mid-trial should an uncontrollable event like flooding ever result in an increase of vector population. The increase in vector population might be falsely attributed to the trial of the modified vector and result in increased public opposition to the trial. Perhaps, in such an event, community opposition to the trial grows from 5% to 30%. Can consent be withdrawn at this stage, as it can by an individuals who are participating in a clinical drug trial? Release of a modified vector is not the same as a clinical trial of a new drug. Once started, all persons in the area have to continue to be subjects, until the point when the whole community decides to stop the trial and the trial is terminated.

On the other hand, a contingency plan for an unexpected adverse event must be ready in case the modified vectors need to be killed. This could either involve a pesticide or a specific chemical designed to selectively kill the modified vectors. It might be possible to insert specific chemical sensitivity in the vector by genetic modification. In this case, the added expense in terms of finance and risks to the environment and health for control of genetically modified vector trials having bad effects would be justified, whereas in the existing situation such control measures would neither be feasible nor appropriate.

After completing the field trial, if the modified vector is recommended for larger scale or general use, it may not be practical to obtain the consent of everyone in the community. A referendum might be the most appropriate method of providing information to the community, but there may be no way to accommodate the wishes of a significant minority if the substantial majority agrees and the scientific evidence supports the intervention. In many endemic areas there are no appropriate political structures to consider a referendum.

4.7 Equality and inequality in access

The rejection of interventions to reduce infectious disease by some members of a society, whether they are national regulatory authorities or isolated local community leaders, will create inequality of access to prevention, therapy and information. Although information should be accessible on the Internet, and in many communities there will be someone who is able to access that information, there will be a number of persons who do not have access or who are not sufficiently literate.

Regarding the actual intervention, a modified vector would likely be introduced in a whole community based on geographical or geo-biological features, regardless of wealth. In this way, the equity concerns may be less than with procedures such as localized pesticide dispersal or insecticide-treated bed-nets, which may be more common in richer areas than poorer ones. However, in case of any geographical clustering, this should not be preferential to the interests of the rich.

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. 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.

Although there is no guarantee that a trial will succeed, the participants should still receive benefits from being involved. These benefits include increased education about the disease and about the vec-

tor's role in transmission, which is essential for the process of informed consent. There should also be immediate benefits from any disease prevention methods offered, e.g. access to pesticide treated bed-nets. The concept of benefit sharing is important and related to compensatory justice, as well as to recognition of the persons themselves.

4.8 Ethics of technology choices and knowledge development

This issue is linked to modernization. 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. Who's science is "good" science? Commonly there is a concept that broader impact issues should be dealt with after a technology has been developed, sometimes called "externalities", rather than concentrating on precautionary and preventive actions. This issue needs long-term vision, which may relate to the short time frame for most political decisions as opposed to the long time frame for social and environmental improvement. The ethics of calculating market costs versus ethical concerns about different options need to be considered part of the choice of technology.

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. This general social background could be considered the underlying basis for establishing the Steering Committee, in TDR, on Strategic Social, Economic and Behavioural (SEB) Research, which states "a better understanding of how social, behavioural, political, economic and health system factors operate to affect disease patterns and disease control methods will be important for identifying future needs, opportunities and innovations for improved control of TDR diseases" (TDR 2000[b]). There is a clear scientific rationale for developing these studies, consistent with the ethical principle of beneficence.

Any professional global organization in the 21st century is expected to give independent, balanced and professional technical advice that is suitable for local conditions. There are still questions to be resolved, such as "When should a professional body or expert offer alternative options beyond a list of two initial choices that the country requested help to choose between, when the options are equally viable and may reflect more the overall ethical mandate of TDR and/or the ethical culture of the member country?" When considering the ethical issues in preparing investment projects that TDR is called upon for advice, lessons can be learnt from the environmental and social impact guidelines of bodies like the Cartagena Protocol on Biosafety (CBD), FAO, and the World Bank. From these, more formal guidelines for assessment of TDR projects can be developed.

4.9 Intellectual property rights and technology transfer

A number of ethical issues have been raised in international debates over the morality of patents (Macer, 2001), and there have been strong calls against the patenting of medical innovations (Nelkin and Andrews, 1998). 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). In light of intellectual property considerations, some might ask whether it is ethical for TDR to provide a pathogen or vector to a local community for reproduction, knowing that the community will reproduce the agent without paying any royalties. The answer appears to be an unequivocal "yes", with the recent international consensus over interpretation of article 31b of the Trade-Related Intellectual Property Rights (TRIPS, 1994) agreement to give priority to medical emergencies. Article 31(b) says that something under intellectual property protection can be used without authorization of the IPR holder where the law of

a member state allows for other use of the subject matter of a patent without the authorization of the IPR holder "in the case of a national emergency or other circumstances of extreme urgency or in cases of public non-commercial use". Thus, even the WTO has accepted that the global economic system is secondary to the ethical mandate to save human lives.

Utilization of genetic diversity as a tool of genetic engineering, and market commodification of genetic resources, are concerns that have been widely debated by FAO and the Intergovernmental Commission on Genetic Resources in Food and Agriculture (CGRFA) (IPGRI, 1997; Macer, 1999). The principle of compensatory justice would say that, since rich countries have benefited so much in past centuries from the use of genetic diversity in poorer countries, the whole concept of recognizing only new genetic variation in intellectual property is ethically questionable.

For a fruitful partnership in developing a technology, there is a need to seek the understanding and support of the holder of the IPR. The original maker may have the best expertise to continue improving the technology based on field experience, so should ideally be a partner in the planning of any field introductions. Therefore, advance negotiation should be held with all patent holders, as in negotiations for the use of vitamin A-enhanced genetically engineered rice in 2000-2001, so that they support use of the technology to save lives in developing countries. With sufficient public pressure, which can be ethically pushed by WHO for the purpose of saving life, and an ethically conscious industrial community, the IPR problem should not be a barrier to any GM medical project in the developing world.

4.10 Inducement to participants

With regard to human genetics sampling, the Human Genome Organization (HUGO) Ethics Committee (1996, 2000) has recommended that the actual or future benefits discussed should not serve as an inducement to participation. Nor should there be any financial gain from participation in genetics research. This does not exclude, however, the possibility of reimbursement for an individual's time, inconvenience and expenses (if any), even if there is a general distribution of benefits to the community. This is an issue that needs to be worked out before the trials begin.

In the case of trials that might be linked to profit-making endeavours, a percentage of the net profits (after taxes) should be donated to all members of the community in the geographical region because they all participated in the research. Limiting the returns to only those leaders who gave consent for their community to participate could create divisions within a group, is inconsistent with solidarity, and could be considered a bribe. The benefits of such trials could include health care infrastructure, vaccines, tests, drugs, treatments, or other humanitarian efforts. While projects on vector control for public health might not initially be seen as profit-making, the results and techniques developed could be of potential profit to agriculture and public health in communities with the ability to pay for related technology. This issue has been discussed widely for human population genetics research (Chee et al., 1996).

5 PUBLIC ATTITUDES TO GENETICALLY MODIFIED ORGANISMS

5.1 Need for public acceptance prior to interventions

One of the major driving forces of TDR is said to be the ability to bring together a large number of partners, donors, researchers and developers, from the North and South, and to catalyse processes to solve public health problems and build research capacity. The goal of the project on social, economic and behavioural factors is to bring in the public at all levels, including the local community, as full partners.

The nature of the work on public health interventions for major diseases necessitates involving several partners, and it is necessary to ensure that all partners maintain core ethical standards. If there is a breach of ethical practice, all partners will be criticized. WHO has not always been applauded for its efforts to reduce tropical diseases since the 1950s. However it is widely recognized that WHO is technically the most competent organization with the highest moral authority for effecting interventions to control diseases (Balter, 2000). Opinion surveys show that when it comes to biotechnology, the United Nations organizations, such as WHO, are the most trusted organizations and regulatory authorities in the world, while only a fraction of people trust their own government or industry (Macer et al., 1997).

In India in the 1970s a WHO/Indian Council for Medical Research project on various forms of SIT for mosquito control was stopped after six years work because a journalist and the Parliamentary Public Accounts Committee claimed that the intention was to research not new methods of vector control, but biological warfare. These claims were echoed by Hanlon (1975), but his article was criticised by Curtis & Curtis (1976). A point-by-point rebuttal of the claims was published by WHO (1976). A 3 page editorial in *Nature*, in 1975, stated that the claims about biological warfare were "tenuous in the extreme" but made the fair criticism of WHO that it should have been more open with the media and taken more time and trouble to explain the work of the unit and answer the journalist's concerns. This advice should be taken very seriously by future researchers with genetically manipulated mosquitos.

The fears of biological warfare have continued. For example, in India there were concerns that strains of cholera found in an outbreak in the late 1990s were more consistent with introduced strains than local strains, and biological warfare concerns were also expressed in regard to the proposed Human Genome Diversity Project in the 1990s (Chee et al., 1996). The 2001 bioterrorism scare involving anthrax in the United States has increased global fears of biological warfare, and because some books on biological warfare have noted that mosquitoes would be good as vectors of biological warfare (BW) agents, it is likely that these concerns will continue. Any project that involves GM mosquitoes will have to be clearly separate from BW research. However, the data gathered in field trials of GM insects will be useful for any purpose, to some degree, and this calls for careful choice of research partner so as not to be associated with researchers linked to BW research projects. Potential ethical issues may arise if results from field trials provide a particular advantage for offensive use of BW as opposed to defensive use, but that is not currently foreseeable and all information should be published openly. There have been times when some countries, e.g. USA, have restricted export of biotechnology knowledge for fears of misuse of that knowledge. However, in opinion surveys that ask open questions over people's concerns about applications of genetic engineering, biowarfare is cited by only 1-2% (Macer, 1992; 1994). We could expect that, subsequent to the terrorist attacks in the USA on 11 September 2001, the use of anthrax-containing letters has increased this concern.

In the past in Africa, some trials to introduce competitor insects resulted in the fear that larger-sized mosquitoes were worse for people than small ones, even though the bigger mosquitoes were not vectors of human disease but were intended to be ecological competitors. Thus, education is needed

before introducing an intervention. The local beliefs of communities need to be studied so that they are documented and known, so that programmes can utilize local knowledge to help educate people and design interventions that will be socially accepted. An intervention that is not socially accepted is not likely to be successful.

Strategies for social behaviour change to reduce vector populations and transmission of disease have had mixed results. Improper waste management and disposal systems, unplanned building activities, stagnant drains, waste management problems, have all been cited as reasons for continued high vector populations. While public education needs to continue in attempts to find low-technology solutions to these problems, the mixed experience suggests that social interventions alone will not be sufficient to reduce vector numbers.

5.2 Results of public opinion surveys on genetically modified organisms

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 (Macer, 1992). In the Asian region however, there is significantly less concern in India, China and Thailand than in Australasia, Japan, the Philippines and Russia (Macer, 1994; Ng et al., 2000). It is a question for further research whether there are differences between countries in the way they balance the benefits and risks of biotechnology.

In a survey conducted at the end of 2002 in Japan I asked two questions relating to GM insects to a randomly selected national sample. 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 encephalopathy, 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.

Among a series of specific examples of GMOs to be released into the environment (Macer, 1994), more public in most countries supports release of bacteria to clean oil spills than to modify plants and animals, suggesting that, despite general concerns over microorganism release, if the purpose is considered worthy, people will be supportive. The majority of concerns people have are of health impact on their family and themselves, fears that the technique is inherently unnatural, lack of trust in the system of safety assessment, and general fear of the unknown. Fewer people mention environmental concerns.

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). Opinions towards applications of biotechnology are formed by a variety of bodies in society, and have been surveyed in many countries (European Federation on Biotechnology, 1999). Episodes such as the human transmission of bovine spongiform encephalopathy (BSE), which causes human deaths from Creutzfeldt-Jakob disease in Europe, have shown that government scientists are not always to be trusted to discuss risks (Dealler, 1995). The failure of the government authorities led to higher public trust in NGOs, including environmental groups such as Greenpeace. 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.

All these 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. 200), are the main criteria 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.

5.3 Wide social and legal discussion of biotechnology

Animal diseases are also transmitted by insect vectors. Biological control programmes have long been used in agriculture, and there has been some discussion of introducing novel insect species into the environment in biological control. Although use of genetic engineering is more recent, already significant work has been conducted by many organizations on risk communication and public acceptance of GMOs, especially in the food and agriculture sectors. Among the UN bodies, FAO has committees on biotechnology, bioethics and biosafety, which may be potential partners for future collaboration about introducing GM vectors.

The positive and negative aspects of genetic engineering are discussed in a wide variety of publications. Many popular books are negative in their portrayal (Ho, 1998; Wheale et al. 1997; Rifkin, 1998), while a few are positive or neutral (Macer, 1990; Reiss and Straughan, 1996; Bruce and Bruce, 1998; Comstock, 2000). The ethics of technology that controls reproduction has mainly been considered for plants, but a 1998 FAO conference dealt with animals and the use of terminator technology. The ethics of reproductive and transgenic technology in land and marine animals has also been discussed, although less so for insects.

Particular ethical concerns have been raised over animal cloning. International instruments have dealt with human cloning, such as the ban imposed by Article 11 of the United Nations Educational, Scientific and Cultural Organization (UNESCO) Universal Declaration on the Human Genome and Human Rights (1997), but this Declaration did not mention animals. The HUGO Ethics Committee Statement on Cloning (1999) recommended that "animal cloning be subject to the same principles concerning animal welfare as other experimentation on animals". It also says "Regard should be had to possible consequences for biodiversity". Cloning technology is now being applied to animals for food production and use in research (Nilson, 1997).

6 REGULATIONS

6.1 General basis for regulation

In the TDR strategy for 2000 to 2005, it is stated that research and development of means to combat disease and improve health must adhere to internationally accepted legal and ethical principles (TDR, 2000b). 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. 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 vectors and pathogens for disease control, that distinguishes them from GMOs for agricultural use and food production, 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. More detailed examination may be necessary before introducing GM pathogens themselves. The general principles of biosafety have always attempted to contain pathogens, with the exception of vaccines.

Decision-making can be contrasted between legalists, who strictly follow guidelines or laws, and situationalists, who use principles to guide case-by-case decision-making (Fletcher, 1966). Often a case-by-case approach is necessary, so committees are needed to interpret the rules. Thus ethics committees are a useful way to implement guidelines, and transparent ethics committees should be established locally to review research trials.

The term international implies that a cross-cultural approach should be used for setting standards. The term cross-cultural includes both a broad representation within one society and a transnational approach. Even in the case of a trial on an isolated island of a single sovereign state, if it involves TDR, it should utilize international expertise. If a trial fails in one site, the failure could hold up progress internationally for years due to negative public images. Thus a trial of a GM vector is not just a national issue.

Once we accept that trials will necessitate international approaches and collaboration, we can ask what is the appropriate international forum to examine the safety of GM pathogens and vectors. 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, genetically modified plants, animals (including for example, insects, molluscs and fish), and microorganisms and their products and by-products".

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 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 D.C., 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

6.2 Cartagena Protocol on Biosafety

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 living modified organisms resulting from modern biotechnology that specifically focuses on transboundary movements of living modified organisms. The parties to this protocol agreed to ensure that "the development, handling, transport, use, transfer and release of any living modified organisms 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 Cartagena 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 living modified organism (LMO) may be relevant to future projects of TDR as it becomes accepted in international law in general because of the Protocol. It is being adopted in documents from other UN bodies, such as those of the Codex Alimentarius Commission. The actual term "living modified organism" is still not as widely used as "genetically modified organism", the term that has been used for two decades in academic and media debates.

If the vector, symbiont or pathogen is a LMO, it would be covered under the Protocol. Because of additional regulatory considerations, some developers may wish to develop pathogens or vectors carefully so they would be deliberately excluded from the provisions of this Protocol, which could be done by making sure the products and processes used do not come under the category of modern biotechnology for the purposes of the Protocol. For example, sterile insects and vectors with chromosomal or gene deletions produced in traditional ways or by traditional ways of selection, may not be considered as LMOs for the purposes of regulation. However, a responsible programme would want to cover any process used to modify the vector so that the vector (product) itself is carefully examined, not just the process of production. One important exclusion of the Cartagena Protocol is in article 5, which states, "the Protocol shall not apply to the transboundary movement of living modified organisms which are pharmaceuticals for humans that are addressed by other relevant international agreements or organizations".

One useful development of the Cartagena 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.

6.3 National and regional regulations

General guidelines for working with recombinant organisms exist in many countries, and international assistance through the Organization for Economic Cooperation & Development (OECD) and UNIDO is available for countries that do not have regulations. Some countries have already established and published guidelines for the safety assessment of genetically modified insects. The international regulations are important as models for countries that lack the means for considering the details on their own.

The United States Department of Agriculture (USDA) has reported the results and approval procedures for six trials of genetically modified organisms. 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 three 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.

Like most medical associations, some professional scientific organizations have ethics codes (e.g. the American Anthropological Association, 1998). More specific to transgenic insects in the USA, Arthropod Containment Guidelines were developed by the American Committee of Medical Entomology (ACME, 2000), part of the American Society of Tropical Medicine and Hygiene. If the transgenic arthropod is assigned to a risk level in the US public health services' Biosafety in Microbiological and Biomedical Laboratories, then institutional biosafety committee approval is required. If the field study involves humans, IRB oversight is necessary. IRBs in the USA require each human subject in a field trial to give informed consent to be involved in the project, as discussed in section 4. This example may be useful as a model for developing international guidelines, and for countries developing their own guidelines.

A few local communities have established GM free areas, but this may require specific national legislation. Australia allows local communities to declare GM-free areas, and in a sense this is consistent with the ethical underpinning that leads to calls for community consent. It is an issue that needs to be considered in the field in particular cultural and political frameworks. If a specific sector of a community has a medical need, their claim to be free of risk of disease does need to be taken into account if other members of the community have blocked efforts towards new strategies that might reduce this disease burden.

7 RECOMMENDATIONS FOR KEY AREAS TO ENSURE ETHICAL INTEGRITY IN THE USE OF GENETICALLY MODIFIED VECTORS AND PATHOGENS

7.1 Establish safety and international standards before field trials

There may be a need to establish an international safety code under TDR. Because of limited resources and experience, there is a need for policy guidance for ethical genetic engineering of microorganisms, plants, animals and ecosystems in each country before release of GMOs. Policy advice in each country should be the product of open social dialogue including all sectors of society. That the process of social debate needs to be held before releasing GMOs is a lesson learned from countries that have attempted to use GMOs before wide social discussion took place. In addition, an international approach is required since vectors do not honour national borders, nor is their behaviour always predictable. Although some international NGOs take a very negative view towards genetic engineering, they do provide a useful sounding board for governments so that a thorough examination of the issues is made before GMO release. However, given the international consensus that some GMOs are safe to release as argued by UNDP and FAO, and the fact that there were already 50 million hectares of land under genetically modified plants in 2001 (James C, 2001 [a], 2001[b]), the question is not whether to release GMOs but how to release them, and what type of GMOs are safest and most effective.

Part of the process is for a society to set values for consensus on risk assessment. There is a need to find a universal minimal standard of risk assessment as diseases and vectors cross national and continental borders. The following areas need to be considered in developing model guidelines:

- Before field release of transgenic organisms, 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 site including consideration of appropriate social and cultural factors.
- Even if there are no perceived 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 TDR auspices to offer advice to researchers seeking guidance on the ethics of projects.
- There should be prior environmental, medical and social studies for site selection, and the most appropriate site should be chosen based on the data obtained (see section 7.4).
- Information should be openly exchanged as broadly as possible to relevant community leaders, members of the community, and mass media. This needs to be done with international collaboration (see section 7.2).
- Consent should be obtained from the communities involved (see sections 4.2, 7.3). Specific mechanisms for this need to be developed and will be useful for other areas of public health interventions.
- A contingency plan for aborting field trials needs to be developed. One approach is to engineer a lethal gene for the vectors that can be induced by a non-toxic chemical to ensure total elimination of those that have acquired the genetic construct.
- Commitment to the local communities involved in field trials should be made that they will be the first beneficiaries of more permanent use of a GM vector should the results indicate that its use is appropriate.

- Intellectual property concerns should not be barriers to implementation of 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.
- To avoid any suspicion by the public that could result in their rejection of this approach, TDR and member governments should not involve partners from military research establishments in the projects.
- The data should be open to all in order to benefit from global expertise and develop international consensus.
- Whatever guidelines are developed, they should be revised as experience with genetic engineering technology grows, as knowledge of ecology and communities grows, and with societal trends.

7.2 Information access and local communities as partners

Numerous cases, from the termination in the 1970s of a WHO-sponsored release programme of chemically sterilized mosquitoes in India, to the international GM debates in the late 1990s, show the need for adequate information to be provided well before implementing genetic technology. In the interests of justice, the last decade has witnessed an emerging international consensus in many fields of research that communities participating in research should, at a minimum, receive some benefit. A benefit is a good that contributes to the well-being of an individual and/or given community (e.g. region, tribe, disease group) (Knoppers et al., 2000); it transcends avoidance of harm (non-maleficence) by promoting the individual's and/or community's welfare. Thus, a benefit is not identical with profit in the monetary or economic sense - some benefits are monetary, others are not. Determining a benefit depends on needs, values, priorities and cultural expectations.

Benefit is seen as the eventual prevention or treatment of a disease. Prior consultation with individuals and communities, and their involvement and participation in the research design, is a preliminary basis for future distribution of the benefit, and may be considered a benefit in itself. Better information is clearly a benefit and may be linked to better compliance and/or use of other methods of disease prevention.

Provision of information through the Internet allows many people who are not policy-makers to have access to basic information about projects involving GM vectors. Disseminating information in this way can be effective in resource-poor communities, but is not a substitute for finding good local communicators to spread the information at public meetings and provide written and pictorial descriptions of the reasons for the project. Not only is there the problem of Internet access but also the difficulty of understanding. Grass-roots initiatives can lead to innovations and pressure upon regulators to change policy, as seen in the history of agricultural interventions in developing countries.

We can envisage several types of scenario. One is technology transfer where a local community decides to embark on its own modification of a vector or pathogen. A more advisable policy, because of the dangers of lack of quality control in the modification event, is local production of GMOs that have already been well characterized in scientifically conducted field trials.

Even in communities without established political structures for public participation, local consumers, women's and mother's groups, etc., may be able to exert political pressure on policy-makers to introduce GMOs into their communities if they are made aware of the potential benefits to save their children's lives. This principle of empowerment is ethically consistent with WHO policy, but could at times lead to conflict if a particular country has already rejected such an intervention at political level. However, women have been distanced from decision-making in most societies (Sherwin, 1992).

Rather than conduct a public opinion survey on the acceptance of GM vectors before it is clear what the specific proposal is, interviews and surveys may be included in educational efforts and prior informed dialogue with local people about the proposal. This should be a two-way educational process

at person-person level in the field, starting with professionals (nurses, doctors, teachers), who then inform their local networks.

People who want extra information can access it through the TDR website and publications. Exercises should be developed for school students, to help them consider ethical and scientific issues, and develop maturity for making decisions they face in the technical age. International partners might include UNESCO, the International Union of Biological Sciences (IUBS), and other bodies attempting to develop bioethics education. The relevance of projects to eradicating disease in a community may act as a trigger to motivate people to become involved in the community engagement process, even if the community has not had the motivation in the past.

7.3 Group consent

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). There are some parallels with seeking group consent from population groups that may be asked to give DNA samples for population genetics research (Greely, 1996; Macer, 1997). The problem is, who represents a community? Is it the political or religious leaders? Another issue that needs to be investigated is the appropriate age of consent in different societies. The more inclusive the process the better. There is inadequate discussion of this procedure to date, and it is a key area for further discussion in order to decide the ethics of such interventions.

The changing economic, social, political and civil structures have implications for the concept of group or community consent to release of modified vectors or pathogens. There are also legal implications in those countries with laws such as patient's bill of rights (Annas, 1989). 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.

7.4 Environmental assessment

This area would contribute to more detailed environmental and social impact guidelines for TDR projects. Environmental impact data need to be collected from long-term studies so they are not subject to climatic variation. It may be useful to start environmental monitoring several years before the introduction of a GMO in target areas so there are local background data to compare future interventions with and to provide scientific accuracy for people to make informed choices.

The ecological and genetic lessons learnt from agricultural studies will be important for future public health applications of GM vectors. Concerns about the environmental safety of GM trials have been expressed by numerous writers (Ho, 1998; Rifkin, 1998) and various groups, e.g. the Union of Concerned Scientists (2001).

Regarding the environmental behaviour of modified vectors, many generations of vectors need to be studied in the laboratory to test gene stability before they are introduced in small field trials (Scott et al. 2002). If possible, there should be an initial trial on a sparsely inhabited island. To adequately test the vector however, there need to be controlled trials in disease endemic areas.

Internationally, a large amount of biosafety research on GMOs has been conducted in connection with human health and the environment, although there is still a need for international cooperation in research on environmental aspects. There needs to be consensus on the time needed for long-term studies, and for coordination and discussion of what amounts to genetic "pollution". Thresholds for acceptable levels of gene flow or ecological perturbation need to be established, and data and experience gathered from studies in countries (with UNEP, UNIDO) under a wide range of environmental con-

ditions. International guidelines and assistance in monitoring field trials of GMOs, including after widespread release has been approved, are urgently needed. Decisions as to what outcome measures are socially and scientifically appropriate, and what methodologies are appropriate to enable this in a way consistent with ethical principles such as beneficence and respect for persons should involve TDR. Because of the inherent uncertainties of ecology and societal stability, it is imperative that each intervention is tested under a range of ecological and social conditions, and that data are stored and shared in a database.

The range of ethical issues and public concerns will not be significantly different whether we are considering GM vectors or pathogens. The approach with the lower overall environmental risk is to be preferred so that research into different mechanisms is simultaneously stimulated. In both cases there are some species-specific concerns.

7.5 International cooperation

Knowledge about ethical issues in connection with GMOs should be expanded by asking member countries to contribute information and enter into dialogue on the issues. The network of contacts, including bioethics institutes, civil society organizations (CSOs)/NGOs, and consultants, can compile relevant facts and values. Molecular entomology has not been discussed amongst the international bioethics community, and there is a need for discussion of the issues at appropriate forums and conferences.

WHO is the joint partner with FAO in international work on safety, e.g. food safety in CAC, animal diseases (there is joint FAO/Office international des epizooties (OIE)/WHO reporting of notifiable animal diseases), and other public and occupational health initiatives. UNEP works on a number of environmental ethics issues indirectly, and the Cartagena Protocol will be applicable to many TDR projects. UNESCO has the COMSTEC committee and the International Bioethics Committee, which also look at the ethical issues raised by genetic engineering. Some of the broader ethical issues are being discussed in these forums, and collaboration should help bring in a wider range of viewpoints to take a more holistic approach than merely the human health aspects of interventions for which WHO has primary responsibility. The other international bodies working on bioethics include the Council for International Organizations of Medical Sciences (CIOMS), the World Medical Association (WMA), the HUGO Ethics Committee, ethics committees of professional associations, the International Association of Bioethics, to mention just a few. There are numerous regional and national associations of bioethics.

7.6 Further next steps in consultation on ethical, legal and social issues

This report is only one step in considering ethical issues. Already there have been social studies of the implementation of TDR projects for disease control, which show that there is variation in the uptake of interventions depending on the community and disease involved (TDR 2000[a]; 2002). In addition to the recommendations above, the following steps need to be effected concurrently and urgently.

(a) Gathering of descriptive data on member countries approaches and values

Data should be gathered on a continuous basis. There are still unknown factors in the way societies apply various types of ethical theories and principles to different aspects of life, so general descriptive ethics studies in the countries that may be likely targets would be useful for developing general social science approaches. More detailed surveys on focused issues may be useful when a project is getting close to the field study stage. Member countries of WHO/UNDP/World Bank could be asked directly to provide information and comments, which would then need to be analysed. The gathering and reporting of data can make countries more conscious of the issue, and may encourage local researchers to explore community attitudes to GM vectors. Some of these concerns may be useful for the design stage of vector programmes, so a general call for comments should be made allowing enough time for focused attention on new areas that arise. Help is needed in gathering data by sound social science methodologies in many countries.

(b) Interactive academic and public forums for debate

Different forums have distinct purposes. Intergovernmental forums aim at consensus, but this may not be necessary as already governments have agreed that combating tropical diseases is a major priority, that biotechnology is one means to do this, and that this needs to be well-regulated. However, for specific target areas when close to field implementation, multilateral consultations should be held with neighbouring jurisdictions to prepare for contingencies in case of a vector migrating across national boundaries.

Another type of forum should specifically aim at identifying the differences and diversity in world views that may affect the way scientific facts are interpreted, by inviting different communities that may be affected, interested civil society organizations (CSOs) (both not-for-profit and for-profit), and experts of diverse opinion. This identification of diversity of thought is also important as part of a systematic approach to ethical analysis. This would allow preparation of adequate responses to all points of view, and allow a chance for gathering descriptive information through forums where persons argue for different approaches.

These issues should be discussed in the bioethics community, in regional and global meetings, so that the full range of the global bioethics community is given a chance to participate. This will also aid information dissemination as case studies will be carried back to different universities and schools for more people to reflect on. Experience of the way science and technology ethical and social issues were discussed by teachers in many countries before introducing curricular changes (Macer et al., 1996) suggests that, if members of a community perceive a need as individuals, they will become involved in the process. TDR could utilize the individual initiatives of interested persons by providing information kits and access to information, and developing networks to encourage them.

The TDR partners have a duty to individual people, individual countries, member countries as a whole, and humankind as a whole. The process of dialogue and negotiation can be a more ethical option than a prescriptive stand if we consider the autonomy of those involved and the consequences. The process of forum is essential for developing methods to obtain group and community consent for public health interventions in general, and in particular for this project. The implications of informed consent for public health projects have not been adequately developed.

(c) Development of model guidelines

Many have called for an international guideline. Whether or not the guideline is legally binding, like the Cartagena Protocol, a consensus text is useful as countries attempt to face these issues with a lack of previous experience. The text should be accompanied by detailed explanation of the process leading up to the text so that each country can explore the arguments behind the guideline and see what is most appropriate for their society. There will still be a fear that companies or governments may go ahead with projects whether or not the guideline is followed, and whether or not they seek advice from TDR. An international secretariat, located in TDR, could be established to coordinate information from field trials. This secretariat could give advice on all aspects outlined in section 7.1, and this could consider ethical and social factors as an integral part.

(d) Education on the guidelines, and feedback

Once model guidelines are developed, it will be important to circulate them for comments. This may be the best stage for an active education process, as it will educate scientists about the guidelines and educate the general community about the mechanism established for field trials. Broad education to open the minds of people, at all levels of society, to the options available for disease control and how to make better decisions for themselves, is considered part of the empowerment of citizens. The process should not just be one way, but interactive and combined with the recommendation to gather descriptive data.

TDR is called upon to take the initiative in coordinating these programmes because release of GM vectors is a question for the global community, and the consequences will potentially impact on many generations to come. There is a moral mandate for these studies to progress rapidly, but carefully.

ACKNOWLEDGEMENTS

The useful and critical advice of WHO staff is gratefully acknowledged, in particular that of Dr Boris Dobrokhotov, Dr Nina Mattock, Ms Kalyani McCullough, Dr Carlos Morel, Dr Ayoade Oduola, Dr Johannes Sommerfeld, Dr Yeya Touré and Dr Daniel Wikler. The useful suggestions of reviewers and conference participants in several countries who gave feedback on the ideas are also warmly acknowledged.

ABBREVIATIONS

ACME	American Committee of Medical Entomology
BW	Biological warfare
CAC	Codex Alimentarius Commission
CBD	Convention on Biological Diversity
CGRFA	Commission on Genetic Resources in Food and Agriculture
CIOMS	Council for International Organizations of Medical Sciences
CSO	Civil Society Organization
FAO	Food and Agriculture Organization
FDA	United States Food and Drug Administration
GFP	Green fluorescent protein
GM	Genetically modified
GMO	genetically modified organism
HUGO	Human Genome Organization
ICGEB	International Centre for Genetic Engineering and Biotechnology
IPGRI	International Plant Genetic Resources Institute
IPR	Intellectual property rights
IRB	Institutional review board
ISAAA	International Service for the Acquisition of Agri-biotech Applications
IUBS	International Union of Biological Sciences
LMO	Living modified organism
NGO	Non-governmental organization
OECD	Organisation for Economic Co-operation and Development
SIT	Sterile insect technique
TDR	UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
TRIPS	Trade-Related Intellectual Property Rights
UN	United Nations
UNDP	United Nations Development Programme
UNEP	United Nations Environmental Programme
UNESCO	United Nations Education, Scientific and Cultural Organization
UNIDO	United Nations Industrial Development Organization
USDA	United States Department of Agriculture
USDOE	United States Department of Energy
WHO	World Health Organization
WTO	World Trade Organization

REFERENCES

- ACME (American Committee of Medical Entomology). *Arthropod containment guidelines*. 2002, available at: <http://www.astmh.org/subgroup/acme.html>
- Alphey, L. et al. Malaria control with genetically manipulated insect vectors. *Science*, 2002, 298: 119-21.
- Alvarez-Castillo FA. *Ethics for social research in health: The PHSSA guidelines*. Manila, Philippines Social Science Association, 2001. Available at: <http://phssa.org/>
- Alvarez-Castillo FA. Limiting factors impacting on voluntary first person informed consent in the Philippines. *Developing World Bioethics*, 2002, 2:21-7.
- American Anthropological Association. *Code of Ethics*. 1998. Available at: <http://www.aaanet.org/committees/ethics/ethcode.htm>
- Angell M. Investigators' responsibilities for human subjects in developing countries. *New England Journal of Medicine*, 2000, 337:847-9.
- Annas, GK. *The rights of patients*. Carbondale, Southern Illinois University Press, 1989.
- Atkinson PW, Pinkerton AC, O'Brochta DA. Genetic transformation systems in insects. *Annual Review of Entomology*, 2001, 46:317-346.
- Aultman KS et al. Research ethics. Managing risks of arthropod vector research. *Science*, 2000, 288:2321-2322.
- Azevedo E, de Moraes Marcilio Cerqueira E. Decisions in circumstances of poverty. *Eubios Journal of Asian and International Bioethics*, 2002, 12:105-7.
- Balter M. Can WHO roll back malaria. *Science*, 2000, 290:430.
- Beard CB, Durvasula RV, Richards FF. Bacterial symbiosis in arthropods and the control of disease transmission. *Emerging Infectious Diseases*, 1998, 4:581-591.
- Beaty, BJ. Genetic manipulation of vectors: A potential novel approach for control of vector-borne diseases. *Proceedings of the National Academy of Sciences (USA)*, 2000, 97:10295-7.
- Beauchamp TL, Childress JF. *Principles of biomedical ethics*. Fourth Edition, New York, Oxford University Press, 1994.
- Berghammer AJ et al. A universal marker for transgenic insects. *Nature*, 1999, 402:370.
- Boyd A, Ratanakul P, Deepudong A. Compassion as common ground. *Eubios Journal of Asian and International Bioethics*, 1998, 8:34-37.
- Bruce D, Bruce A (eds.). *Engineering Genesis. The Ethics of Genetic Engineering*. London, Society, Religion and Technology Project, Earthscan, 1998.
- CAC (Codex Alimentarius Commission). *Ad hoc Task Force on Foods Produced by Biotechnology*. 2002. Available at: http://www.codexalimentarius.net/ccfbt3/bt02_01e.htm
- Callahan D, Jennings B. Ethics and public health: forging a strong relationship. *American Journal of Public Health*, 2002, 92:169-176.
- Capron AM. Protection of research subjects: Do special rules apply in epidemiology? *Law, Medicine and Health Care*, 1991, 19:184-190.
- Capurro MDL et al. Virus-expressed, recombinant single-chain antibody blocks sporozoite infection of salivary glands in *Plasmodium gallinaceum* – infected *Aedes aegypti*. *American Journal of Tropical Medicine and Hygiene*, 2000, 62:427-33.

- Catenhusen WM, Neumeister H (eds.). Enquete-Kommission des Deutschen Bundestages, *Chancen und Risiken der Gentechnologie*. Frankfurt, Campus Verlag, (German). [German Bundestag, *Report of the commission of enquiry on prospects and risks of genetic engineering*.] Paper m10/6775, 1990, (06.01.87).
- Catteruccia F et al. Stable germline transformation of the malaria mosquito *Anopheles stephensi*. *Nature*, 2000, 405:959-962.
- CBD (Convention on Biological Diversity). *Cartagena Protocol on Biosafety*. 2000. Available at: <http://www.biodiv.org/biosafety/protocol.asp>
- Chee HL et al. Bioethics and human population genetics research. In: *Proceedings of the UNESCO International Bioethics Committee Third Session*, Volume I, pp.39-63, Paris, UNESCO, 1996.
- Chinsembu K, Kambikambi T. Farmers' perceptions and expectations of genetic engineering in Zambia. *Biotechnology and Development Monitor*, 2001, 47:13-14.
- Comstock GL. *Vexing nature? On the ethical case against agricultural biotechnology*. Boston, Kluwer Academic, 2000.
- Council for International Organizations of Medical Sciences (CIOMS). International guidelines for ethical review of epidemiological studies. *Law, Medicine and Health Care*, 2001, 19:247-258.
- Curtis CF. The case for de-emphasizing genomics in malaria control. *Science*, 2000, 290:1508.
- Curtis J, Curtis CF. 1976. Mosquito programme. *New Scientist*, 8 January 1976:89
- D'Alessandro U et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme, *Lancet* 1995, 345:479-483.
- Dalton R. Growers cotton on to GM bollworm. *New Scientist*, 3 March 2001:11.
- Dealler S. BSE and the ethics of not doing research. *Bulletin of Medical Ethics*, 1995, 104:13-7.
- Dickens BM. Issues in preparing ethical guidelines for epidemiological studies. *Law, Medicine and Health Care*. 1991, 19:175-183.
- Durant J (ed). *Biotechnology in public: a review of recent research*. London, Science Museum for The European Federation of Biotechnology, 1995.
- Editorial. *Nature*, 1975, 256:355-7.
- Edmonds Institute, The Scientists' Working Group on Biosafety. *Manual for assessing ecological and human health effects of genetically engineered organisms*. Washington, Edmonds Institute, 1998.
- Ekunwe EO, Kessel R. Informed consent in the developing world. *Hastings Center Report*, 1984, 14:22-4.
- Engelhardt HT. *The Foundations of Bioethics*. New York, Oxford University Press, 1986.
- Enserink M. Building a disease-fighting mosquito. *Science*, 2000, 290:440-1.
- European Federation on Biotechnology (EFB) Task Group on Public Perceptions of Biotechnology. *Ethical aspects of agricultural biotechnology. Bioethical aspects of biotechnology in the agrofood sector (BABAS)*. Cambridge Biomedical Consultants, 1999.
- FDA. U. S. Food and Drug Administration. Center for Food Safety and Applied Nutrition Guidance for Industry. *Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering*. Draft Guidance (January 2001) <<http://www.cfsan.fda.gov/~dms/biolabgu.html>>
- Fine GA. Ten lies of ethnography: Moral dilemmas of field research. *Journal of Contemporary Ethnography*, 1993, 22:267-94.
- Fletcher J. *Situation Ethics: The New Morality*. London, SCM Press, 1966.

- Food and Agricultural Organization. *Biotechnology and Food Safety*. FAO Food and Nutrition Paper 61, 1997, FAO/WHO.
- Food and Agricultural Organization. *Genetically modified organisms. Consumers, food safety and the environment*. FAO Ethics Series 2, Rome, FAO, 2001.
- Food and Agricultural Organization. *New developments in biotechnology and their implications for the conservation of farm animal genetic resources, 1: Reversible DNA quiescence and somatic cloning*, A joint FAO/Istituto per la Zootecnia workshop, Rome, Nov1997, FAO, 1998.
- Gillon, R. *Philosophical Medical Ethics*, London, Wiley Medical, 1986.
- Gostin L. Ethical principles for the conduct of human subject research: Population-based research and ethics. *Law, Medicine and Health Care*. 1991, 19:191-201.
- Greely HT. North American Regional Committee of the HGDP. Model ethical protocol for collecting DNA samples. Prepared by the North American Regional Committee of the Human Genome Diversity Project. *Houston Law Review*, 1996, 33(5):1431-1473. Available at: <http://www.stanford.edu/group/mor-rinst/hgdp/protocol.html>
- Gupta A, Guha, K. Tradition and conservation in Northeastern India. *Eubios Journal of Asian and International Bioethics*, 2002, 12:15-19.
- Hanlon J. Germ-war allegations force WHO out of Indian mosquito project. *New Scientist*, 1975, 68:102-103.
- Heinrich JC, Scott MJ. A repressible female-specific lethal genetic system for making transgenic insect strains suitable for a sterile-release program. *Proceedings of the National Academy of Sciences of the United States of America*, 2000, 97:8229-32.
- Ho M-W. *Genetic engineering: dream or nightmare?* London, Gateway Books, 1998.
- Hoffman SL. Research (genomics) is crucial to attacking malaria. *Science*, 2000, 290:1509.
- Holt RA. The Genome Sequence of the Malaria Mosquito *Anopheles gambiae*. *Science*, 2002, 298:129-49.
- Hoy MA. Impact of risk analyses on pest-management programs employing transgenic arthropods. *Parasitology Today*, 1995, 11:229-232.
- Huffman MA. Self-medicative behaviour in the African great apes: an evolutionary perspective into the origins of human traditional medicine. *BioScience* 2001, 51:651-61.
- HUGO Ethics Committee. *Statement on benefit sharing*. April 2000.
- HUGO Ethics Committee. *Statement on cloning*. March 1999.
- HUGO Ethics Committee. *Statement on the principled conduct of genetics research*. April 1996.
- ICGEB (International Centre for Genetic Engineering and Biotechnology). 2002, <http://www.icgeb.trieste.it/>.
- IPGRI (International Plant Genetic Resources Institute). *Ethics and equity in conservation and use of genetic resources for sustainable food security*. Proceeding of a workshop to develop guidelines for the CGIAR, Brazil, 21-25 April 1997.
- Ito J et al. Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite. *Nature*, 2002, 417:452-5.
- James AA et al. Present and future control of malaria (letters). *Science*, 2001, 291:435-6.
- James C. Global review of commercialized transgenic crops: 2000. New York, Ithaca, *International Service for the Acquisition of Agri-biotech Applications (ISAAA) Briefs*, No. 23, 2001[a].

- James C. *Preview. Global review of commercialized transgenic crops: 2001*. New York, Ithaca, *International Service for the Acquisition of Agri-biotech Applications (ISAAA) Briefs*, No. 24, 2001[b].
- Johnson B et al. Inhibition of luciferase expression in transgenic *Aedes aegypti* mosquitoes by Sindbis virus expression of antisense luciferase RNA. *Proceedings of the National Academy of Science (USA)*, 1999, 96:13399-13403.
- Kass NE. An ethics framework for public health. *American Journal of Public Health*, 2001, 91:1776-82.
- Kleinman A. *Ethics and experience: an anthropological approach to health equity*. 1999. Available at: <http://www.hsph.harvard.edu/Organizations/healthnet/HUPapers/foundations/kleinman.html>
- Knoppers BM et al. HUGO urges genetic benefit sharing. *Community Genetics*, 2000, 3:88-92.
- Krafsur ES, Lindquist DA. Did the sterile insect technique or weather eradicate screwworms (Diptera: Calliphoridae) from Libya? *Journal of Medical Entomology*, 1996, 33:877-887.
- Krafsur ES. Sterile insect technique for suppressing and eradicating insect population: 55 years and counting. *Journal of Agricultural Entomology*, 1998, 15:303-17.
- Lacey LA, Kaya HK (eds). *Field manual of techniques in invertebrate pathology: application and evaluation of pathogens for control of insects and other invertebrate pests*. Dordrecht, Kluwer Academic Publishers, 2000.
- Lachance LE. Status of the sterile-insect release method in the world, in: *The sterile-insect technique and its field applications. Proceedings of a panel*, pp.55-62. Vienna, International Atomic Energy Agency, 1974.
- Ladeveze V et al. Dynamics of the hobo transposable element in transgenic lines of *Drosophila melanogaster*. *Genetical Research* 2001, 77:135-42.
- Laird M. *The natural history of larval mosquito habitats*. London, Academic Press, 1997.
- Lamborn RH. *Dragon flies vs. mosquitoes. Can the mosquito pest be mitigated? Studies in the life history of irritating insects, their natural enemies, and artificial checks by working entomologists*. New York, D. Appleton Co, 1890.
- Lawler A. US questions Harvard research in China. *Science*, 2002, 296:28.
- Legner EF. Biological control of Diptera of medical and veterinary importance. *Journal of Vector Ecology*, 1995, 20:59-120.
- Levine RJ. Informed consent: Some challenges to the universal validity of the Western model. *Law, Medicine and Health Care*, 2001, 19:207-213.
- Lewis DL et al. Ectopic gene expression and homeotic transformations in arthropods using recombinant Sindbis viruses. *Current Biology*, 1999, 9:1279-87.
- Lycett GJ, Kafatos FC. Anti-malarial mosquitoes? *Nature*, 2002, 417:387-8.
- Macer D. Uncertainties about 'painless' animals, *Bioethics*, 1989, 3:226-235.
- Macer DRJ (ed.). *UNESCO/IUBS/Eubios Bioethics Dictionary*. Christchurch, Eubios Ethics Institute, 2002. Available at: <http://www.biol.tsukuba.ac.jp/~macer/biodict.htm>
- Macer DRJ et al. Attitudes to biotechnology in Japan and New Zealand in 1997, with international comparisons. *Eubios Journal of Asian and International Bioethics*, 1997, 7:137-151.
- Macer DRJ et al. *Bioethics in high schools in Australia, New Zealand and Japan*, Christchurch, Eubios Ethics Institute, 1996. Available at: <http://www.biol.tsukuba.ac.jp/~macer/BHS.html>
- Macer DRJ, Ng MC. Changing attitudes to biotechnology in Japan. *Nature Biotechnology*, 2000, 18:945-7.

- Macer DRJ. *Attitudes to genetic engineering: Japanese and international comparisons*. Christchurch, Eubios Ethics Institute, 1992. Available at: <http://www.biol.tsukuba.ac.jp/~macer/AGE.htm>
- Macer DRJ. Bioethics and genetic diversity from the perspective of UNESCO and non-governmental organizations. In: Knoppers BM et al (eds), *Human DNA: law and policy. International and comparative perspectives*, pp.265-274. The Hague, Kluwer Law International, 1997.
- Macer DRJ. *Bioethics for the people by the people*, Christchurch, Eubios Ethics Institute, 1994. Available at: <http://www.biol.tsukuba.ac.jp/~macer/BFP.html>
- Macer DRJ. *Bioethics is love of life*. Christchurch, Eubios Ethics Institute, 1998. Available at: <http://www.biol.tsukuba.ac.jp/~macer/bll.html>
- Macer DRJ. Inventions, patents and morality, entry E6-58-09-03. In: *Encyclopedia of life support systems*. Paris, UNESCO, 2001.
- Macer DRJ. *Report of the visiting scientist on ethics in food and agriculture*, Rome, FAO, 1999.
- Macer DRJ. *Shaping genes*. Christchurch, Eubios Ethics Institute, 1990. Available at: <http://www.biol.tsukuba.ac.jp/~macer/SG.html>.
- MacIntyre A. *After virtue*. University of Notre Dame Press, 1984.
- Mansour M., and Franz G. Gamma radiation as a quarantine treatment for the Mediterranean fruit fly (Diptera:Tephritidae). *Journal of Economic Entomology*, 1996, 89:1175-1180.
- McCullough K. *ELSI briefing paper on bio-science status of GM insects*. Geneva, TDR, August 2001.
- Moreira LA et al. Robust gut-specific gene expression in transgenic *Aedes aegypti* mosquitoes. *Proceedings of the National Academy of Sciences (USA)*, 2000, 97:10895-10898.
- Morel CM, Touré YT, Dobrokhotov B, and Oduola AMJ. The Mosquito Genome--a Breakthrough for Public Health. *Science*, 2002, 298: 79.
- Munro L. The future animal: Environmental and animal welfare perspectives on the genetic engineering of animals. *Cambridge Quarterly of Healthcare Ethics*, 2001, 10:314-24.
- Nelkin D, Andrews L. Homo economicus: The commercialization of body tissue in the age of biotechnology. *Hastings Center Report*, 1998, 28 (5):30-39.
- New Zealand Royal Commission on Genetic Modification. *Final report and recommendations*. New Zealand, 2002. Available at: www.gmcommission.govt.nz
- News report. *Science*, 2001, 294:45.
- Ng, M.A.C., Takeda, C., Watanabe, T. & Macer, D.R.J. Attitudes of the Public and Scientists to Biotechnology in Japan at the start of 2000. *Eubios Journal of Asian and International Bioethics*, 2002, 10: 106-13.
- Nilson, A. ed., *Transgenic animals and food production, Proceedings from an international workshop*, Stockholm, May 1997, *K. Skogs-o. Lantbr.akad. Tidskr.* 136: 20. 1997.
- Nowak R. Gene warfare. *New Scientist*, 11 May 2002:6.
- Nuffield Council on Bioethics. *Genetically modified crops: the ethical and social issues*. 1999[a]. Available at: <http://www.nuffieldbioethics.org/>
- Nuffield Council on Bioethics. *The ethics of clinical research in developing countries*. 1999[b]. Available at: <http://www.nuffieldbioethics.org/>
- O'Brochta DA, Atkinson PW. Building the better bug. *Scientific American*, 1998, 279:90-95.
- Olson K et al. Genetically engineered resistance in mosquitoes to dengue virus transmission. *Science*, 1996, 272:884-886.

- Organization for Economic and Industrial Development. OECD Reports sent to Okinawa G8 meeting, and other documents, 2001. Available at: <http://www1.oecd.org/subject/biotech/>
- Peloquin JJ et al. Germ-line transformation of pink bollworm (Lepidoptera: gelechiidae) mediated by the piggyBac transposable element. *Insect Molecular Biology*, 2000, 9:323-333.
- Ramsey P. *The patient as person*. New Haven: Yale University Press, 1970.
- Rawls J. *A Theory of Justice*. Cambridge, MA.: Belknap Press 1971.
- Reich WT (ed.). *Encyclopedia of bioethics*. Revised edition. New York, Simon and Schuster, Macmillan, (5 volumes), 1995.
- Reiss MJ, Straughan R. *Improving nature? The science and ethics of genetic engineering*. Cambridge, Cambridge University Press, 1996.
- Rikfin J. *The biotech century. Harnessing the gene and remaking the world*. New York, Tarcher/Putman, 1998.
- Rolston H III. *Conserving natural value*. New York, Columbia University Press, 1994.
- Schweitzer A. *The teaching of the reverence of life*. London, Peter Owen, 1966.
- Scott M. Progress towards the development of a transgenic strain of the Australian sheep blowfly suitable for a sterile-release program. *New Zealand BioScience*, 2001 (May):11-3.
- Scott TW et al. The ecology of genetically modified mosquitoes. *Science*, 2002, 298: 117-9.
- Service MW. Can we control mosquitoes without pesticides? A summary. *Journal of the American Mosquito Control Association*, 1995, 11:290-293.
- Sherwin S. *No longer patient: feminist ethics and health care*. Philadelphia, Temple University Press, 1992.
- Singer P. *Animal liberation*. London, Jonathan Cape, 1976.
- Spielman A, D'Antonio M. *Mosquito: the story of mankind's deadliest foe*. Faber and Faber, 2001.
- TDR. *Scientific Working Group on Insect Disease Vectors and Human Health*. Geneva, WHO/HQ, 12-16 August 2002.
- TDR *Scientific Working Group on Strategic Social, Economic and Behavioural Research, 31 May-2 June 2000*. Geneva, TDR, document TDR/STR/SEB/SWG/00.1, 2000[a].
- TDR. *Strategy 2000-2005 (TDR/GEN/SP/00.1/Rev.1 October 2000)*. Geneva, TDR, 2000[b].
- Tiedje JM et al. The planned introduction of genetically engineered organisms: ecological considerations and recommendations. *Ecology*, 1989, 70:298-315.
- TRIPS *Agreement on trade-related aspects of intellectual property rights*. Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco, 15 April 1994. Available at: http://www.wto.org/english/tratop_e/trips_e/t_agm0_e.htm
- Tsai DF-C. Ancient Chinese medical ethics and the four principles of biomedical ethics. *Journal of Medical Ethics*, 1999, 25:315-21.
- UNDP. *Human Development Report 2001. Making New Technologies Work for Human Development*. New York, UNDP, 2001.
- UNEP web page, www.unep.org, 2002.
- UNESCO *Universal Declaration on the Human Genome and Human Rights*. General Assembly of UNESCO, November 1997.

- UNIDO/UNEP/WHO/FAO Working Group on Biosafety. *Voluntary code of conduct for the release of organisms into the environment*, ICGEB Biosafety WebPages, 1991. Available at: <http://www.icgeb.trieste.it/~bsafesrv/bsfcode.htm>
- Union of Concerned Scientists, Statements, 2001. Available at: <http://www.ucsusa.org/index.html>
- United Kingdom Royal Commission on Environmental Pollution, thirteenth report. *The release of genetically engineered organisms to the environment*. London, H.M.S.O., 1989.
- USDA (United States Department of Agriculture). 2002, available at: <http://www.aphis.usda.gov/biotech/arthropod/>
- USDOE (United States Department of Energy). *DOE Human Genome Project*. 2002. Information homepages: <http://www.ornl.gov/hgmis/elsi/gmfood.html>
- Veatch RV. *Medical ethics*. New York, Jones and Bartlett Publishers, 1989.
- Ward TW et al. *Aedes aegypti* transducing dengue virus pathogenesis and expression in *Aedes aegypti* and *Anopheles gambiae* larvae. *Insect Molecular Biology*, 2002, 10:394-405.
- Weed DL, McKeown RE. Ethics in epidemiology and public health I. Technical terms. *Journal of Epidemiology and Community Health*, 2001, 55:857.
- Wheale P et al. (eds.). *The social management of genetic engineering*, London, Ashgate Publishing, 1997.
- World Health Organization. *WHO-supported collaborative research projects in India: the facts*. WHO Chronicle, 1976, 30:131-139.
- World Health Organization. *Joint FAO/WHO expert consultations on food derived from biotechnology*. 2001. Available at: http://www.euro.who.int/eprise/main/WHO/Progs/FOS/NewsEvents/20010912_2.
- World Health Organization. *Operational guidelines for ethics committees that review biomedical research*. Geneva, World Health Organization, 2000 (document No. TDR/PRD/ETHICS/2000.1).
- World Medical Association. *Helsinki Declaration*. 2000.
- Wright B. Gene-spliced pesticide uncorked in Australia. *New Scientist*, 4 March 1989: 23.



Mailing address:

TDR
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

Street address:

TDR
World Health Organization
Centre Casai
51-53 Avenue Louis-Casai
1216 Geneva
Switzerland

Tel: (+41) 22-791-3725
Fax: (+41) 22-791-4854
E-mail: tdr@who.int
Web: www.who.int/tdr